Printed by: DCL Print & Sign
Zelzate | Belgium | www.dclsigns.be

A practitioner is a person that knows how, but not why,
A theoretician is a person that knows why, but not how,
I have combined the two:
I can't make it work and I don't know why.
(after P. Harremoes - Heineken Prize for Environmental Sciences, September 2000)

Members of the Jury:

Prof. dr. ir. W. Steurbaut (Chairman)
Prof. dr. ir. R. Orru
Dr. W. Van Brussel
Prof. dr. E. Van der Eycken
Prof. dr. ir. P. Van der Meeren
Prof. dr. ir. J. Dewulf
Prof. dr. ir. R. Verhé

Promoter:

Prof. dr. ir. C. Stevens
Research Group SynBioC, Department of Organic Chemistry
Faculty of Bioscience Engineering, Ghent University

Dean:

Prof. dr. ir. H. Van Langenhove

Rector:

Prof. dr. P. Van Cauwenberghe

ir. Davy ACKE

EVALUATION OF MICROREACTOR TECHNOLOGY FOR MULTICOMPONENT REACTIONS

Thesis submitted in fulfilment of the requirements
For the degree of Doctor (PhD) in Applied Biological Sciences:
Chemistry

Dutch translation of the title:
Evaluatie van microreactortechnologie voor multicomponentreacties

ISBN-number:
978-90-5989-202-6

Ghent, November 2007

The author: ir. Davy Acke

The promoter: Prof. dr. ir. C. Stevens

Woord Vooraf

Waarom heb ik, ondertussen zoveel jaar geleden, voor bio-ingenieur gekozen? Wel, hoofdzakelijk voor het ruime gamma aan wetenschappen die ons aangeboden werd. Dat ik die brede basis altijd geapprecieerd heb, getuigt mijn curriculum: een masterthesis in de voeding, een doctoraat in de organische scheikunde gecombineerd met technologie en sinds kort terug de stap naar de voedingsindustrie. De zijstap naar dit doctoraat heeft me enorm gesmaakt. Na 4 jaar wordt het dan ook tijd om een aantal mensen te bedanken.

Het afleggen van een doctoraat gaat niet alleen om de resultaten, want de boog kan niet altijd gespannen staan. Ik denk hierbij aan bbq's, fuiven, snooker, minivoetbal, atletiek, film, de afsluitende party in Spa, ... Op die manier leer je je collega's, waarvan sommigen ondertussen vrienden geworden zijn, ook op een andere manier kennen. Kortom, An A., Eva, Dominick, Guido, Sven C., Sven M., Matthias, Jan, Marijke, Kurt, Vera, Sarah, Erika, Pascal, Ann DB, Bart R., Karel, Stijn, Mudiganti, Filip, Riccardo, Viviana, Ana, Camelia, Mirjana, Thomas, Fien, Nicola, Nicolai, Griet, David, Bert, Yves, Tina, Inge, Bart V., Berten, Willem, Bram, Kristof, Ellen, Diederica, Pieter, Aziz, Tamer, Viviane en Sandra. Bedankt voor de leuke sfeer in en buiten het labo! Ik kom zeker nog eens af voor een babbel, een matchke minivoetbal of voor het zoveelste rondje rond de Watersportbaan.

Enkele mensen wil ik hierbij extra bedanken. Om praktische redenen (zijnde een blauwgeschilderde constructie) werd ik 4 jaar geleden 'verbannen' naar het vierde verdiep en mocht ik dus constant pendelen tussen het vierde en het vijfde. Die verbanning vond ik alles behalve negatief, want ze heeft me de kans gegeven om met een aantal fantastische mensen samen te werken, zoals David, Bert, Yves, Griet, Camelia en Mirjana. En uiteraard zal ik me de leuke babbels met Vera zeker blijven herinneren. Ellen en Kristof wil ik speciaal bedanken voor de leuke samenwerking. Samen hebben we een stukje 'mooie chemie' verwerkt tot een boeiend artikel. En Dominick, mijn bureaumakker,

samen uit, samen thuis: Proficiat ook met je doctoraat! Bedankt voor de leuke momenten op het werk. Samen met Eva en An heb je het schrijven een heel stuk aangenamer gemaakt.

Bij een doctoraat hoort vanzelfsprekend ook een promotor. Ik had daarbij de eer om professor Chris Stevens als mijn promotor te mogen hebben. Bedankt dat ik zomaar kon binnenlopen als er eens iets niet goed lukte om dan samen tot een oplossing te komen. Ik hoop dat dit werk een aanzet mag zijn tot verdere studies met microreactoren.

Verder zou ik de leden van de examencommissie van harte willen bedanken voor het kritisch nalezen en becommentariëren van mijn werk. I also want to thank Wojciech Piotr Bula and professor Han Gardeniers from the MESA$^+$ Institute for Nanotechnology, University of Twente, Enschede, The Netherlands for the comparative study with the 1-line chip.

Ik ben ervan overtuigd dat je dit enkel maar kunt verwezenlijken als je een aantal mensen achter je staan hebt. Daarom zou ik mijn vrienden en vriendinnen willen bedanken. Een extra dank naar PJ en Sam om mijn Engels wat begrijpelijk te maken. Joke, jij bent eigenlijk onlosmakelijk verbonden met mijn doctoraat. Ik wil je bedanken voor de aangename tijd die we samen gehad hebben. En voor het boeiend luisteren als ik voor de zoveelste keer over die pompen en verstoppingen aan het zagen was: hét bewijs dat alfa en beta samen gaan.

En ten slotte zou ik ook graag mijn ouders en mijn broer willen bedanken. Het was jullie heel waarschijnlijk nooit echt duidelijk waar ik precies mee bezig was. Ik hoop dat dit nu wat duidelijker is geworden. Bedankt moe'tje, pa en Andy (aka kleine broer) voor de steun en de motivatie die jullie mij gaven om dit tot een goed einde te brengen.

Davy Acke
23 november 2007

Table of Contents

List of Abbreviations

μreactor	microreactor
μ-SYNTAS	micro synthesis and total analysis system
μ-TAS	micro total analysis system
τ	residence time
AFRICA®	automated flow reaction, incubation and control apparatus
AO	amberzyme oxirane resin
Bn	benzyl
bp	boiling point
CFD	computational fluid dynamics
c-Hex	cyclohexyl
CSTR	continuous stirred tank reactor
DABCO	1,4-diazabicyclo[2.2.2]octane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
EGDMA	ethylene glycol dimethacrylate
EOF	electro-osmotic flow
EPA	Environmental Protection Agency
Et	ethyl
EtOH	ethanol
EWG	electron withdrawing group
FLIM	fluorescence lifetime imaging
GPC	gel permeation chromatography
HCN	hydrogen cyanide
HOAc	acetic acid
IL	ionic liquid
IMM	Institut für Mikrotechnik Mainz (Germany)
IMRET	International Conference on Microreaction Technology
i-Pr	isopropyl
LCA	life cycle assessment

MCR(s)	multicomponent reaction(s)
Me	methyl
MeOH	methanol
MFFD	microfluidic flow-focusing device
n-BuOH	*n*-butanol
NH_4OAc	ammonium acetate
NMP	*N*-methylpyrrolidinon
NOE	nuclear overhauser effect
PCR	polymerase chain reaction
PDI	polydispersity index
PDMS	polydimethylsiloxane
Ph	phenyl
PRV	pressure relief valve
p-TsOH	p-toluene sulfonic acid
r	flow rate
RDS	rate-determining step
rmf	reaction mixture fraction
RT	room temperature (standardised at 22 °C)
RTU	residence time unit
sec-BuOH	secondary butanol
TBD	1,5,7-triazabicyclo[4.4.0]undec-3-ene
TFA	trifluoro acetic acid
THF	tetrahydrofuran
TPGDA	tripropylene glycol diacrylate
Ts	tosyl
X-CR	X-component reaction (whereby X is a numerical value)

Chapter 1 - Introduction and Goal

1.1 INTRODUCTION

Chemists have been using almost the same equipment for many hundreds of years now. Even though batch methods are mostly slow and inefficient, they are still performed mainly on expensive products, such as e.g. perfumes, wines or pure maple syrups. The process of extracting oils from flowers by means of distillation, which is the procedure that is most commonly used nowadays to produce perfumes, was already developed in the 10th century by Avicenna, an Arabian doctor who was also a chemist. The round-bottom flask in the organic lab and the conventional large-scale batch reactor in the pharmaceutical and chemical industry were and still are inherent facilities in synthetic chemistry.[1] In this way, chemists have been able to synthesise a broad range of molecules, and to provide large quantities of potentially biological active molecules. Although the access through classical synthetic chemistry is quite successful, there is also another side of the coin. Very often, these syntheses are accompanied with insufficient conversions, production of by-products and a lot of waste, mainly due to insufficient mixing or heat removal.

Having in mind the fast decreasing petroleum feedstock, one must constantly search for new methods to cope with these disadvantages. Therefore, during the last decennia, several attempts have been made to increase the synthetic efficiency. These efforts can roughly be divided in two groups, namely synthetic and technological improvements, which both have the goal to improve the reaction efficiency.
Important synthetic improvements include the development and use of solid phase reactions,[2-4] combinatorial chemistry,[5-7] homogeneous[8] or heterogeneous[9,10] catalysis and library syntheses *via* multicomponent reactions (MCRs)[11,12].

Technical improvements that are studied most intensively are process intensification methods. This includes the optimisation of reaction engineering by changing the instrumentation to reduce waste, energy usage and equipment, including the search for new analytical tools for online monitoring and the change of equipment such as packed bed reactors and microreactors.

Next to the decreasing petroleum feedstock, a second incentive exists to develop and study microreactor technology, mainly from a pharmaceutical point of view. Nowadays, it takes on average 10 to 15 years for an active substance to travel from being an experimental drug in the lab to a medicine.[13] The procedure to develop a new drug can be divided in three different steps. Firstly, a variety of potentially biological active compounds are developed in the laboratory producing several milligrams to grams of the product. After incorporating these compounds in preliminary activity tests, the lead compounds are selected for further intensive clinical testing in a second step. The approval of the medicine is the final phase in the drug development. Only five in 5,000 compounds that enter preclinical testing make it to human testing, according to the Pharmaceutical Research and Manufacturers of America.[14] One of these five tested in people is approved for medical use.[13,14] According to a recent study, the total cost involved with this process is estimated at 800 million USD.[15] An important issue in this context to reduce the time-to-market, and thus the total cost, during the drug design is the fast supply of several kilograms of the active product for the preclinical and clinical studies. Unfortunately, here lies often the bottleneck due to an incompatibility of the laboratory procedure with pilot scale or large scale production. The scale up of mixing tanks from laboratory to plant size is indeed a crucial issue in the design of industrial processes to find optimal configurations and operating conditions. Depending on the physical process limiting the performance of the mixing vessel, it is commonly suggested that at least one of the mixing characteristics such as power input per unit volume, impeller discharge flow, impeller tip speed, Weber number, and Reynolds number, should be maintained constant. The most significant problem in scale up occurs when different physical processes become limiting at different

scales. Industrial scale reactors must perform several functions simultaneously (dispersion, reaction, and heat transfer) which do not scale up in the same manner.[16] The main scale up problems of organic reactions are associated with heat and mass transport, and can result in increased formation of by-products and lower yields. In the worst cases, shortcomings can lead to thermal runaway and other hazardous situations such as the release of large amounts of toxic reagents.[17] Approximately 20 to 30 runaways occur each year.[18] As a consequence, a lot of time needs to be spent to optimise the large scale production. Microreactors could lead to a solution for this problem by using the principle of numbering up (*vide infra*, § 2.4.5).

Microreactor technology is a rather new type of technology which has gained a high interest during the last 2 decennia. The first literature about chemistry related microstructures appeared in 1986 as a German patent that describes how a microreactor should be built.[19] In 1989, the Forschungszentrum Karlsruhe (Germany) already built the first micro-heat exchanger and stated its application for chemical engineering.[20] Especially since 1997, a lot of literature has appeared on microreactors as such, which is probably closely related to the first International Conference on Microreaction Technology (IMRET 1). Organic synthesis in microreactors is only a very small part of it because the technology is used in a much broader concept than organic synthesis alone. In 2001, a specific journal for microreactor and microfluidic technology, Lab on a Chip, was founded. The increasing interest in microreactor technology since the end of the '90s is illustrated in Figure 1.1.

1.2 GOAL OF THE CURRENT RESEARCH

Microreactors are especially suitable for fast reactions with a large heat effect,[21] since it is possible to maintain isothermal conditions, even at high concentrations. Several experiments were performed as a proof-of-concept for this technology. Most of these studies however were performed on easy, well known reactions.

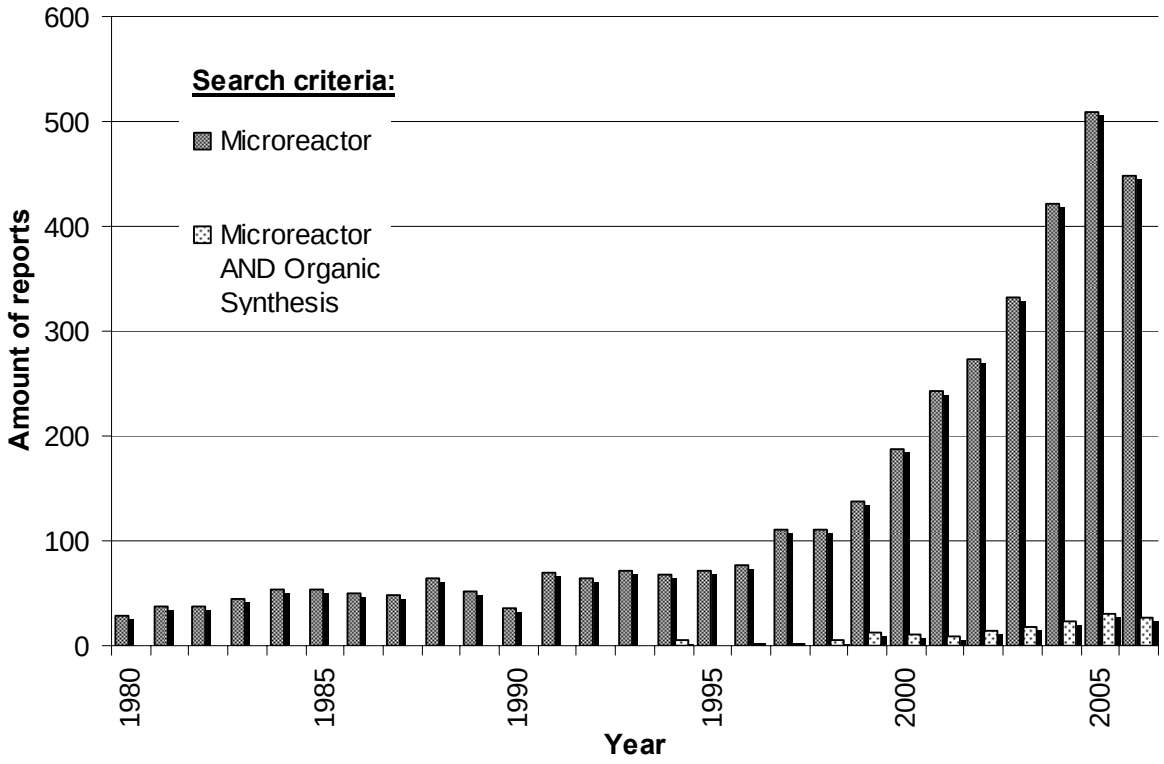


Figure 1.1: Appearance of articles about microreactor subjects (source: SciFinder Scholar 2006).

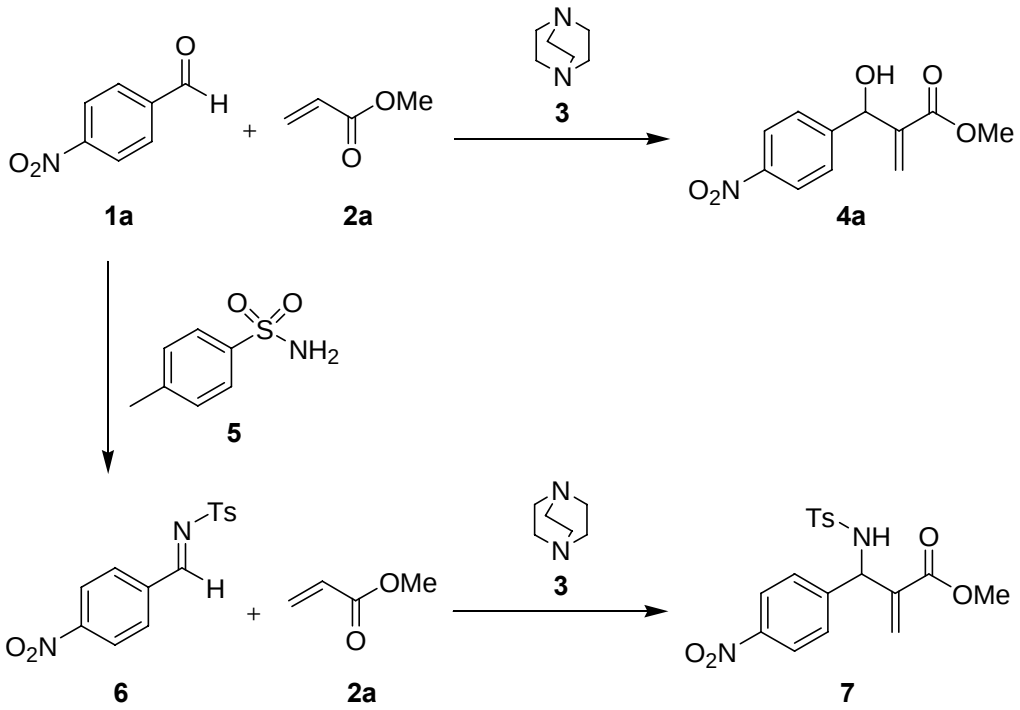
Despite the large interest in MCRs during the last decennia,[11,12,22-26] due to their potential to produce large libraries in combinatorial chemistry, no studies were performed yet on the use of microreactors for the production of compounds *via* this promising entry. Our goal will be to enlarge the scope of the technology and investigate what the possibilities are towards the use of MCRs in microreactor technology, both concepts to improve the efficiency in organic synthesis. Starting from a commercially available microreactor setup, several MCRs will be evaluated.

To test the applicability of microreactor technology for the production of chemical compounds *via* multicomponent reactions, 5 types of reactions are chosen. Firstly, the Baylis-Hillman, which is known to be a very slow reaction,[27,28] is selected, expecting that microreactor technology could cope with this disadvantage. A second reaction that will be evaluated is the production of imidazoles *via* a 4-CR. This reaction is currently optimised using microwaves.[29,30] However, because of the problems of the scalability of

microwave technology, microreactor technology might be more suitable. Since the type of microreactor used in this doctoral study is specially designed for the production of larger quantities of products, it is also interesting to test the production of chemical compounds on a larger scale. Therefore, a multicomponent reaction producing α-aminophosphonates will be thoroughly studied. A penultimate interest in this study is the ability to work with toxic products in a safe way. For this study, the multicomponent reaction to produce 3-amino-4-(arylamino)-1*H*-isochromen-1-ones is chosen as an interesting example. This last compound will be converted to 1*H*-isochromeno[3,4-*d*]imidazol-5-ones in a final study.

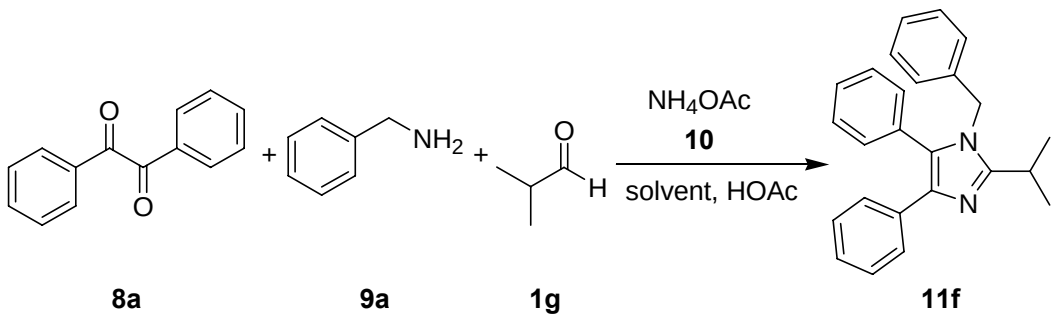
In a first research project, the applicability of microreactor technology to the interesting Baylis-Hillman reaction will be evaluated. This reaction is known to be very slow in particular cases.[27,28] To optimise the procedure, different conditions will be evaluated such as the order of mixing, the temperature, the solvent and the residence time. After evaluating the optimised reaction conditions for the Baylis-Hillman reaction between 4-nitrobenzaldehyde **1a** and methyl acrylate **2a** (Scheme 1.1), a comparison between a conventional batch setup and this microreactor setup will be given. The optimisation study will be followed by a generality test of this procedure. To allow slow reacting compounds to go to completion in the optimised procedure, a technique called stopped-flow will be tested. The aza-Baylis-Hillman reaction, which starts from the imino compound **6** instead of the aldehyde **1a**, will also be investigated (Scheme 1.1).

In a second part of the Baylis-Hillman study, a comparison will be made between 2 types of microreactors. Therefore, the commercially available CYTOS® College System, mainly used in this doctoral study, is compared with a microfluidic chip prepared by the MESA+ Institute for Nanotechnology of the University of Twente in order to evaluate differences in performance or reaction rate due to the difference in microstructure. Next to this, the influence of performing reactions in the microreactor unit with or without the use of the residence time unit (RTU) will be evaluated.



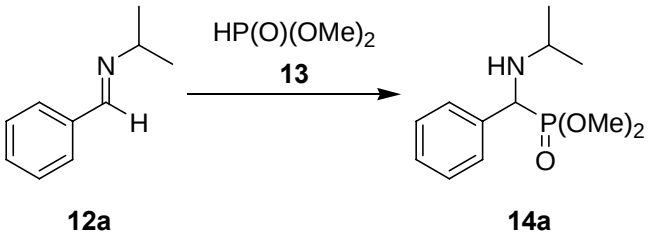
Scheme 1.1: (Aza)-Baylis-Hillman reaction.

Imidazoles are an important class of compounds, which are widely available in nature and by organic synthesis.[31] An interesting way to produce imidazoles is the four-component reaction starting from a modified Radziszewski reaction (Scheme 1.2).[32] The performance of this reaction will be evaluated using the microreactor approach. An optimisation study towards these tri- and tetrasubstituted imidazoles also includes the order of mixing, the temperature and the solvent. Furthermore, in the case of the tetrasubstituted imidazoles, efforts will be made to increase the selectivity to avoid producing the trisubstituted compounds. Finally, a small library of imidazoles will be prepared to test the generality.



Scheme 1.2: Imidazole synthesis *via* the modified Radziszewski method.

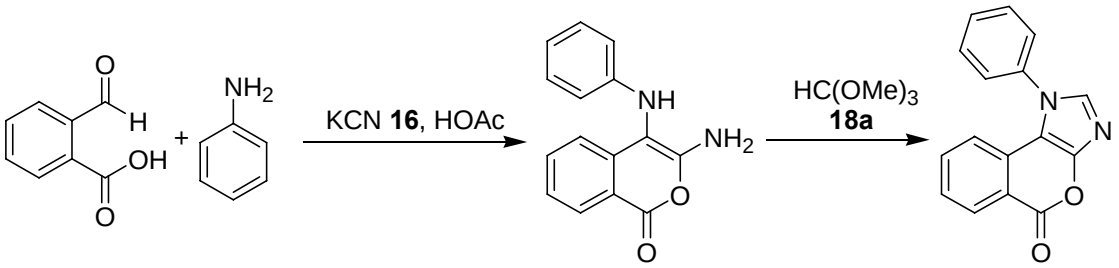
α-Aminophosphonates, with glyphosate as a well-known total herbicide,[33,34] are structures with important biological activities.[35-37] In a preliminary research performed by the Research Group SynBioC at the Department of Organic Chemistry, Faculty of Bioscience Engineering at Ghent University, a procedure was optimised to produce these compounds in a simple, high yielding way starting from a neat reaction between an imine and a dialkyl phosphite.[38] In a first stage, this two-component addition reaction of phosphite **13** to an imine **12a** (Scheme 1.3) will be evaluated and optimised to be performed under microreactor conditions. Attention will be paid to conserve high yields, but the optimisation will be performed towards high throughput synthesis. The general applicability will also be evaluated. After this approach, a shift towards the three-component reaction, starting from the aldehyde and the amine, will be studied. The selectivity towards the α-aminophosphonates **14** instead of the α-hydroxyphosphonates will be studied in detail.



Scheme 1.3: Formation of α-aminophosphonates starting from imines.

In a penultimate research topic, the production of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones **17** under microreactor conditions will be evaluated (Scheme 1.4). During this reaction, the hazardous hydrogen cyanide is produced *in situ*. An evaluation (qualitatively and quantitatively) between the batch and microreactor setup will be made to study the safety of both setups during hazardous reactions. In the batch procedure, reaction completion is induced *via* crystallisation of the end product.[39] During optimisation in the microreactor however, this crystallisation must be avoided to prevent blockage of the microchannels. Furthermore, the optimised procedure will be tested for a small library of compounds to obtain a high throughput.

Finally, in order to further explore these 3-amino-4-(arylamino)-1*H*-isochromen-1-ones, a ring closure of the vicinal amino groups will be studied to obtain a new scaffold, namely 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19**, containing an imidazole ring (Scheme 1.4). Therefore, several ring closing procedures will be evaluated and the optimum method will be transformed to a microreactor setup to produce a small library after an optimisation study.



15 **9b** **17a** **19a**

Scheme 1.4: Production of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones and subsequent ring closure to 1*H*-isochromeno[3,4-*d*]imidazol-5-ones.

Chapter 2 - Literature Overview

2.1 INTRODUCTION

This literature overview gives a general introduction about the concept 'microreactor', followed by a short overview of the different applications. Because of the wide applicability of this technology and in the context of this doctoral thesis, the review will focus on the use of microreactors in organic synthesis. Special attention will be given to the possible advantages and disadvantages of the use of microreactor technology in close relation to the applications in organic synthesis.

2.2 DEFINITION

Microreactors, as part of the wide group of microsystems, were generally defined as 'miniaturised reaction systems fabricated by using, at least partially, methods of microtechnology and precision engineering'.[40] This rather old-fashioned definition is recently revised.[41] Nowadays the broader definition also contains down-scaled designs of existing reactors and modern reactor concepts such as falling-film reactors,[42] packed-bed reactors,[43] structured catalysts e.g. foams,[44] and capillary-in-tube reactors.[45] During the last decades, a wide variety of different microreactors has been developed.[46,47]

2.3 APPLICATIONS

As mentioned in the introduction, organic synthesis in microreactors has gained attention during the last decade. Meanwhile, a lot of review articles about this issue appeared in literature.[48-55] Next to this application, a wide variety of other applications is known, most of which are situated in the field

of the analysis, especially for the development of micro total analysis systems (μ-TAS),[17,56] and the study of basic biology[57] such as the interaction between different cell types[58]. Generally, a μ-TAS includes the miniaturisation of an overall analytical process from sample preparation through reaction and separation to detection.[59]

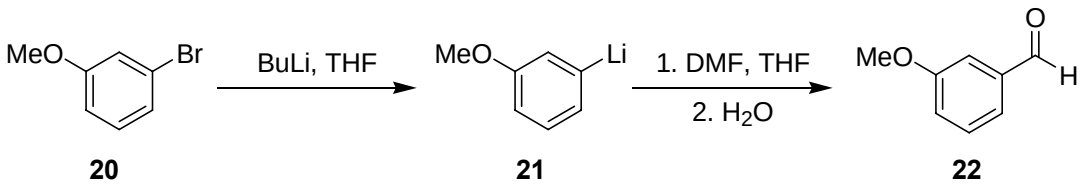
Important issues herein are the study towards DNA polymerase chain reaction (PCR) microchips[60-62] and the subsequent separation of different DNA strains[63]. Recently, researchers were able to purify DNA on-chip *via* the merging, mixing and splitting of droplets.[64] For the study of kinetic interactions between DNA and dyes, fluorescence lifetime imaging (FLIM) was tested in microfluidic systems. The authors state that this technique is applicable to resolve and quantify several multistate chemical and biological systems.[65] The development of microchips that evaluate the activity of enzymes,[66,67] or the use of enzymes, immobilised or not, for analytical methods is also well known[68,69]. Furthermore in the context of enzymatic activity, both research of protein digestion by enzymes[70] and protein synthesis by using microbial extracts[71] were successfully accomplished using microstructures. Recently, some microfluidic reactors were developed with on-chip analysis. The performance is comparable with a bench scale reaction followed by HPLC[72] or MS analysis[73,74]. Another on-chip analysis system used a microcoil NMR to evaluate the conversion towards an imine synthesis.[75]

Detection and separation of proteins was successfully performed by the production of self-assembled monolayers on a microchip. Separation of the low concentration protein in a 1:1000 mixture of 2 proteins was possible.[76] Another chip that was developed contained an integrated optical Young interferometer sensor for ultrasensitive, real-time, direct detection of viruses. The herpes simplex virus type 1 (HSV-1) was detectable in clinically relevant concentrations.[77] Various studies were able to detect and eventually quantify single[78-80] or more[81] cells by using different analysis techniques on microchips. This gave the opportunity to monitor growth curves.[78] Wang *et al.* developed a μ-TAS for metabolic analysis of a mixture of metabolites including glucose, uric acid, ascorbic acid and acetaminophen. Enzymatic oxidation of glucose was carried out in a microchannel, followed by the

separation and electrochemical detection of the end products. The chip-based protocol integrated a miniaturised bioassay, separation and amperometric detection in a single device.[82] In a second example of a μ-TAS, a Duchenne muscular dystrophy diagnosis microdevice was developed. An extraction of genomic DNA from whole blood using a novel sol-gel matrix, followed by IR-mediated PCR amplification of a β-globin fragment of the genomic DNA and electrophoretic analysis was thereby integrated on a single microdevice.[83] In the same context, Mitchell *et al.* developed a μ-SYNTAS system, which combines a chemical microreactor and a total analysis system. This microdevice was used to study a sub-reaction of the Ugi-MCR.[74]

2.4 ADVANTAGES

Generally, a lot of advantages for organic synthesis are suggested by developers and manufacturers of microreactor systems of which a better mass and heat transfer, a safer handling of reactions and a higher selectivity are the most important.[40,84-86] A wide variety of organic syntheses were already performed in microreactor systems to prove these concepts.[87-89] Some of these reactions are discussed below. From an economical point of view, studies conclude that approximately 50 % of today's chemical reactions could benefit from continuous processes which are mainly based on microreaction technology.[1] Recently, a life cycle assessment (LCA) investigated the microreactor technology potential. As a model reaction, the production of 3-anisaldehyde **22** *via* an exothermic 2-step synthesis starting from 3-bromoanisole **20** was evaluated (Scheme 2.1).



Scheme 2.1: Model reaction for the LCA.

A study was made between a conventional batch reactor and 2 CYTOS® Lab System modules in serial. Both laboratory and industrial scale productions

were evaluated. The research clearly pointed out that the application of microreactors can lead to significant reductions in the environmental impact of chemical processes. On the laboratory scale, a reduction of 20 to 60 % was observed. The main reasons for this reduction were found in the increased yield, the reduction of solvents and energy consumption savings. The use of microreactor technology on the industrial scale was advantageous due to the avoidance of a cryogenic system for temperature control, which led to reductions of approximately 20 to 30 %. In order to get long term advantages, special attention has to be paid to the longevity of the microstructured system. However, it must also be emphasised that this study was specifically for this particular reaction and conclusions could not be generalised.[90]

2.4.1 Mass transfer

In conventional chemistry, mixing is usually performed by convection because a diffusion controlled reaction would mean a very slow mixing in conventional batch reactors. The main reason being the diffusion time, that is proportional with the square of the distance:

$$t_d = \frac{d^2}{D} \tag{2.1}$$

with t_d = diffusion time (s)
d = distance of diffusion (m)
D = diffusion coefficient (m^2/s)

Indeed, a molecule with a diffusion coefficient of 10^{-9} m^2/s needs approximately 15 min to travel only a distance of 1 mm.[17,56] Therefore, turbulence is introduced in conventional batch reactors. To obtain this turbulent mixing, different techniques such as baffles and stirrers were developed. However, a problem which mostly occurs is the existence of concentration gradients in the system.

Compared with the conventional batch system, a better mass transfer is possible in microreactors. Due to the very small channels (mostly between 50 and 500 μm) in microreactors, it is not possible to obtain turbulence in microchannels and therefore a laminar flow regime is observed.[91] Because the Reynolds number is proportional to the characteristic length, a small value will be obtained for miniaturised systems, indicating laminar flow (*vide infra*, § 3.2.5).[17] So mixing of compounds will happen *via* diffusion between the parallel flowing layers.[91] This occurs very fast, because the chemicals do not need to travel a large distance due to these small channels. As an example, the same molecule needs only 10 s and 100 ms to travel 100 μm respectively 10 μm.[17,56] This gives the possibility to mix to homogeneity within milliseconds to seconds.

Although the better mass transfer is often given as a main reason for the better conversion and yields of a chemical reaction using microreactor technology, to date no real in-depth study of the influence of the mixing characteristics of microreactors on the performance of chemical reactions is performed. The literature that is found related to this topic, are experimental data concerning the mixing performance[92,93] or theoretical calculations of the mixing effect on chemical reactions[94,95].

Calculations of the mixing behaviour, together with an experimental validation, proved the statement that a size reduction of a T-shaped micromixer, leads to faster chemical reactions and a better heat transfer, as long as the geometry stays similar. Given below is the theoretical study of the mixing behaviour in a T-shaped micromixer.[96]

The transport of mass and momentum is described by the non-dimensional Navier-Stokes equations. For incompressible Newtonian fluids, with a constant density, these equations are:

$$\nabla \cdot \mathrm{u} = 0 \tag{2.2}$$

$$\frac{\partial \mathrm{u}}{\mathrm{dt}} + \mathrm{u} \cdot \nabla \mathrm{u} = -\nabla \mathrm{p}' + \frac{1}{\mathrm{Re}} \cdot \Delta \mathrm{u} \tag{2.3}$$

$$Re = \frac{U \cdot d_H}{\nu} \tag{2.4}$$

with u = non-dimensional velocity field (-)
p' = modified pressure (-)
Re = Reynolds number (-)
U = reference velocity (m/s)
d_H = hydraulic diameter (m)
ν = kinematic viscosity (m^2/s)

This means that, in the case of geometrical similarity and if the inlet and outlet conditions are scaled correspondingly, the flow behaviour is only determined by the Reynolds number. Therefore, microsystems have no advantage if the flow behaviour is considered alone, considering the mentioned assumptions. In this fluid flow, the transport of an ideally diluted non-reactive species is given by:

$$\frac{\partial c}{dt} + u \cdot \nabla c = \frac{1}{Re \cdot Sc} \Delta c \tag{2.5}$$

$$Sc = \frac{\nu}{D} \tag{2.6}$$

with c = non-dimensional concentration (-)
Sc = Schmidt number (-)
D = diffusion coefficient (m^2/s)

For reaction flows, an additional kinetic term has to be included. For a first order reaction, the transport equation becomes:

$$\frac{\partial c}{dt} + u \cdot \nabla c = \frac{1}{Re \cdot Sc} \Delta c - \frac{d_H}{l} Da_I c \tag{2.7}$$

$$Da_I = \frac{k \cdot l}{U} \tag{2.8}$$

with l = length (m)
Da_I = Damköhler(I) number (-)
k = kinetic constant (1/s)

The Reynolds number depends on the product Ud_H, while the Damköhler(I) number depends on the quotient l/U. For a fixed ratio d_H/l, both numbers cannot be kept fixed while changing the size. This means that physico-chemical and hydrodynamical similarity cannot be achieved for reactors of different size. To quantify the scale effect, a geometrical scaling factor λ is introduced, with $\lambda << 1$. By introducing $l' = \lambda l$, $d'_H = \lambda d_H$ and $U' = U/\lambda$ to obtain the same flow conditions, the dimensionless numbers for the micro- and macroscale system become:

$$\begin{aligned} Re' &= Re \\ Sc' &= Sc \\ Da'_I &= \lambda^2 Da_I \end{aligned} \qquad (2.9)$$

This means that the apparent rate constant $(d_H/\lambda)Da_I$ of the chemical reaction decreases massively if the geometric dimensions are reduced by a factor $\lambda << 1$ at fixed Re and Sc.

Because of the laminar flow regime, a lot of research is done towards the improvement of the mixing zone.[97-99] A concept that is used in several designs of microreactors to improve mixing is the multilamination structure.[100] To obtain a faster mixing, the microchannel of one input is divided in several parallel smaller channels. Each small channel is then united with the same parallel channels from the other input (Figure 2.1). This gives faster mixing compared to joining the 2 starting channels because of the smaller diffusion distances.[97] Based on computational studies, it is proven that the lamination width greatly affects the yield for the desired product.[94] Consider following reaction type:

$$A + B \rightarrow R \quad r_1 = k_1 \cdot C_A \cdot C_B$$
$$B + R \rightarrow S \quad r_2 = k_2 \cdot C_B \cdot C_R$$

with A, B = reactants
R = desired product
S = by-product
r_i = reaction rate of step i (mol/m³.s)
k_i = rate constant of step i (m³/mol.s)
C_j = molar concentration of product j (mol/m³)

Using computational flow dynamics (CFD), the relation between the mass average conversion of reactant A at the reactor exit (x_A) and the yield of the desired product R (Y_R) was calculated for different rate constants k (= k_1 = k_2) and lamination widths W. An important factor in this context was the dimensionless number Φ_i, which represents the ratio between the reaction rate and the diffusion rate.

$$\Phi_i = \frac{k_i \cdot C_{B_0}^{n-1} \cdot W^2}{D} \qquad (2.10)$$

with $C_{B_0}^{n-1}$ = initial concentration of reactant B (in this case: 27.7 kmol/m³)
n = order of the reaction
R = desired product
W = lamination width (m)
D = diffusion coefficient (~ 10^{-9} m²/s)

This number gives a criterion to determine the controlling step of reactions. The reaction is the controlling step when $\Phi_i < 1$ and the diffusion is the controlling step when $\Phi_i > 10^4$. So, at high rate constants, a smaller lamination width is necessary because otherwise the diffusion limits the reaction rate to the desired product. For a rate constant k of 0.01 m³/kmol.s, Φ_i is 2.8 when W = 100 μm and 0.17 when W = 25 μm. Calculations showed that in these cases the yield Y_R approached the yield obtained in ideally mixed situations. In the case the reaction rate k is 100 m³/kmol.s, Φ_i is 2.8 x 10^4 when W = 100 μm and 1.7 x 10^3 when W = 25 μm. In this case, diffusion becomes the limiting factor, especially at high lamination widths. This strongly affects the conversion to the desired product R, since the diffusion

length between A and B is longer than between B and R, which means the side-product S is more easily formed. Using different CFD simulations, the authors stated that the mixing conditions in the reactor can be controlled by the design.[94]

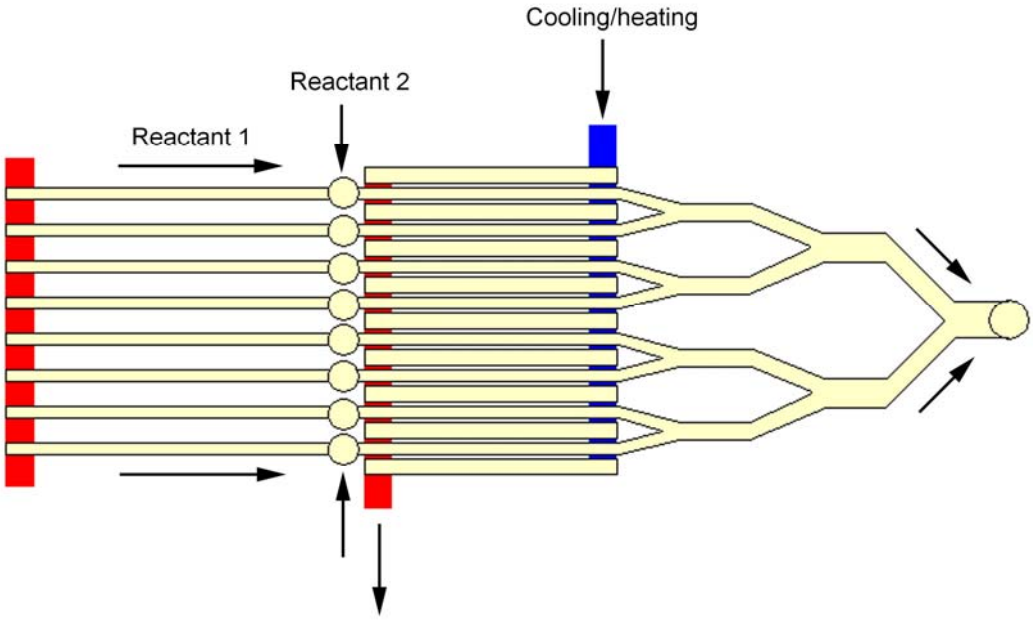


Figure 2.1: Example of multilaminar mixing.

2.4.2 Heat transfer

In addition to the better mass transfer, the heat transfer is also ameliorated due to the geometry of the devices. Small channels give higher surface-to-volume ratios. Typical values are in the range of 10,000 to 100,000 m^2/m^3.[40] These values range from 10 to 100 m^2/m^3 in conventional batch reactors. So, heat or cold is transferred faster through the microreactor walls. A similar approach as for the mass transfer calculations shows that better thermal control is achieved in microsystems.[96] A combination of the previously mentioned fast mixing and the fast heat transfer, avoids the formation of hot spots.

As an example, Swern oxidations with a high selectivity were possible at room temperature in a sequential micromixer device, while in batch reactions the temperature had to be kept below -50 °C to avoid side-product formation. This meant a lower energy expenditure together with a higher yield.[101]

2.4.3 Safety

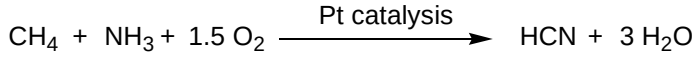
Another advantage of microreactors is the safety. Due to the small inner volume (typically less than 5 mL), dangerous reactions, such as Grignard reactions,[102] methyl carbamate formations[102] and nitrations,[103,104] are better controlled. All reaction products are continuously present in low amounts. Moreover, in contrast with the batch reactions, only small amounts of the end product are released at the end of the process.

A risk in conventional reactors is thermal runaway, a process by which an exothermic reaction goes out of control, often resulting in an explosion. This is mostly caused by failure of the reactor vessel's cooling system. Failure of the mixer can result in localised heating, which initiates thermal runaway. Exothermic side reactions and combustion begins at higher temperatures, accelerating this process. It has contributed to industrial chemical accidents, most notably the 1984 explosion of a Union Carbide plant that produced methyl isocyanate in Bhopal, India. This accident resulted in the direct death of 3,000 people, while another 15,000 died because of related illnesses. A second example is the catastrophe in Seveso, Italy in 1976. The clogging of one of the reactors, which produced 2,4,5-trichlorophenol (a herbicide), caused thermal runaway. Thereby, a large amount of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was exposed to the environment and tens of thousands of farm animals and pets died. This gave rise to numerous scientific studies and standardised industrial safety regulations, known as the Seveso II Directive.

Due to the high level of control in microreactors, it is easier to avoid the occurrence of thermal runaway. One example of a dangerous reaction that is performed safely in a microreactor unit is the formation of the highly reactive

diazomethane. This compound is very interesting for incorporation of a one-carbon unit in a molecule. However, a major problem is the explosive character of diazomethane. A lot of care has to be taken during the production in the laboratory and contact of diazomethane with sharp parts of laboratory glassware has to be prevented. Using a microreactor setup, Ferstl *et al.* were able to produce diazomethane in high concentrations within seconds with a conversion of 82 ± 2 %. There was no need for special safety precautions.[105]

An interesting way to incorporate cyanides in chemical molecules or to produce cyanohydrins is by in situ production of hydrogen cyanide. Because of the high toxicity of this gas (acute lethal oral dose: 50-90 mg), the use in large scale production is avoided as much as possible. Nevertheless, due to the interesting applications in organic synthesis, HCN gas is industrially produced *via* the Andrussov process in which methane and ammonia react in the presence of oxygen (Scheme 2.2). In the past, specialised microreactor systems were already assembled to synthesise HCN *via* this highly exothermic process. Therefore, some modifications of the original process were necessary: the distance between the hot reaction zone and the cold heat exchanger were minimised and the catalyst structure was modified. Comparison with the industrial process showed a lower, but safer, conversion in the microreactor: 60 % *versus* 31 % respectively.[40]

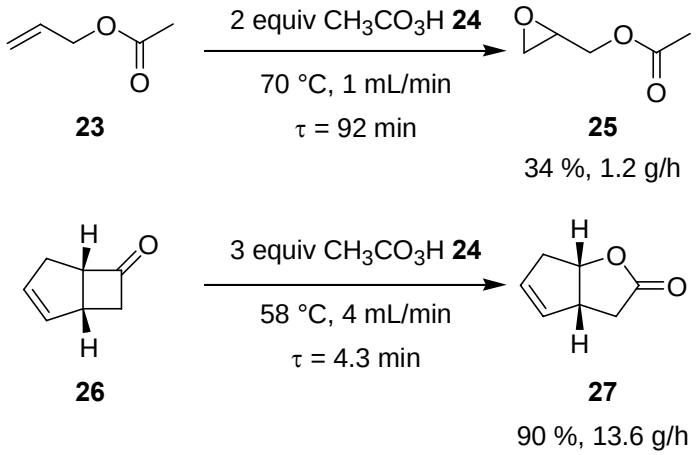


Scheme 2.2: The industrial Andrussov process.

Several epoxidations and the Baeyer-Villiger lactonisation were successfully performed in a similar microreactor (CYTOS® Lab System) as the one used in this doctoral research. For these reactions the dangerous peracetic acid **24** was used as one of the reagents. It is known that batch reactions mostly need long reaction times, because peracetic acid is explosive at reaction temperatures exceeding 60 °C.[1] Moreover, because of the formation of acetic acid a lot of

[1] due to an explosion point of 110 °C, this temperature buffer is applied in many chemical companies, especially with exothermic reactions.

degradation reactions can occur, which decreases the final yield. Therefore, in labscale synthesis the safer and cleaner m-chloroperbenzoic acid is mostly used. In the microreactor procedure however, it was even possible to perform the epoxidation of allyl acetate **23**, which is known for its low reactivity towards epoxidation, at temperatures up to 90 °C, in reasonable yields and without safety risks. The lactonisation of bicyclo[3.2.0]hept-2-en-6-one **26** could be performed at elevated temperatures to reduce the reaction time from several hours in batch to approximately 4 min in the microreactor (Scheme 2.3).[106]



Scheme 2.3: Safe epoxidation and Baeyer-Villiger oxidation with peracetic acid using a microreactor.

2.4.4 Selectivity

Another important advantage linked to microsystems is the improved selectivity of chemical reactions.[104,107] This is strongly related to the aforementioned advantages, especially the better heat transfer. An explanation of this improved selectivity is given in Figure 2.2. Consider a product A which can form 2 different products, B and C. Assume that the activation energy to form product B is much smaller than to form the undesired side-product C. Then, the smaller temperature range obtained in the microreactor system -due to a better heat control in the small channels- provides that the activation energy to form product C is never reached. To the contrary, a wider

temperature range is obtained in a batch reactor due to less sufficient mixing. This can give rise to the formation of product C.[92]

An interesting example herein is the selective monoiodination of aromatics. First the iodine was converted to the active species *via* electrochemical oxidation. This active I^+ compound **29** was then mixed in a micromixer with different aromatic compounds, such as 1,3-dimethoxybenzene **30**, to obtain a mixture of monoiodinated an diiodinated aromatics (Scheme 2.4). Comparison with batch reactions showed a higher selectivity in all the iodinations performed in the microsystem.

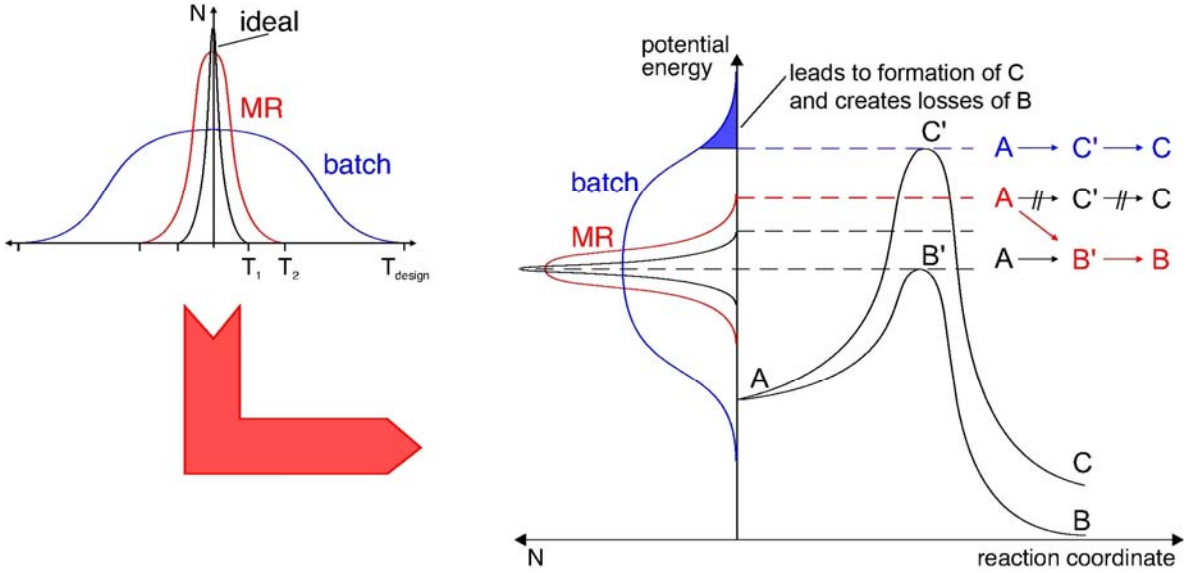
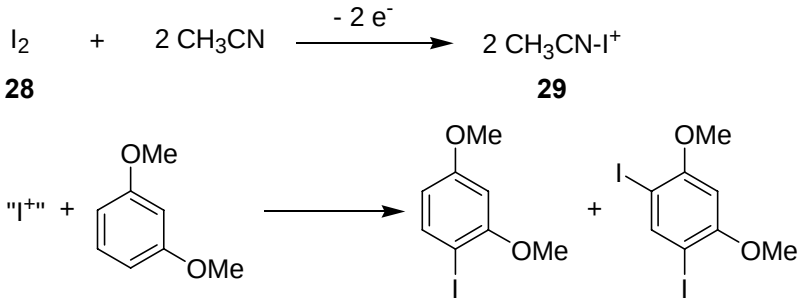


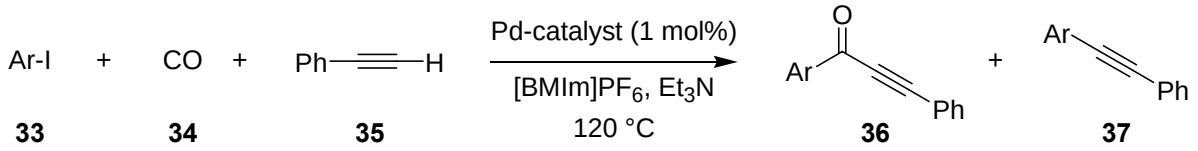
Figure 2.2: Correlation between temperature range and selectivity in organic synthesis, using conventional or microreactor synthesis.

An important effect that was observed was the dependence of the selectivity on the flow rate. The higher the flow rate, the better the selectivity. This was related to the better mixing performance of this type of micromixer at larger volume flow rates.[108] CFD simulations also showed the importance in mixing efficiency to obtain a high mono/dialkylation selectivity in the Friedel-Crafts aminoalkylation of (hetero)aromatics.[109] A larger flow rate seemed also to have an influence on the conversion rate, as proved in the Claisen-Schmidt reaction.[110]

The improved selectivity in the microsystems was also proven in the Pd-catalysed carbonylative Sonogashira coupling of aryl iodides **33** and phenylacetylene **35** (Scheme 2.5). While in the batch reaction a mixture of the acetylenic ketone **36** and the expected by-product **37** occurred, the reaction under microreactor conditions provided solely the ketone **36**, even at reduced CO pressure. In addition, the yield was also markedly improved. This increase in selectivity was attributed to the occurrence of a plug flow in the microreactor system. The substrate dissolved in the ionic liquid phase and diffusion of CO in the ionic liquid plug was facilitated due to the large specific interfacial area. Such a high specific interfacial area-to-volume ratio, which is necessary for the efficient CO diffusion, does not occur in a batch reactor because of the inefficiency of mechanical stirring.[111]



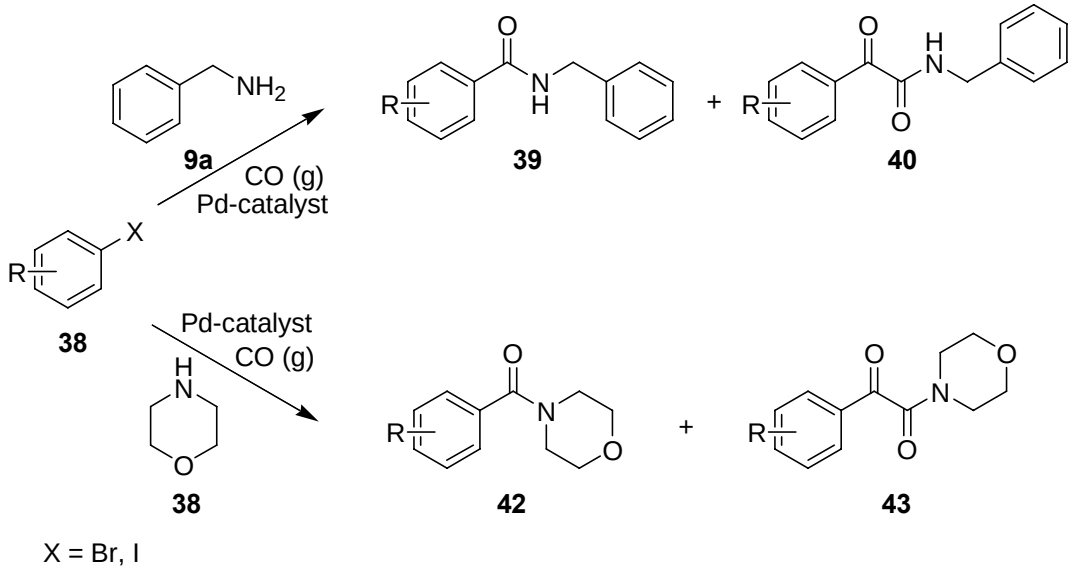
Scheme 2.4: Selective monoiodination of aromatics using an IMM (Institut für Mikrotechnik Mainz) single mixer.



Scheme 2.5: Pd-catalysed carbonylative Sonogashira coupling.

The selectivity issue of microreactor technology was also clearly demonstrated by some aminocarbonylation reactions (Scheme 2.6).[112-115] In most batch procedures, no or minimal formation of the α-ketoamides **40** and **43** is observed, because the reaction is mostly performed at near atmospheric pressure.[112] Using microreactor systems, higher yields of the amides **39** and

42 were obtained and also significant amounts of the side-products were formed.[113] By adjusting the process parameters, it was possible to increase the selectivity towards one of the end products. An increased temperature selected for the amide, while increasing the CO pressure yielded more α-ketoamide.[112] Using the optimised procedure for amide **39**, radiolabeling experiments with ^{11}CO were successful and thus microfluidics offers an entry to positron emission tomography.[114,115]



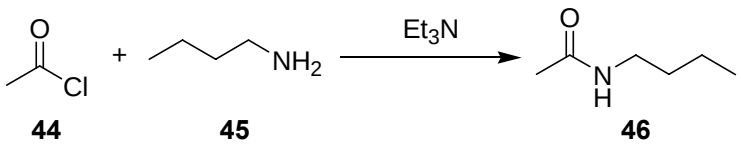
Scheme 2.6: Aminocarbonylation of halogenated aromatics.

Using a multichannel continuous flow modular microreactor, it was possible to fluorinate 1,4- and highly deactivated 1,3-disubstituted aromatics. Although the conversions were quite low in the latter case, the reaction proved to be highly selective towards the monofluorinated compound. Using a recycling system, in which the crude reaction mixture was passed several times through the microreactor device, higher conversions were obtained without loss of selectivity.[116]

2.4.5 Scaling up of chemical reactions

The major advantage for this kind of technology is the scalability. If a conventional labscale process has to be scaled up, the normal method is to work in several steps. First the process is scaled up to the litre or several litres

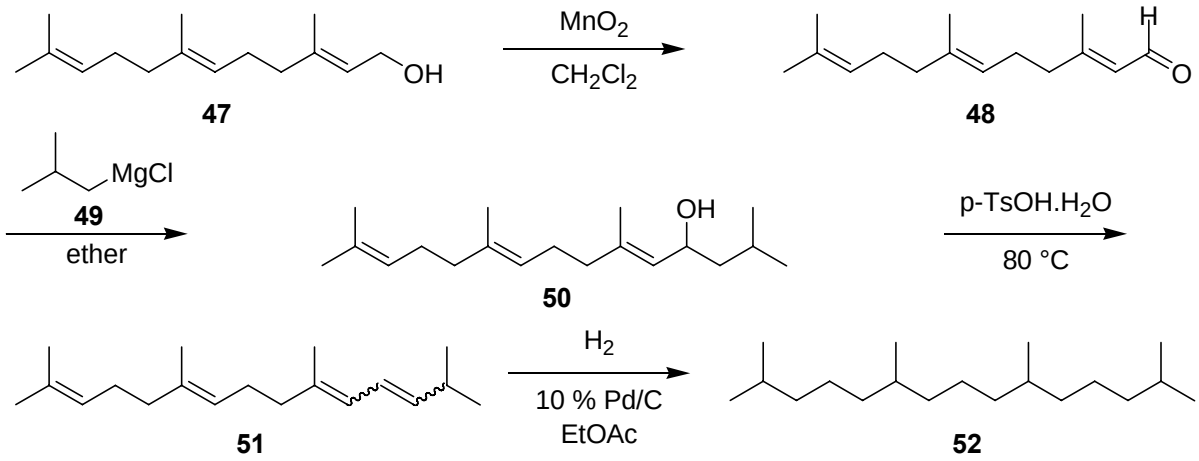
scale. The next step is the pilot plant and finally the process is scaled up to production scale. Every step needs careful control of different process parameters like temperature, pressure, rate of addition of reagents and removal of products in order to keep the process under control. Especially for exothermic and endothermic reactions or reactions using toxic reagents, the differences between labscale and production scale parameters can be extreme. Scale up is therefore a time-consuming and expensive process in industry. By contrast, once a process is optimised under microreactor conditions, there is no need anymore to scale up the reactor. Instead of scaling up a microreactor, numbering up is the expression that is used in this technology. This principle means that several microreactors are placed in parallel to produce higher quantities. Using this method, no modifications of the labscale conditions are necessary anymore. This means that a lot of time and money can be gained during process development and to further improve a process.[117] As a proof-of-concept, Schenk *et al.* developed a liquid-flow splitting unit, that was connected to 6 parallel micromixers. To test the performance of this device, a fast organic reaction between acetyl chloride **44** and *n*-butylamine **45**, with formation of the corresponding amide **46** was evaluated (Scheme 2.7). The yield in a single micromixer device varied between 87 and 100 %. Using the parallel micromixers, an overall yield of 88 % was achieved, with a standard deviation of 16 % between the parallel micromixers. The relative high standard deviation had two main reasons. Firstly, in one of micromixers clogging occurred, which gave a lower product outcome. Excluding this device gave a standard deviation of 8 %. Secondly, salt formation occurs during the reaction, which resulted in higher variations in the flow distributions between the micromixers.[118] Another concept that is recently introduced in microreactor technology, next to the numbering up, is equalling up.[119] The concept is more or less the same, but instead of having several microreactors in parallel, there is one reactor in which several microreactors are built in. In fact, this is a kind of internal numbering up.



44 **45** **46**

Scheme 2.7: Synthesis of *n*-butyl acetamide **46**.

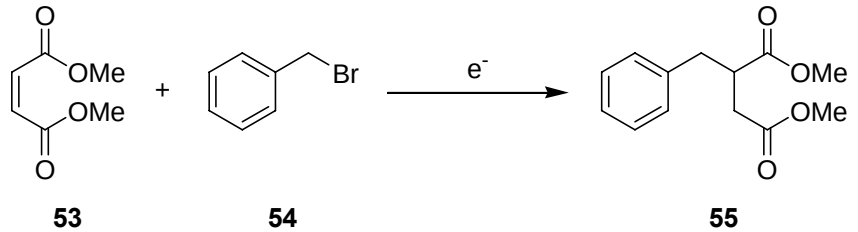
Although this advantage is mentioned in several scientific papers, only few researches have applied this in practice. One of them is the large scale synthesis of pristane **46**, an important adjuvant for monoclonal antibody production. The overall synthesis is given in Scheme 2.8.



Scheme 2.8: Synthesis of pristane **52**.

The batch synthesis of the key step, which is the dehydratation of the allylic alcohol **50**, yielded 55 % on a 100 mg scale and less than 20 % (due to inseparable by-products) on a 100 g scale. Optimisation of this step using a micromixer gave an overall yield starting from farnisol **47** to pristane **52** of 80 %. For the large scale production, a Comet X-01 microreactor, containing 10 micromixers in parallel, was used for producing 8 kg dehydration product within 3 to 4 days. An overall yield of 50-55 % of **52** was obtained with > 99 % purity.[120]

The easy scale up procedure was also proven in the cathodic coupling of activated olefins with benzyl bromide to produce for example dimethyl 2-benzylsuccinate **55** in a micro flow reactor (Scheme 2.9). Two microreactors in parallel gave twice the output of a single reactor.[121]



Scheme 2.9: Synthesis of dimethyl 2-benzylsuccinate **55**.

2.5 DRAWBACKS

The introduction of a new technology not only brings several advantages, but also involves some disadvantages. These slow down the introduction of industrial applications. During the last decennium different research groups have tried to overcome several of these issues.

2.5.1 Clogging of the system

The small dimensions of the microdevices make them prone to clogging. Especially when highly viscous products or crystalline compounds are formed, high risks of clogging of the system occurs. This necessitates a regular flushing of the system to avoid pressure from building up, which is a major drawback in continuous processing. Another important problem that can occur during the processes is the limitation of start product concentration (in the case of solids), the formation of precipitates, crystallisation or polymerisation in the system.

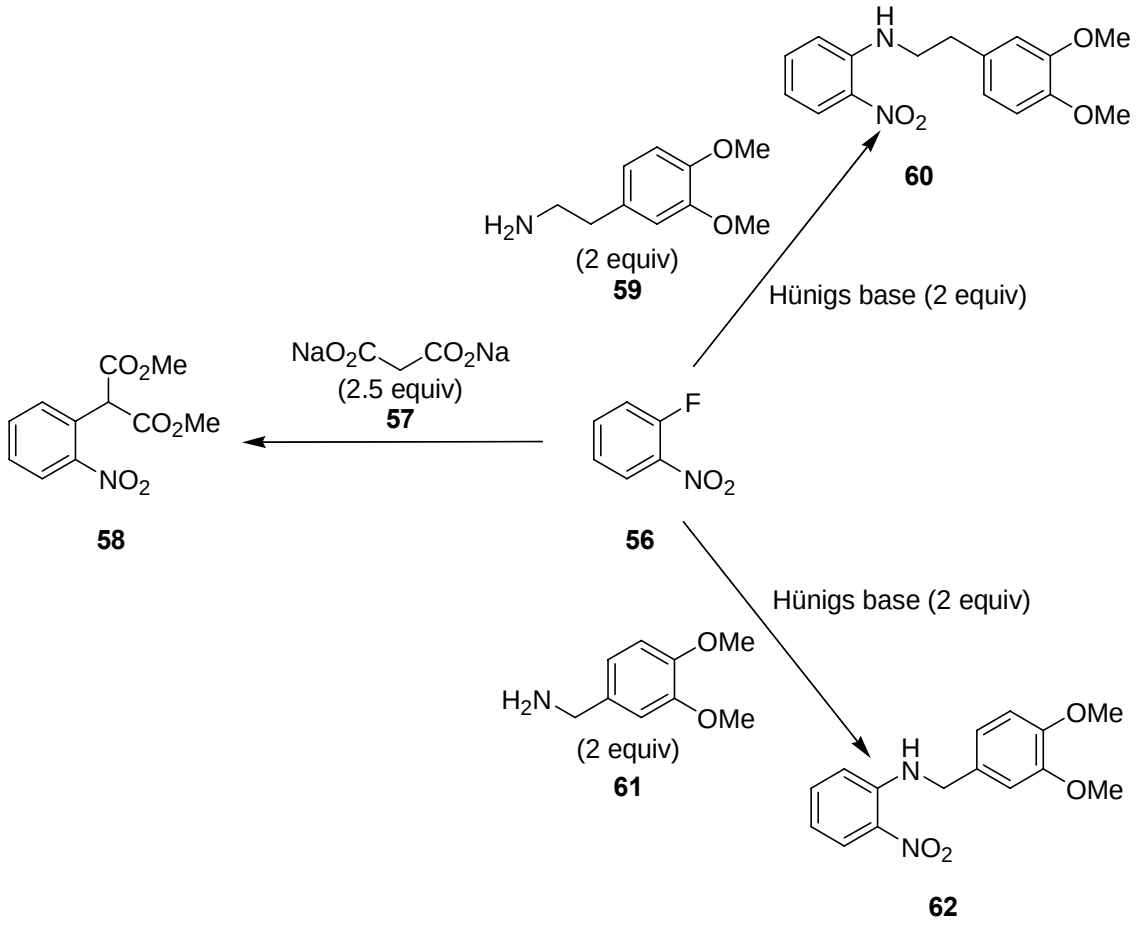
During the last years, some research has been done to work with solid particles or high viscous compounds, despite the risk of clogging the microsystem. For example, Ismagilov and coworkers did some fundamental research about the crystallisation of proteins in microchannels. They developed a setup to avoid crystallisation by using a two phase system to give the crystals no opportunity to adsorb to the surface.[122,123] Moreover, they were able to crystallise the proteins inside the microchannels in a controlled way to obtain X-ray pure crystals.[124-126] Another microreactor design to perform reactions in droplets was based on a tube reactor in which carrier fluid was pumped. The tube was pierced with syringes containing the disperse phase. It was possible to create bubbles containing solid reaction products, such as indigo, N,N'-dicyclohexylethylenediimine and 4-chloro-N-methylbenzamide, in the microtubular reactor.[127] Performing reactions in droplets is also an efficient way to screen for optimised reaction parameters, since many droplets per time unit can be created. Some possible methods for

fast screening are the use of cartridges and the variation of the reagent concentration. The cartridge technique can be used for screening a large number of reaction conditions against one target sample. Therefore, an array of plugs, which contain different reagents or reaction conditions, is stored in a preformed cartridge. The target sample is than introduced in the plugs by a T-junction microchannel. In the other method, the variation of reagent concentrations is accomplished by varying the relative flow rates of the different reagents.[128]

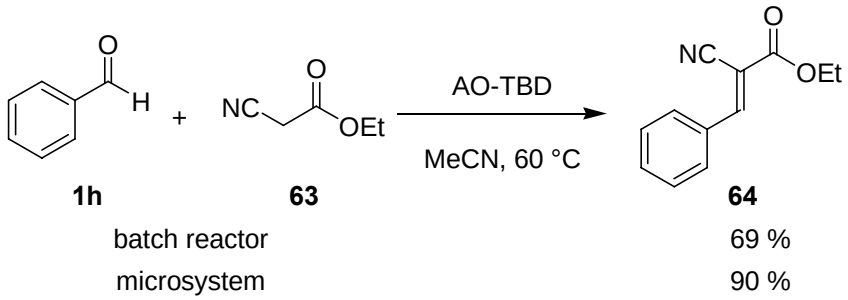
By combination of a micromixer and a microwave irradiated capillary tube, several nucleophilic aromatic substitutions (Scheme 2.10) were performed successfully without clogging, although crystallisation was detected. The substitution of the fluorine of 1-fluoro-2-nitrobenzene **56** to products **58**, **60** and **62** gave 72, 66-100 and 68-80 % conversion respectively.[129,130] In some previous work, this was already done using a continuous flow system under microwave conditions. Clogging of the system occurred after a while, although no microcapillar was involved in this case.[131] The reason of the success in the first case was assigned to the reactor design which was a short and straight tube instead of a spiral one. Further optimisation provided a multireactor assembly with a continuous flow, sequential, parallel synthesis.[129] Recently, the researchers also performed some MCRs in this microwave-assisted microreactor.[132] In an attempt to use a combination of micromixers and tubular reactors for the industrial phenyl boronic acid process, also some fouling occurred in the system. By tuning the internal dimensions, it was possible to avoid this clogging phenomenon in the system.[133]

Although the clogging is a hot issue in the microreactor technology, also experiments are performed in which the (solid-supported) catalyst is incorporated into the microchannels as a packed-bed. Care has to be taken that in this case, the resin or silica package does not swell in the system because this would create pressure and consequently won't give a reproducible output. Successful results were obtained in the Knoevenagel condensation using 1,5,7-triazabicyclo[4.4.0]undec-3-ene (TBD) on a methacrylate-based Amberzyme Oxirane resin (AO). By using the packed-bed

microreactor setup, an increase in conversion from 69 to 90 % was achieved without loss of catalyst activity after 30 trials (Scheme 2.11). Moreover, there was, in contrast to the batch procedure, no need for catalyst recovery from the reaction mixture.[43]



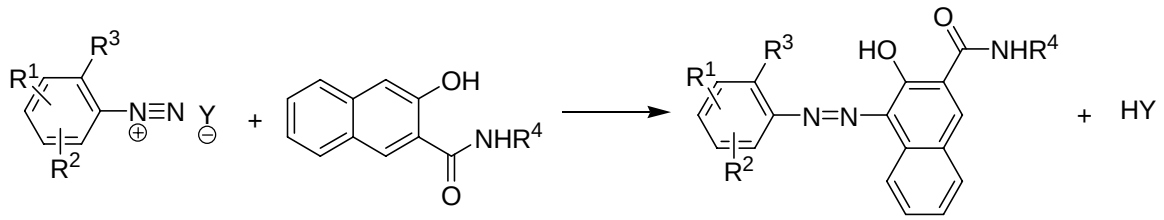
Scheme 2.10: Examples of nucleophilic aromatic substitutions performed in a microreactor-microwave system with formation of crystalline end products.



Scheme 2.11: Knoevenagel condensation.

2.5.2 Particles

Although it is generally accepted that the formation of particles in microreactor equipment is not possible, some examples of particle handling in microreactors were already reported.
The coupling step for the production of azo-pigments is already performed in a CYTOS® type microreactor. Firstly, the diazotation takes place in a batch-wise manner. The next step, the exothermic electrophilic substitution of the diazonium compound **65** with a coupling compound **66**, was performed in a microreactor (Scheme 2.12). Final pigmenting also took place in a batch reactor. The diazonium salt was used in a suspension and resulted in a better particle formation, i.e. smaller particles with a smaller particle distribution. The process was scaled up to a pilot plant without any problems.[134,135] Only a regular cleaning was necessary to avoid pressure loss due to fouling or coating of the system.[136]



65 **66** **67** **68**

R^1 = H, Cl, NO_2, (Ph)carbamoyl, (Ph)sulfamoyl, (di)alkylsulfamoyl
R^2 = H, Cl
R^3 = H, Cl, NO_2, C1-C4 alkyl, alkoxy or alkoxycarbonyl
R^4 = H, Cl, NO_2, Ph, naphthyl, benzimidazonolyl, C1-C4 alkyl or alkoxysubstituted Ph
Y = Cl^-, HSO_4^-

Scheme 2.12: Example of a coupling step in the formation of pigments.[135]

Others use microfluidics to study the effect of mixing on the nucleation of protein crystals. A plug-based flow initiates the formation and transportation of crystals without clogging of the system.[137] As an example, diffraction-quality proteins of oligoendopeptidase F from *Bacillus stearothermophilus* and the N-terminal domain of the SARS nucleocapsid (the "SARS protein") were obtained in this manner.[126] The concept of using plugs for the transportation

of particles in microstructured reactors was also applied to form CdS and CdS/CdSe nanoparticles.[123]

2.5.3 Polymerisations

Although polymerisation of reagents was already stated as a major drawback because of the possibility of clogging the microreactor channels, several examples were published which show that polymerisation in microchannels might occur under special conditions.[138]

One research group studied the formation of polymeric microdroplet capsules. An oily phase containing sebacoyl and trimesoyl chloride, is injected *via* a needle in a PVC tubing containing a continuously flowing aqueous phase in which polyethyleneimine is present. As a result oil-filled capsules are formed, surrounded by a polyamide shell due to interfacial polymerisation.[139]

Another research group developed a polyurethane microfluidic reactor with a microfluidic flow-focusing device (MFFD).[140] This system was used to produce droplets surrounded by a polymer shell. A conventional MFFD starts with three parallel channels. The central channel contains a fluid (e.g. oil phase) that is immiscible with the fluid in the outer channels (e.g. water phase). The three flows come together in a small orifice after which the channel broadens again. Due to shear effects, small droplets of the inner phase are sheared off by the two outer flows. This type of microdroplet formation system is used in different setups.[80,141-143]
First, a ternary phase diagram was developed, because of the different outcome of the droplet size and core-shell in relation to the flow rates of monomer, water and oil phase. By tuning one flow rate (while the other 2 were constant), a precise control of droplet size, core diameter and shell thickness was possible, which is an example of the previous mentioned reaction optimisation by the adjustment of the reagent concentrations (§ 2.5.1). At certain flow rates of the 3 fluids, it was even possible to produce core-shell droplets with more cores inside. Using this technology, polymeric microbeads with a variety of shapes were produced without clogging the

system. The polymerisation itself was an *in situ* photopolymerisation of the monomer ethylene glycol dimethacrylate (EGDMA) or tripropylene glycol diacrylate (TPGDA) in the core-shell droplets.[144]

Previous examples of polymerisation were all based on the formation of beads or droplets in a microreactor system. Next to these droplet based results, also solution based polymerisations are evaluated using microreactor technology.

For the industrial radical acrylate polymerisation, a tube reactor in combination with static mixers was used. The mixers were used to form a homogeneous solution of initiator and monomer directly after mixing. However, due to imperfect mixing of this premixer, precipitation of the polymers and subsequent fouling occurred. Gel permeation chromatography (GPC) analysis showed that a high molecular weight fraction of polymers (range 10^5-10^6 g/mol) was formed, leading to this precipitation. As a solution, the tubular reactor was preceded by 32 interdigital micromixers. Interdigital micromixers are mixers that make parallel lamination. First many parallel flows are generated and then all these flows are set side by side ('interdigital'). In one step the final lamellae width is reached and then diffusion is the only mixing mechanism. Using this setup, a better mixing of initiator and monomer was achieved, so that no high molecular weight fraction was formed anymore. *Via* this optimised process, an output of 2000 ton per year was achieved.[40] It must be emphasised that in this case no actual polymerisation occurs in the microreactors, but they serve as premixing controlling units for better polymerisation afterwards. In the following examples the polymerisation actually occurs in the microreactors.

The batch cationic homopolymerisation of vinyl ethers was compared with the polymerisation in a T-shaped micromixer in combination with a microtube reactor. In the batch reaction, the polymerisation was difficult to control. Even at -25 °C, the reaction occurred too fast with molecular weight distributions of 2.73-4.71. When applying the microsystem, living polymers were obtained with a high level of molecular weight control. A polydispersity

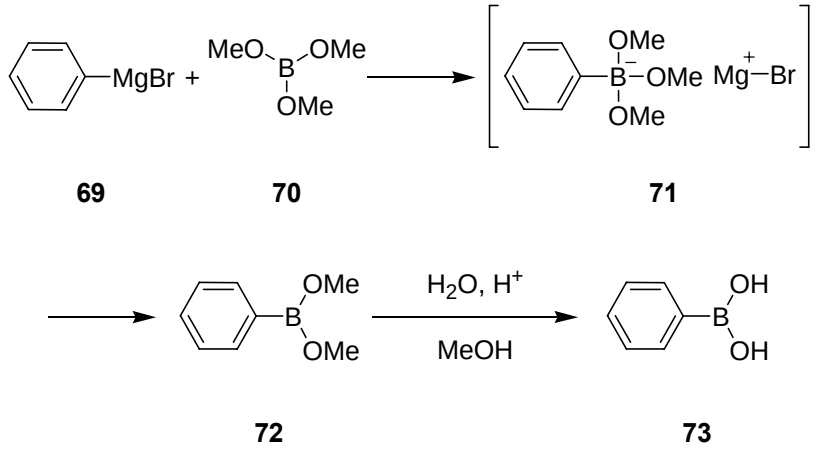
index (PDI) of 1.19-2.34 was obtained, depending on the residence time and thus the flow rate. Subsequently, a second serial microsystem was built to provide block copolymers of vinyl ethers. Also here, narrow polydispersity ranges were obtained (1.41-1.55). Importantly, no clogging was observed during the experiments because the produced polymers serve as lubricating oils and conditions were tuned for low molecular weights.[145,146]

Serra *et al.* studied both the free radical polymerisation of styrene and *n*-butylacrylate. By using the less reactive monomer (styrene), comparable PDIs were obtained with the batch reaction when low molecular weights were desired. For high molecular weights targeted, the microsystem proved to be superior. In the case of highly reactive monomers (*n*-butylacrylate), controlled polymerisations were only possible in the microreactor, with a PDI lower than 1.5.[147] Similar results were obtained in another study with substrate dependent effects on the PDI.[148]
The copolymerisation was tested *via* a continuous two-stage process. In the copolymerisation procedures, two types of micromixers were compared for mixing the second monomer with the first homopolymer block. The interdigital multilamination micromixer allowed higher incorporations of the second monomer and also a lower overall PDI was obtained, compared to a T-junction micromixer (bilamination). To move the polymers through the microreactor system, very harsh conditions were necessary. The viscous solutions were pumped *via* HPLC pumps with use of pressure relief valves (PRVs) controlled at 50 bar.[147]

2.5.4 Bulk production

Due to the very small dimensions, microreactors are not suitable for use in the bulk industry since it would take too many devices to produce an annual amount comparable to conventional systems. Besides, these conventional systems are mostly sufficiently optimised. Important intermediates, such as products in the pharmaceutical industry, are more economical producible under microreactor conditions. Given below are some examples of semi bulk productions.

A comparative study on the production of phenyl boronic acid **73** was performed (Scheme 2.13). Phenyl boronic acid is a start product of the intensively studied Suzuki(-Miyauri) coupling reaction in microreactor technology.[129,149-152] A pilot scale microreactor produced the end product in 89 % yield, exceeding the industrial continuous stirred tank reactor (CSTR) process with 25 %. Another advantage was the lower energy expenditure. The success of the study was dependent on the microreactor type.[133]



69 **70** **71** **72** **73**

Scheme 2.13: Production of phenyl boronic acid **73**.

Xi'an Huian Chemical Industrial Group in China was able to build a microreactor plant to produce nitroglycerine to use as a treatment for heart disease.[153] The microstructured reactor consists of three main parts: the part where mixing of highly concentrated sulphuric acid and nitric acid occurs, the reactor itself where the mixing of the acid and the glycerine occurs and finally the phase separation, washing and purification device. An output of 15 kg/h of highly pure nitroglycerine was achieved.[154] Recently, a Starlam 3000 microreactor, fabricated by the IMM (Germany), was incorporated as the first step of a (not specified) 2-step batch process in an existing plant with the aim to double the production capacity. An improvement in production rate from 1.8 ton/h to 3.6 ton/h was achieved. Moreover, additional energy savings were obtained because no cooling of the first step was necessary anymore.[155]

2.5.5 Material of construction

An important issue in the construction of microreactor devices for organic synthesis purposes is the choice of the material. Nowadays, microreactors are fabricated from a wide variety of materials of which the most important are silicon (e.g. polydimethylsiloxane or PDMS), glass, quartz, metals (e.g. stainless steel) and polymers.[87] However, once the material is chosen, it can limit the applications. In stainless steel microreactors, for example, it is not possible to work with hydrochloric acid or any other compound containing bromine, chlorine or fluorine ions because of corrosion risks. Using PDMS on the other hand, limits the solvent use because PDMS swells in most organic solvents.[156]

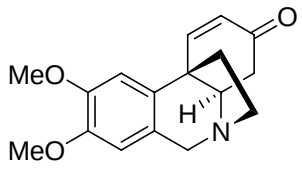
2.5.6 Pumping mechanism

Also the transportation method of the products and solvents in the microreactor is an important factor, because once a mechanism is chosen, this limits the possible applications. Two important types are known: electro-osmotic flow (EOF) and hydrodynamic (or pressure-driven) pumping. The main disadvantage in the case of EOF is the need for a polar solvent such as water, methanol or acetonitrile and EOF is restricted to microreactors constructed from silicon, glass and treated PDMS. An important advantage in this system is the nearly equal velocity across the channels, which means low dispersions and thus very strict residence times. Hydrodynamic pumping on the other hand has the advantage that it can be used in almost every device and with almost every solvent. The main drawback is the parabolic flow profile inside the channels. This leads to dispersion in the flow rate direction and subsequent distribution in residence times, which can decrease yield and selectivities. Moreover, these pumps apply a pulsed flow, which can be disadvantageous at low flow rates.[48]

2.5.7 Solvent changes

In multistep organic synthesis, one of the bottlenecks that frequently occurs is that different reaction steps in a synthesis require different solvents. This means that between the two steps, a solvent switch is needed. Between different batch production steps, this is more easily incorporated as an intermediate purification step. With a continuous procedure, such as in microreactor technology, this solvent switch is much harder to realise. Therefore, this is an important drawback for the application of multistep syntheses in a continuous microreactor mode.[153] One of the procedures developed in this doctoral thesis suffered from this drawback (*vide infra*, § 3.6.3).

An illustrative example of this solvent related drawback is the multi-step synthesis of the alkaloid natural product oxomariditine **74** (Figure 2.3) *via* flow synthesis.[157] The whole synthesis was continuous, except for one step in which a solvent switch from THF to dichloromethane was necessary. The advantage of this batch step was a preconcentration of the intermediate. Starting from the commercially available products 4-(2-bromoethyl)phenol and 3,4-dimethoxybenzyl alcohol, the oxomariditine **74** was formed in 7 steps with an overall yield of 40 %. During the whole synthesis, 2 types of microreactors were used: a Syrris AFRICA® system and a microfluidic chip.



74

Figure 2.3: The natural product (±)-oxomaritidine **74**.

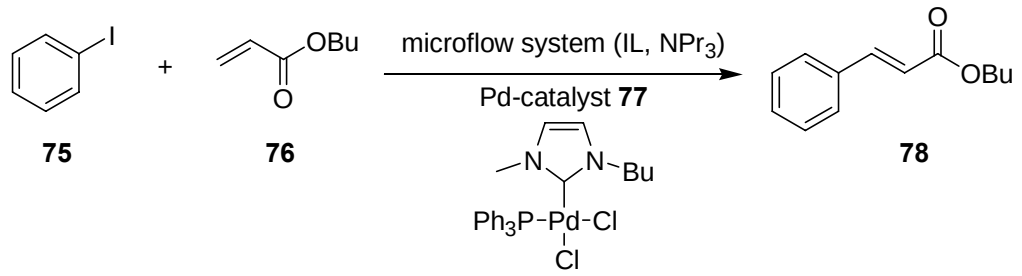
If no solvent switch is necessary, microreactor technology is well suited for continuous multistep synthesis. This is shown by enolate formation and subsequent 1,4-addition to α,β-unsaturated carbonyl compounds. In all the investigated examples, higher conversions than the batch procedure were obtained, although sometimes a stopped-flow technique was necessary (*vide*

infra, § 3.2.4). However, even in this latter procedure, the reaction time was considerably shorter (20 min) compared to the batch process (24 h).[158]

2.5.8 Work up

A major drawback mostly found in literature is the lack of an efficient work up procedure, compatible with the continuous process. In many cases, the advantage created by using a microreactor is lost, due to the need of a batchwise reaction work up.

One of the exceptions is the formation of butyl cinnamate **78** described by Liu and coworkers (Scheme 2.14). They were able to combine a CYTOS® Lab System with a continuous microextraction and catalyst recycling system, using a low-viscosity ionic liquid. To achieve this continuous work up, the ammonium salt and the end product were extracted *via* T-shaped micromixers. The CYTOS® Lab System ionic liquid outlet mixture was mixed in a first micromixer with a 0.5 M aqueous NaOH solution to remove the ammonium salt. The residual mixture was then introduced in a second micromixer where hexane was used to extract the product. As a result, the final outcome separated in three phases: a hexane layer containing tripropylamine and the end product, an aqueous layer containing the inorganic salt and the ionic liquid layer containing the Pd catalyst. This last layer was pumped back to one of the microreactor inlets to maintain continuous recycling, while the end product was continuously extracted. It was possible to produce 10 g/h of the end product in 80 % yield.[159] In case the design consists of reaction bubbles, it is possible to extract the solid reaction product by using a suitable carrier phase. This was demonstrated for the continuous production of N,N'-dicyclohexylethylenediimine.[127] Using an on-column purification step directly after the mixing and reaction of the reagents, highly pure 4,5-disubstituted oxazoles were obtained in a mesofluidic flow reactor.[160] Microfuidic solvent extraction has been studied as well.[161]



Scheme 2.14: Production of butyl cinnamate **78**.

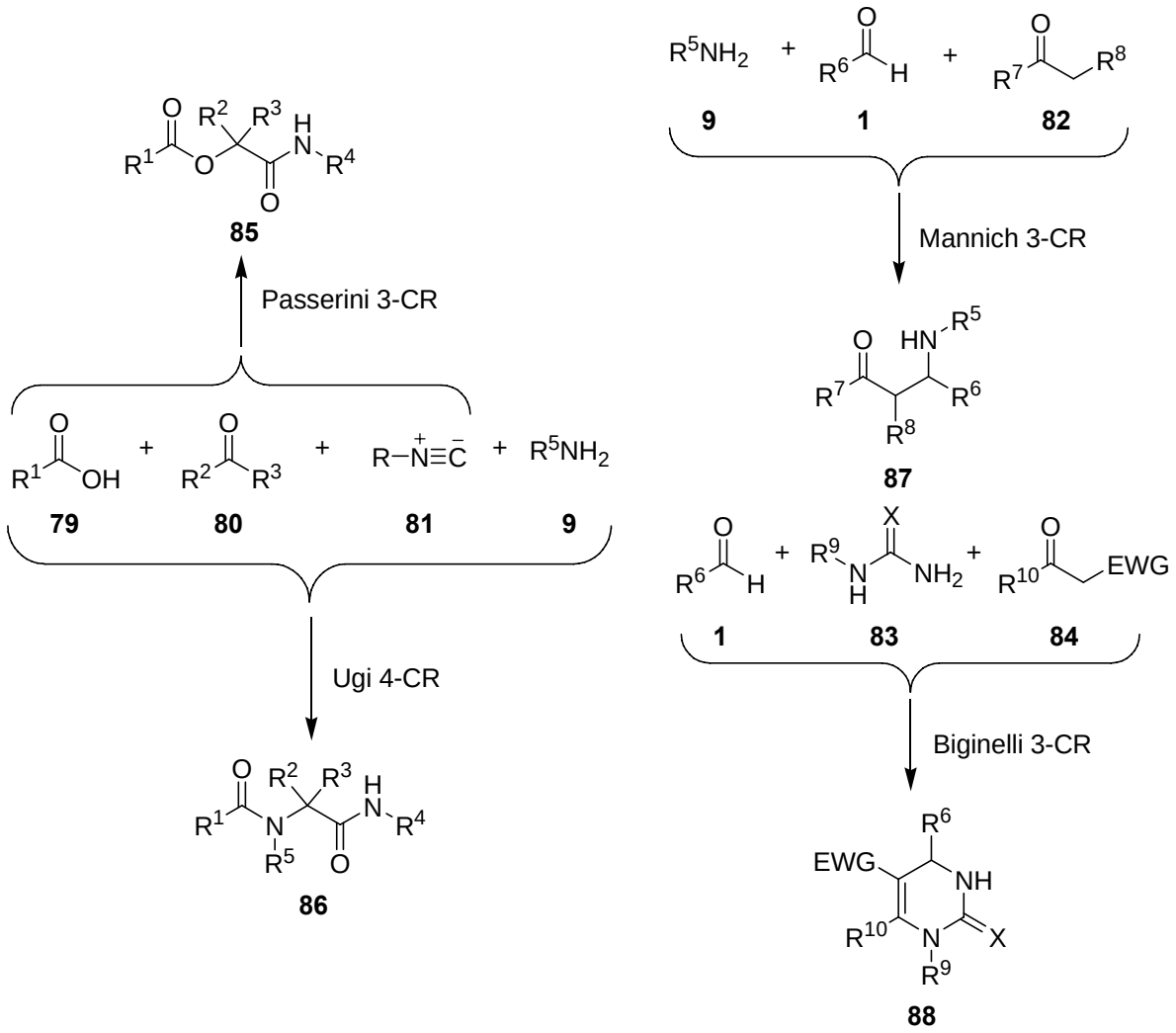
2.6 MULTICOMPONENT REACTIONS

2.6.1 Introduction

A very efficient way to access complex structures, such as heterocycles, using simple starting materials is the use of MCRs.[162-164] In this type of reactions three or more easily accessible components are reacted in a one-pot process to form ideally one product which incorporates essentially all the atoms present in the initial reactants. Generally, MCRs contain a very large chemical space, due to the variability possible in the different components of one reaction.[11] Important characteristics of MCRs are their convergency, atom efficiency and flexibility.[162] Starting from the Strecker reaction, discovered in 1850, a wide range of different types of MCRs has been designed.[12] Some important examples (Scheme 2.15) are the Biginelli reaction (1891),[165,166] the Mannich reaction (1912),[167-169] the Passerini reaction (1921),[12] and the Ugi reaction (1959).[170]

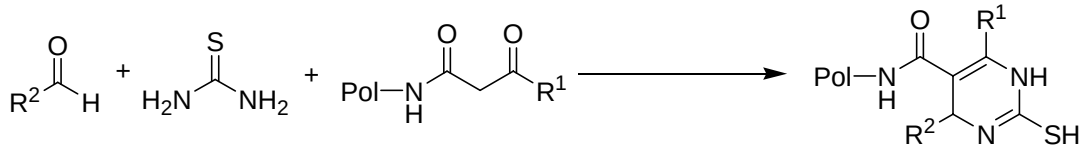
2.6.2 Application of microreactor technology in multicomponent reactions

Until now, only one real microreactor procedure is applied in the production of MCRs.



Scheme 2.15: Some important MCRs.

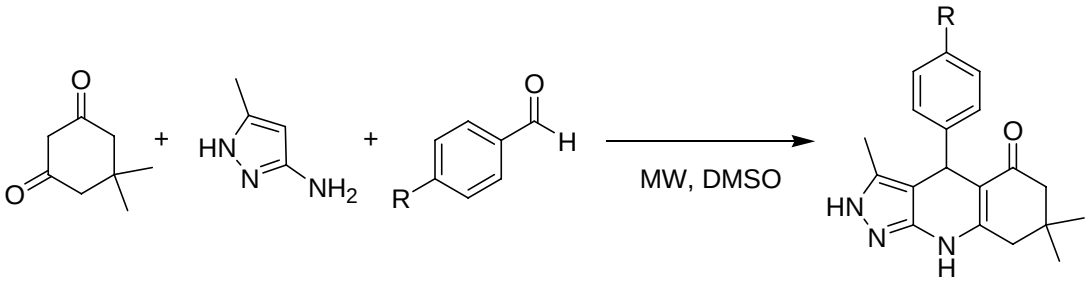
One research group focuses on the library synthesis of 4,6-diaryl-1,3-dihydropyrimidin-2(1*H*)-ones **89** in a nanochip system based on 3 microstructured silicon wafers, using the Biginelli reaction on single beads (Scheme 2.16). The chip needed to be pressurised to avoid evaporation of the solvent and cross-contamination between the different microwells. Comparison with macroscopic batch beads showed that this technology seemed to be promising for high throughput production of compounds on a solid-phase support. It must be emphasised that this was a batch procedure.[171]



1 **83a** **84a** **89**

Scheme 2.16: Formation of 4,6-diaryl-1,3-dihydropyrimidin-2(1*H*)-ones **89**.

Another recent paper describes the use of a micromixer-microwave combination for the formation of tetrahydropyrazolo[3,4-*b*]quinolin-5(*6H*)-ones **92** (Scheme 2.17) and tetrasubstituted furans *via* MCRs. However, the enhanced conversion and yield were attributed to the microwave irradiation and not to the micro-channels.[132]



90 **91** **1** **92**

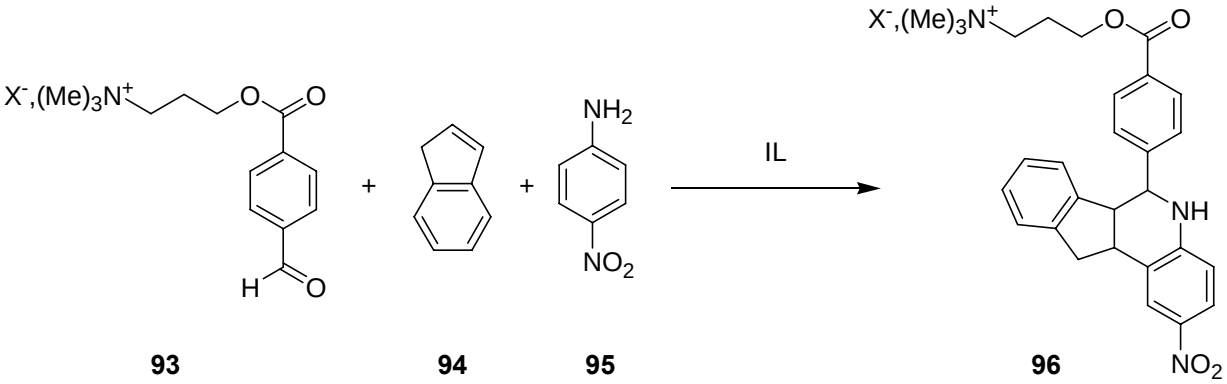
R = $N(CH_3)_2$, CN, CO_2Me, Br, OH, OMe

Scheme 2.17: Formation of tetrahydropyrazolo[3,4-*b*]quinolin-5(*6H*)-ones **92**.

The Grieco 3-CR reaction (Scheme 2.18) was performed using a droplet microfluidic system based on an ionic liquid (IL) solvent system. Optimisation was performed towards the IL and the problem of slow mixing in microdroplets was overcome by heating the droplet to decrease viscosity. Comparable reaction rates as the macroscale system were obtained.[172,173]

A manufacturer of microreactor modules recently published some results about the reaction optimisation of a Passerini 3-CR in an AFRICA® flow reactor system.[174] AFRICA stands for Automated Flow Reaction, Incubation and Control Apparatus and is a complete flow chemistry system. The system contains a glass microreactor chip. High-accuracy pumps and temperature control systems are used to control the chemical process *via* integrated sensors. Samples are collected in a fraction collector.[174,175] In the Passerini 3-

CR, a shift from 62 % yield in a 60 h batch reaction to 91 % yield in a 1 h residence time microreactor system was obtained.[174]



93 **94** **95** **96**

X = BF_4^-, NTf_2^-

Scheme 2.18: The Grieco 3-CR.

Chapter 3 - Results and Discussion

3.1 INTRODUCTION

3.1.1 Description of the microreactor device

Unless otherwise stated, the microreactor that is used in this doctoral research is the commercially available CYTOS® College System, produced by CPC - Cellular Process Chemistry Systems GmbH.[176] Figure 3.1 shows the entire device, consisting of 2 piston pumps, the microreactor itself, and a residence time unit (RTU). The different parts of the CYTOS® College System were connected *via* PTFE tubes.

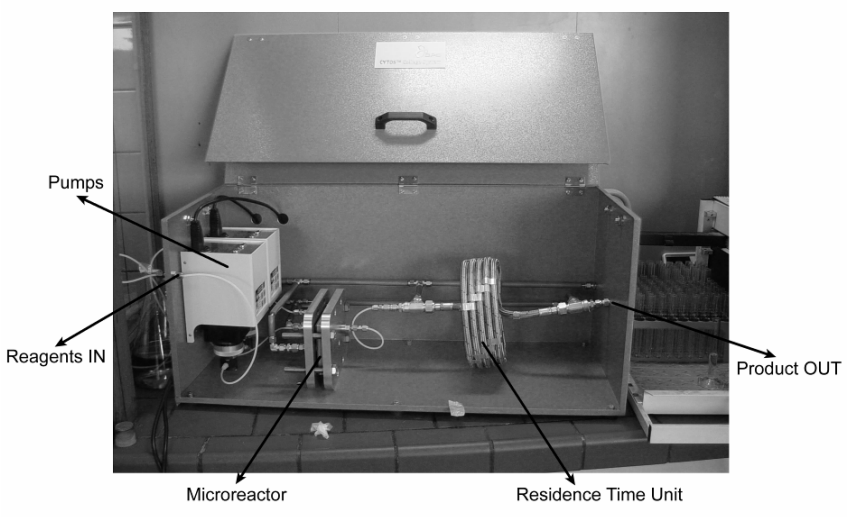


Figure 3.1: Setup of the CYTOS® College System.

The microreactor itself consists of 16 plates, which are fabricated using stainless steel (type 1.4571 according to the German standard). Each plate has at least one opening. The advantage of such a design is the ease of manufacturing. Machining or stamping openings in a flat surface is less complicated than producing grooves or channels that not fully penetrate the plate. The design of the different plates is in such a way that, when stacking the plates together, 2 physically separated fluid pathways are formed: one for

the chemicals and also one for the heating or cooling medium. To obtain an excellent heat exchange between the heating or cooling medium and the reactant flow, the plates between both media have a thickness of maximum 300 μm. The different plates can be held together by exerting pressure on the outer plates or they can be permanently joined together *via* vacuum soldering or diffusion welding, as is the case of the device that was used in this doctoral study. The advantage of the latter setup is that there is no danger of leakages, while the disadvantage is the loss of modularity. This microreactor is designed for the mixing of two chemical solutions, containing only liquid and/or completely dissolved compounds (i.e. a liquid/liquid phase reaction). The fluid pathway of the chemicals is given in Figure 3.2, and consists of 3 zones: the entrance zone of both chemical solutions (plate 1-5), the mixing zone (plate 6 and 7) and the reaction zone (plate 8-16). The mixing in this microreactor is based on the interdigital principle (*vide supra*, § 2.5.3), which is constructed by plates 3 to 5. These plates separate and align both reactant flows into a plurality of individual fluid paths. All individual fluid paths (of both reactants) are then joined in a laminar flow pathway, constructed by plates 4 to 7, to provide a stacked laminar flow of the first and second reactant (Figure 3.3). The fluid channel geometries are in the range of 100 to 500 μm, depending on the location in the microreactor. Another important part of the mixer design is that both reactant flows enter from the same side to provide the preferred stacked laminar flow and no side-by-side flow. This is shown in Figure 3.4. In the upper design, both reactants enter from opposite sides on plate 4. *Via* the holes in plate 5 (see Figure 3.2), these flows enter the mixing zone of plate 6 and 7. The direction of each fluid path is thereby changing by approximately 90 degrees. As a consequence, the fluid path has the tendency to propagate faster along the inside of that corner, because the distance is shorter. This behaviour favours an unwanted side-by-side flow. Therefore, the design is adjusted in such a way that both reactants enter the mixing zone from the same side (see lower design in Figure 3.4). This design eliminates the velocity difference between both reactants and provides the desired stacked flow shown in Figure 3.3.

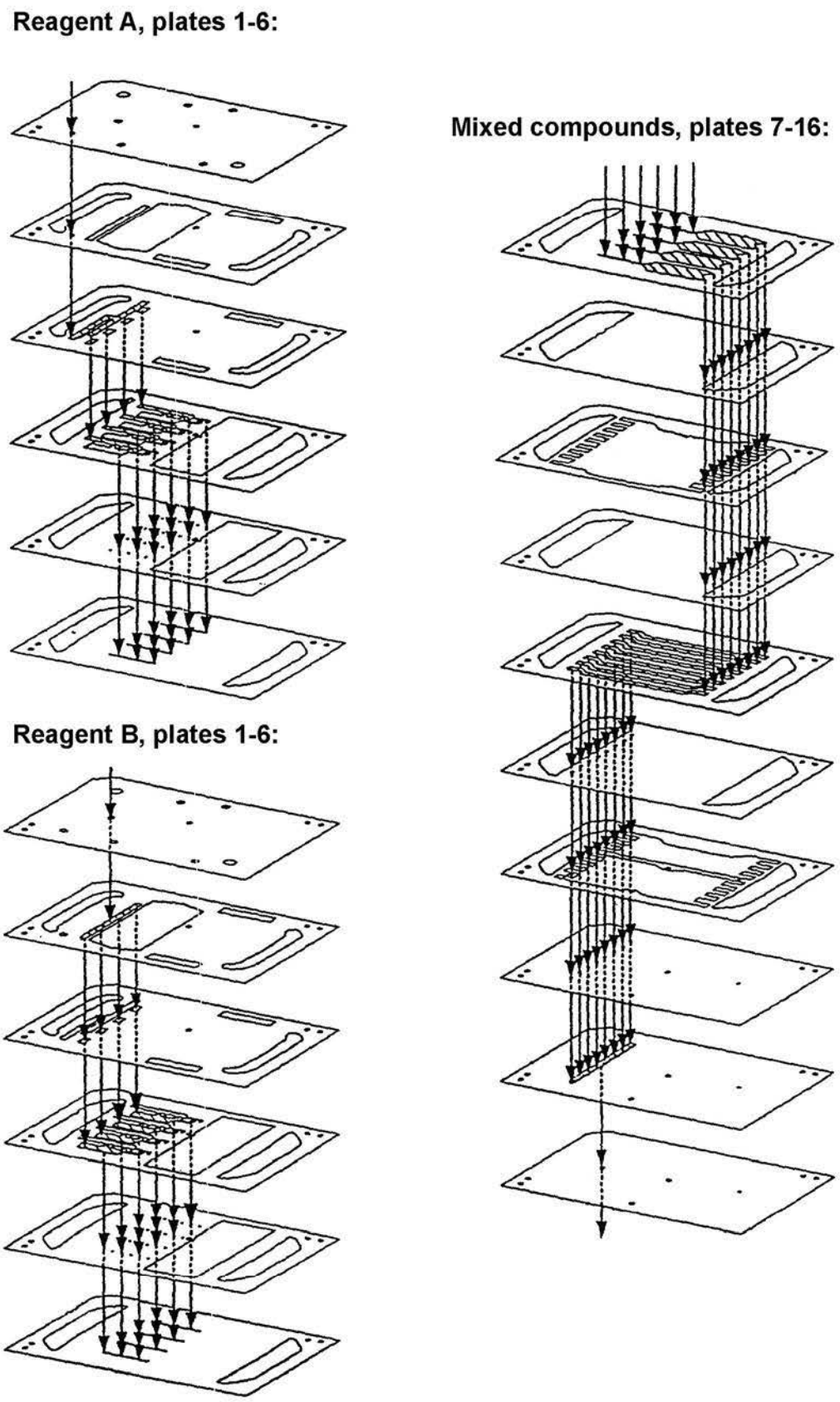


Figure 3.2: Flow pattern of the reactant flows through the microreactor unit. Upper left: reagent A entrance zone; Lower left: reagent B entrance zone; Right: mixing and reaction zone of both reagents.

After the mixing, the reaction mixture is allowed to react (plates 8-14). Finally, all individual flows are merged again on plate 15 to leave the microreactor *via* plate 16. The fluid path of the heating or cooling medium will not be discussed in detail, but follows a similar profile.

The pumps that were used were valveless rotary piston dispensing pumps, a type of positive displacement pumps. The advantage of these pumps is the conservation of a constant flow, whenever the maximal differential pressure of 6.9 bar is not exceeded. This is of great importance to maintain a well-defined residence time. The piston itself is of ceramic material. The speed of the piston can be set between 40 and 1800 rpm, which means a flow rate of 0.04 to 90 mL/min.

The RTU consists of a stainless steel tube which is surrounded by another tube wherein the heating or cooling medium flows (for dimensions and typical Reynolds numbers, *vide infra*, § 3.2.5). The combination of these different types of materials in the pumps and microreactor makes it necessary to study the chemical resistance intensively before using a certain chemical compound. The use of e.g. $AlCl_3$ is not allowed because of the corrosion risk of the stainless steel, while the use of toluene is limited due to the possible reaction with certain parts of the pumps.

3.1.2 General procedure

In all the experiments described in this doctoral thesis, some standard operations were necessary to obtain reliable results. Every time a new MCR was evaluated, it was necessary to check the batch procedure since not all reactions are suitable in a microreactor.[1] If it was feasible to perform the reaction in a microreactor, the next step in the procedure was the flushing of the system with the solvent that will be used in the reaction. Meanwhile, the reaction solutions were prepared. According to the flow rate, the residence time was calculated and sample collection was started after at least 1.6 times the residence time was passed to be sure that steady state conditions were reached. After collection of the sample(s), the microreactor and the RTU

were again thoroughly flushed to remove any residual products. During the whole experiment, the input and output volumes were constantly measured and the corresponding flow rates were calculated to control for clogging or leakage problems.

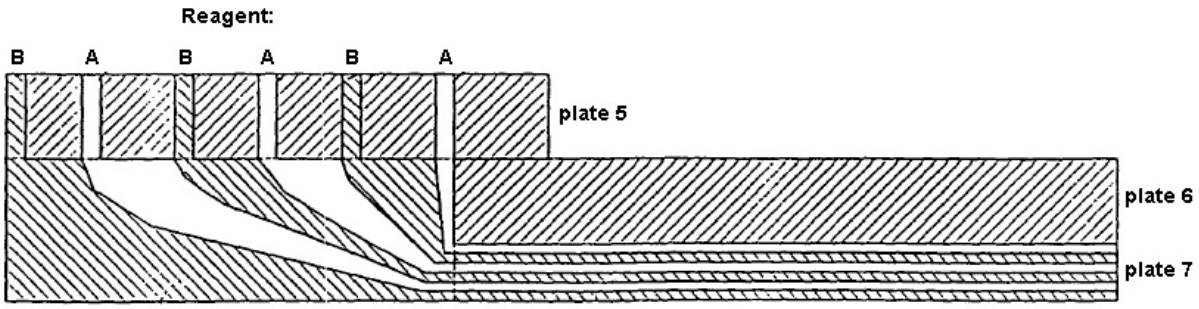


Figure 3.3: Construction of the stacked laminar flow pattern.

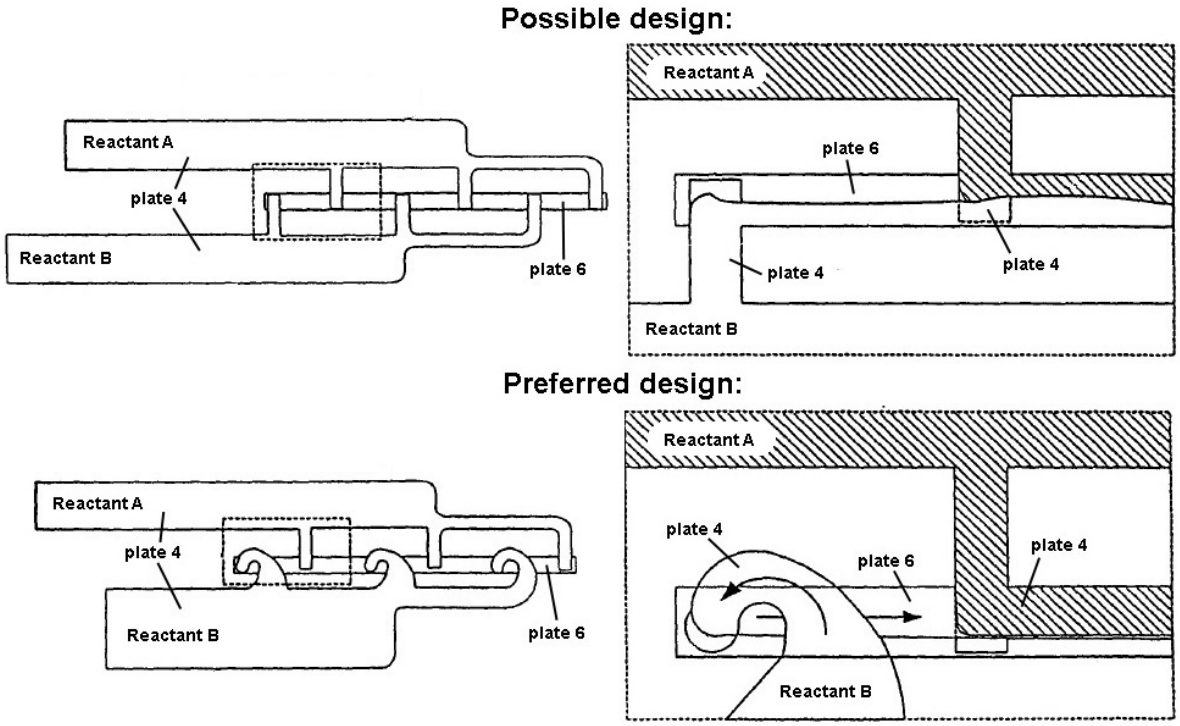
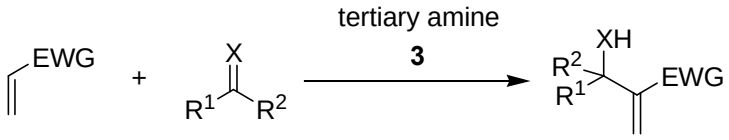


Figure 3.4: Different mixer designs. Upper left: plate 4 on top of plate 6. Upper right: detailed view of the reactant fluid paths providing a side-by-side flow pattern. Lower left: plate 4 on top of plate 6. Lower right: detailed view of the reactant fluid paths providing a stacked flow pattern. (plate 5 is not shown in both designs).

3.2 BAYLIS-HILLMAN REACTION

3.2.1 Introduction

The (Morita-)Baylis-Hillman reaction was first described in a patent by Morita *et al.* in 1968.[177,178] They described a carbon-carbon bond formation between an aldehyde and an acrylate with the aid of a phosphine catalyst, yielding highly functionalised β-hydroxy-α-methylene esters. In 1972, Baylis and Hillman reinvestigated the reaction and found a threefold higher yield if 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as a catalyst.[179] Ever since, the Baylis-Hillman reaction has gained a lot of importance in organic synthesis.[27,28] Generally, the Baylis-Hillman reaction is a three-component reaction in which an activated alkene **97** couples to a carbon electrophile **98** with the aid of a tertiary amine **3** (mostly DABCO) as a catalyst. A carbon-carbon bond is formed at the α-position of the alkene (Scheme 3.1). When phosphines are used as a catalyst, the reaction is mostly called Morita-Baylis-Hillman. In the case imines are used as electrophilic reagents, with the final formation of a β-amino-α-methylene compound, an aza-Baylis-Hillman reaction is performed (*vide infra*, § 3.2.7).



97 **98** **99**

EWG = COR, CN, CHO, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh
R^1 = aryl, alkyl, heteroaryl
R^2 = H, COOR, alkyl
X = O, NCOOR, NTs, NSO_2Ph

Scheme 3.1: General Baylis-Hillman reaction.

The wide variety of the different building blocks made this reaction of high synthetic interest because of the possibility of creating highly functionalised building blocks in a one-pot reaction. In the context of industrial applications, in which the microreactor technology could play an important role, it should be mentioned that this reaction is a 100 % atom efficient conversion which is an important characteristic in the green chemistry concept. Unfortunately, the

Baylis-Hillman reaction is a slow reaction, often requiring days or weeks to go to completion.[180] This depends mostly on the reactivity of the reagents, i.e. the activated alkene and the electrophile. Nowadays, literature about the Baylis-Hillman reaction can be divided into 4 main topics:

1. Finding new procedures or reaction conditions to improve reaction rate and yield.[181-196]

Ever since the discovery of the Baylis-Hillman reaction, a wide variety of different reaction conditions are already tested to obtain better yields and reaction rates. A general classification can be made.

- the use of different catalysts, such as quinuclidine, 3-hydroxyquinuclidine and DABCO,[181] or diethylaluminum iodide.[182]
- the importance of the solvent use e.g. aqueous solutions,[183-185] sulfolane,[186,187] *N*-methylpyrrolidinon (NMP),[186] N-methylmorpholine[186] or poly(ethyleneglycol).[188]
- the study of physical effects such as temperature,[189] pressure[190,191] and ultrasound[180,189].
- the influence of Lewis acids e.g. lithium perchlorate[192] and titanium(IV) chloride[193].
- other effects such as the co-catalysis between DABCO and phosphonium salts[194] or between L-proline and imidazole,[195] or the use of cyclodextrin complexes[196].

2. Mechanistic studies of the reaction.[197-204]

A lot of research has already been done to unravel the mechanism of the Baylis-Hillman reaction. Recently, this mechanism has been revised, under aprotic, protic, polar and nonpolar conditions.[201,202] It was found that the Baylis-Hillman reaction appeared to be a first order reaction in the tertiary amine and the activated alkene and a second order reaction in the aldehyde moiety, although this latter was believed to be first order until then. The Baylis-Hillman reaction consists of an addition-elimination sequence which

involves the tertiary amine. Scheme 3.2 illustrates the mechanism of the reaction between an aldehyde, methyl acrylate, and DABCO as the catalyst. The tertiary amine **3** attacks the double bond of the activated alkene **2a** with the formation of a zwitterion **100**, which then reacts with the aldehyde **1**. According to the revised mechanism, the intermediate **101** then attacks a second equivalent of the aldehyde, with formation of an intermediary hemiacetal, before the final proton transfer. This last step, in which the catalyst is eliminated, is also considered as the rate-determining step (RDS). Another research group obtained similar results, showing that the catalyst elimination was the RDS. However, their data suggest also that, in the absence of protic solvents, there is a switch of the RDS from the catalyst elimination step to the aldehyde addition step (which is believed to be the RDS in the former mechanism) once there is built up enough end product.[203]

3. Study towards an increase in enantioselectivity.[205-214]

The generation of a chiral centre in the Baylis-Hillman reaction has been the subject of several investigations towards enantiopure adducts. Chirality is induced *via* the use of chiral aldehydes,[205,206] chiral activated alkenes,[205] chiral solvents[205,207] or chiral catalysts. Most of these chiral inducing catalysts are derived from quinidine,[208-211] binaphthol[212,213] or camphor[214].

4. Developing new compounds starting from Baylis-Hillman adducts.[27,28,215-230]

Due to the creation of several functionalities in one molecule, the Baylis-Hillman adduct is an interesting starting material for the further development of other compounds. A wide variety of interesting compounds are already synthesised of which antibiotics,[217,218] isoxazoles,[219,220] β- and γ-lactams,[206,215,216,231] isobenzofurans,[232] [1,4]oxazepine-7-ones,[233] coumarin and chromene derivatives[234,235] are only a few examples.
In literature, it is stated that the use of microreactor technology for organic synthesis is advantageous because the reaction rate is often increased. Indeed, several examples are known in which this is the case.[102,149,150] Since the

Baylis-Hillman reaction is known as a very slow multicomponent reaction,[180] it was interesting to investigate if this technology would be advantageous for solving this major drawback of the reaction.

3.2.2 Optimisation study using microreactor technology

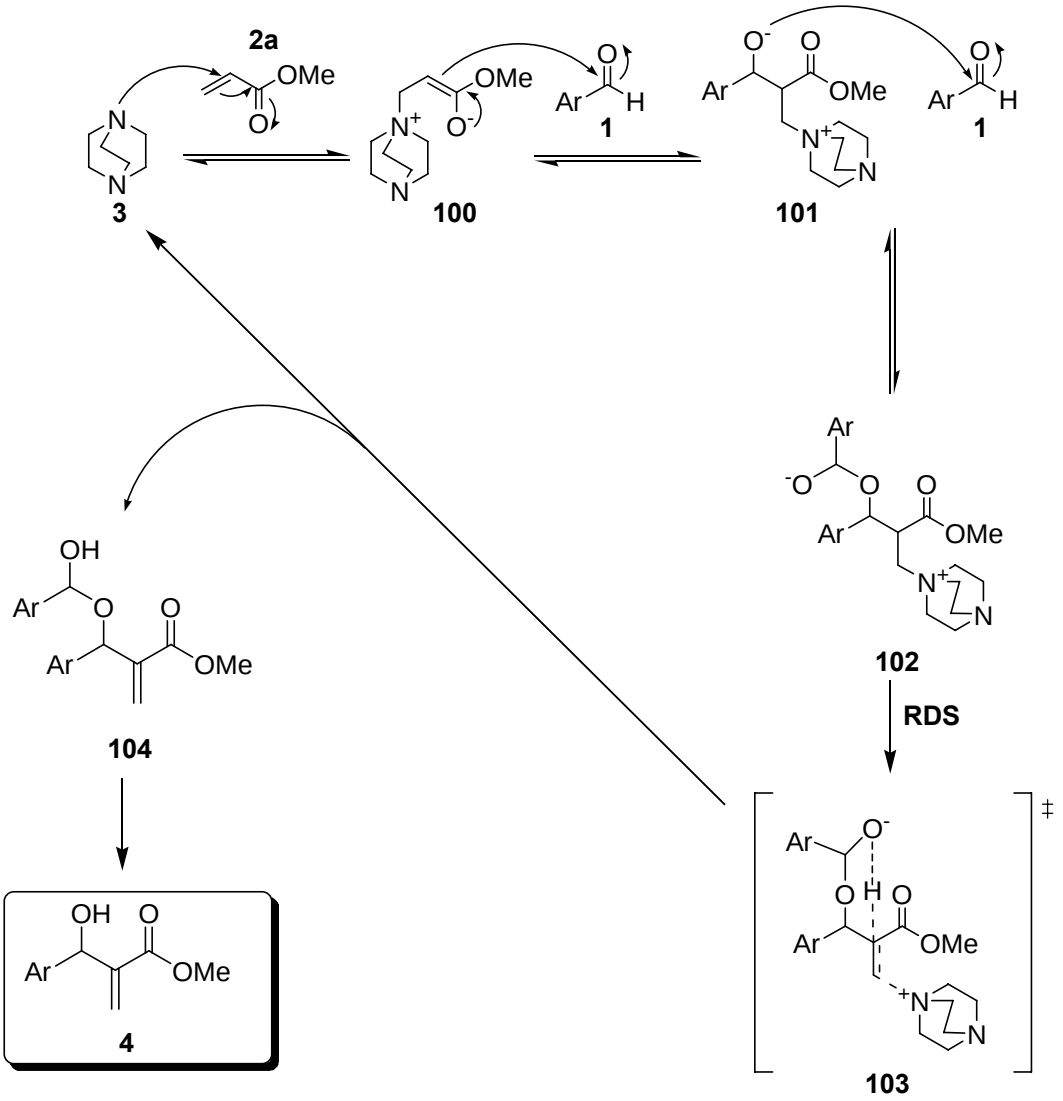
3.2.2.1 Choosing an appropriate test reaction

As the maximal possible residence time in the microreactor (plus RTU) is calculated and experimentally validated to approximately 2 h, a rather fast Baylis-Hillman reaction was evaluated first. It is possible to have longer residence times by using lower flow rates. However, this is not feasible, due to reproducibility problems of the pumps.[2] The research was initiated therefore using starting materials of which the reaction time for the Baylis-Hillman reaction was comparable to the maximum residence time of the microreactor used in this study.

The reaction between 4-nitrobenzaldehyde **1a** and methyl acrylate **2a** with DABCO **3** as catalyst (Scheme 3.3) seemed suitable, because of the short reaction time and the good yields of this particular Baylis-Hillman reaction under batch conditions.[180,185,236] Interestingly, compound **4a** has a high *in vitro* antiproliferative activity against a variety of human tumor cell lines.[237] Since the goal was to study the impact of a switch from a batch process to the microreactor system, the same catalyst was used in both systems. It has to be mentioned that, next to DABCO, a lot of catalysts or co-catalysts are studied for this type of reaction.[192,194,195,221-230,238-244] Several of these catalysts give similar or better results, but DABCO was chosen from an economic as well as an industrial point of view.[3]

[2] The piston pumps are pumping at a speed of 40 to 1800 rpm while the volume pumped per pump cycle (i.e. stroke volume) is between 1 and 50 µL. This means the flow rate range of the piston pumps is between 0.040 and 90 mL/min. However, to maintain accuracy, the manufacturers recommend not to work below 10 % of the maximal stroke volume i.e. 5 µL. This means the minimal recommended flow rate is 0.2 mL/min. At lower stroke volumes, the relative variation of the stroke volume is too high (there is a tendency for pulsation at lower flow rates).

[3] Prices: 22.10 € per 100 g of DABCO versus 80.60 € per 1 g of quinuclidine.



Scheme 3.2: Revised mechanism of the Baylis-Hillman reaction.

3.2.2.2 Defining the critical concentration

Initially, a suitable solvent for the microreactor setup was needed. According to literature, the best results were obtained using a mixture of water and 1,4-dioxane (v/v 1:1).[236] Some initial experiments in a batch setup showed a considerable concentration effect with a higher concentration of the reagents leading to better conversions (Table 3.1, entries 1, 4, and 6). However, a concentration limit needs to be determined when solid reagents (such as in this case DABCO and 4-nitrobenzaldehyde) are used, because of the risk of clogging the capillaries of the microreactor (width approximately 100 μm) when reagents or the product precipitates from the reaction medium.

Moreover, the supply medium of the reactor needs to be double concentrated for each storage solution compared to the reactive concentration inside the reaction cell, provided that both pumps are operating at the same flow rate.

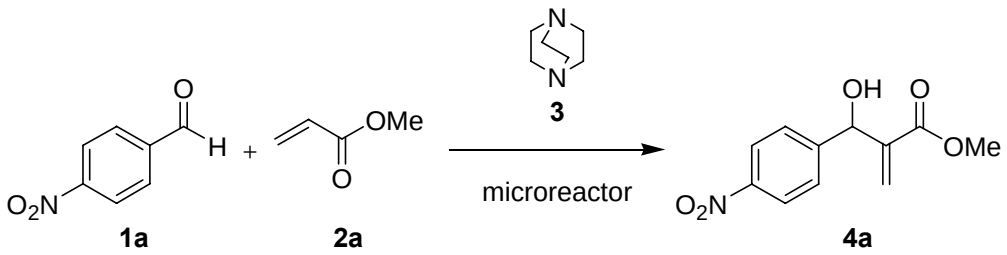
Table 3.1: Baylis-Hillman reaction of 4-nitrobenzaldehyde and methyl acrylate in batch mode using DABCO as a catalyst in water/1,4-dioxane (v/v 1:1) as solvent.[a]

Entry	*4-nitro-benzaldehyde (M)*	*DABCO (M)*	*Methyl acrylate (M)*	*Degree of conversion (mol %)*[b]	*Yield (%)*[c]
1	0.1	0.1	0.3	81	74
2[d]	0.1	0.1	0.3	--	83
3[e]	0.1	0.1	0.3	75	69
4	0.05	0.05	0.15	51	43
5[f]	0.05	0.05	0.15	49	44
6	0.033	0.033	0.1	21	22

--: Not determined. [a] Reaction time: 3 h; a solution of 1 equiv 4-nitrobenzaldehyde and 3 equiv methyl acrylate in 10 mL of water/1,4-dioxane (v/v 1:1) was stirred at room temperature in the presence of 100 mol % DABCO.[236] [b] Based on the integration signals in the ^{1}H-NMR spectrum. [c] Based on total mass of end product collected in the crude mixture and degree of conversion. [d] Reference [236]. [e] Reaction time: 2 h. [f] Without stirring the mixture.

Therefore, the maximum concentration that could be investigated in the microreactor was 0.1 M of 4-nitrobenzaldehyde, since concentrations higher than 0.2 M became insoluble in the case that water/1,4-dioxane (v/v 1:1) was used. Dissolving 0.2 M of 4-nitrobenzaldehyde in the water/1,4-dioxane (v/v 1:1) mixture was not possible, even with gentle heating of the mixture. First dissolving the 4-nitrobenzaldehyde in 1,4-dioxane worked well. When the water was added then (in which the DABCO was dissolved), at a critical concentration, the 4-nitrobenzaldehyde started to precipitate. This was more or less when a v/v 1:1 mixture of the solvents was reached. Gentle warming of the medium up to 35 °C at the inlet was required to prevent precipitation in the supply medium. So, a concentration of approximately 0.2 M of 4-nitrobenzaldehyde was the critical concentration. It must be emphasised that

this concentration is in the presence of DABCO in the mixture, so normally the critical concentration is somewhat higher.



1a 2a 4a

Scheme 3.3: Investigated Baylis-Hillman reaction.

To optimise the reaction in the microreactor, several conditions were tested by altering the residence time, the initial concentration of the substrates, the ratio between the substrates, the temperature, and the mixing of the substrates. Table 3.2 summarises these results.

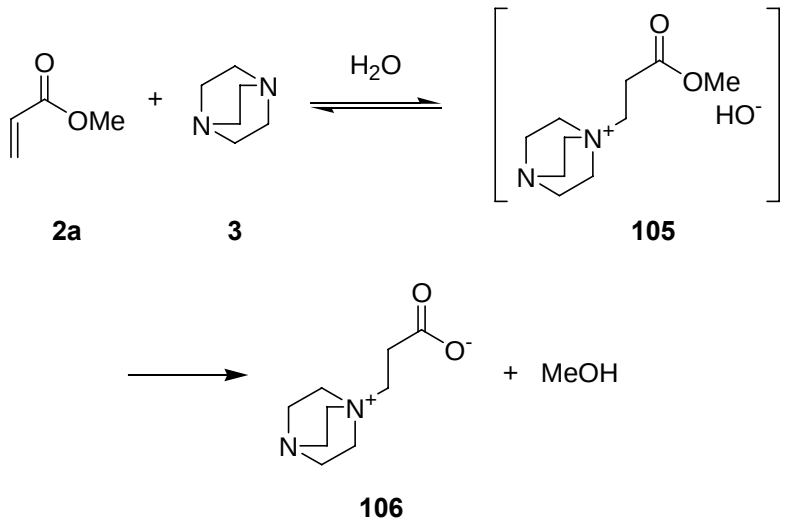
3.2.2.3 Mixing order

First, the order of mixing of the substrates was investigated. Considering the mechanism (*vide supra*, § 3.2.1), the mixing of methyl acrylate and the catalyst prior to the entrance of the microreactor seemed advantageous. However, compared to the use of a mixture of the aldehyde and the catalyst, this resulted in lower conversions and yields (entries 2, 3, 4 and 5). This is in accordance with the results obtained by Yu *et al.*, who stated that preincubation of 100 mol% DABCO with 3 equivalents of methyl acrylate in a water/1,4-dioxane (v/v 1:1) mixture before the addition of aldehyde resulted in a ninefold decrease of the product yield due to a side reaction.[236] In this side reaction the hydrolysis of the Michael adduct leads to a stable betaine **106** which consumes both the catalyst and the methyl acrylate (Scheme 3.4). This was also seen by a light yellow colouration of the mixture, while the separate solutions were transparent. Although the difference in conversion and yield was not as big as in the batch case, mixing 4-nitrobenzaldehyde and DABCO indeed proved to be the best option for the continuous reaction.

Table 3.2: Baylis-Hillman reaction of 4-nitrobenzaldehyde and methyl acrylate in continuous mode using DABCO as a catalyst in water/1,4-dioxane (v/v 1:1) as solvent.[a]

Entry	*4-Nitrobenzaldehyde (M)*	*DABCO (M)*	*Methyl acrylate (M)*	*T (°C)*	*Degree of conversion (mol %)[b]*	*Yield (%)[c]*
1	**0.1**	**0.1**	0.3	RT	83	64
2	**0.05**	**0.05**	0.15	RT	57	48
3	0.05	**0.05**	**0.15**	RT	38	40
4	**0.05**	**0.05**	0.05	RT	17	17
5	0.05	**0.05**	**0.05**	RT	11	11
6	**0.05**	**0.1**	0.05	RT	26	40
7	**0.05**	**0.1**	0.1	RT	48	69
8	**0.05**	**0.025**	0.025	RT	10	7
9	**0.05**	**0.05**	0.15	40	33	31
10	**0.033**	**0.033**	0.1	RT	29	27
11	**0.033**	**0.067**	0.1	RT	46	66
12	**0.017**	**0.017**	0.05	RT	7	11
13	**0.05**	**0.05**[d]	0.15	RT	64	34
14[e]	**0.2**	**0.2**	0.6	**RT**	**93**	**82**

[a] Residence time: 1 h 58 min; products in bold are mixed together before they enter the microreactor system; concentration of the reagents as in the reactor; reaction quenched with HCl (1 N). [b] Based on the integration signals in the ^{1}H-NMR spectrum. [c] Based on total mass of end product collected in the crude mixture and degree of conversion. [d] Quinuclidine as catalyst instead of DABCO. [e] 4-Nitrobenzaldehyde and DABCO dissolved into a 3:7 (v/v) water/1,4-dioxane mixture; methyl acrylate stirred into a 7:3 (v/v) water/1,4-dioxane mixture.



Scheme 3.4: Side reaction of the Baylis-Hillman reaction with formation of betaine **106**.

3.2.2.4 Concentration optimisation

In a second step, different concentrations were tested. As can be seen from entries 1, 2, 10, and 12 the same concentration effect appears as in a batch setup. Moreover, the conversions and yields in the batch reaction after 3 h appear to be more or less the same as these in the microreactor with a residence time of 2 h (Table 3.1, entry 1 and Table 3.2, entry 1). Since the reaction profile under batch conditions at the highest concentration (for the continuous reaction i.e. 0.1 M aldehyde in the microreactor) proved that the reaction is still not completed after 2 h (Figure 3.5), it can be concluded that this Baylis-Hillman reaction is faster under microreactor conditions. Table 3.1, entry 3, also shows the conversion after 2 h, which is lower compared to the microreactor reaction at the same time (Table 3.2, entry 1). Although better results were expected using this technology, in analogy to other reactions,[102,149,150,245-247] no important improvement was achieved. However, in this particular case a rate enhancement of approximately 30 % was observed. A possible explanation for this rather small enhancement, compared to some classical examples of rate enhancement in microreactors, is shown in Table 3.1, entries 4 and 5. These results show that the intensity of mixing of the reagents is not important in achieving higher conversions and

yields. This means that the mass transfer advantage of the microreactor technology is minimalised for the Baylis-Hillman reaction.

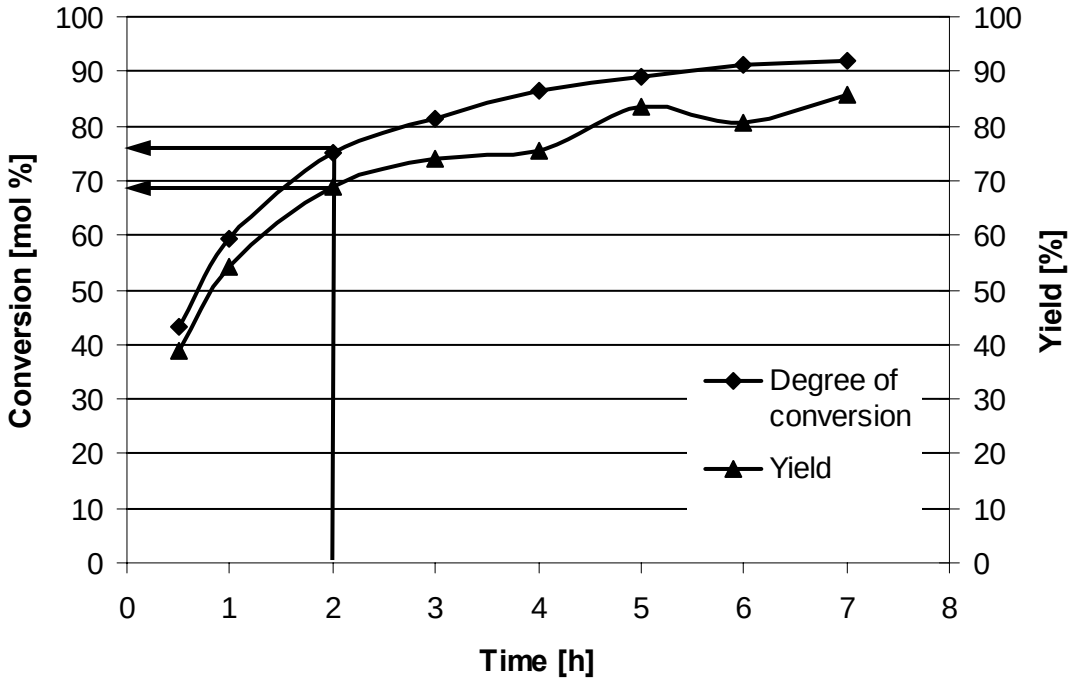


Figure 3.5: Course of the batch reaction of 4-nitrobenzaldehyde and methyl acrylate in the presence of DABCO.

Another important issue is that since the reagents also react upon standing at room temperature (without stirring), the reaction mixture had to be quenched immediately with an equal amount of hydrochloric acid (1 N) so that further conversion was prevented after leaving the RTU of the microreactor. This was tested to prove the effect. Indeed, immediately quenching the mixture led to a conversion of 33 % (entry 9), while waiting until the sample was collected (which took about 25 min) gave a conversion of 69 %.

Since the conversion was not complete at the highest possible concentration of the substrates, no higher flow rates (resulting in smaller residence times) were tested. Also no higher residence times were tested with continuous flow because the applied flow rate was the lowest reproducible one the piston pumps could handle. To increase the residence time, the stopped-flow technique was evaluated (*vide infra*, § 3.2.4). Since the initial concentration of the reagents was of great importance (Table 3.2), attempts were made to

further increase the concentrations. It is already stated that 4-nitrobenzaldehyde is very well soluble in 1,4-dioxane. So it was possible to make a 0.4 M solution of 4-nitrobenzaldehyde and 0.4 M of DABCO if the solvent mixture was changed to 3:7 (v/v) water/1,4-dioxane. Because a 1:1 (v/v) mixture proved to give the highest yields,[236] the methyl acrylate was dissolved in a 7:3 (v/v) mixture of water and 1,4-dioxane to have a 1:1 (v/v) mixture in the microreactor. Table 3.2, entry 14 shows that the conversion and yield were further improved. Importantly, it was necessary to continuously stir the starting solution with the high methyl acrylate concentration, in order to keep the solution homogeneous.

3.2.2.5 Reaction temperature

A third aspect was the evaluation of the optimal reaction temperature. Due to the small capillaries (width approximately 100 μm), the microreactor provides a narrower temperature profile than that in batch systems (*vide supra*, § 2.4.4). At higher temperatures no improvement was noticed (Table 3.2, entry 9), although sometimes this is the case.[248] Since in some cases lower temperatures have a positive effect on the reaction rate of the Baylis-Hillman reaction,[249] attempts were made to improve the rate by decreasing the reaction temperature beneath room temperature. However, in the case of the 1:1 (v/v) mixture of 1,4-dioxane and water, lower temperatures (significantly below room temperature) could not be investigated due to the melting point of 1,4-dioxane.[4] Although no solidification occurred at 5 to 15 °C in the batch reaction due to the dissolved compounds, partial to complete clogging already occurred at these temperatures in the microreactor, probably due to the capillaries, the high concentration of the substrates in a low temperature environment and the considerably low flow rate. In the batch system, a high turbulence prevents solidification. So, the optimal reaction temperature under microreactor conditions was set at room temperature, which was standardised to 22 °C.

[4] 1,4-dioxane has a melting point of 12 °C.

3.2.2.6 Final optimisation

A further investigation consisted of varying the ratio of the substrates. Table 3.2, entry 4 shows that lowering the concentration of the methyl acrylate to 1 equivalent gave less favourable results compared to the excess of 3 equivalents. This was expected since in most procedures an excess of the activated alkene is used.[243,250-252] An excess of catalyst (Table 3.2, entry 6) instead of an excess of methyl acrylate also increased the yield. However, because of the low enhancement it was not a breakthrough in the optimisation process. Since the Baylis-Hillman reaction proved to be a second-order reaction in the aldehyde,[201,202] an experiment with an excess of aldehyde was also evaluated. Entry 8 shows the very low conversion and yield in this case. It was also found in the literature that quinuclidine was more active than DABCO in this particular Baylis-Hillman reaction,[181] so an experiment was performed under the same conditions. The degree of conversion was somewhat higher than in the case of DABCO. Further optimisation with quinuclidine was not done since DABCO is a much cheaper catalyst.[5]

Also other solvents were evaluated to obtain better results. In one study, sulfolane was used as the solvent in combination with DABCO as a base. According to the authors, this gave better results than the aqueous 1,4-dioxane mixture.[187] A major disadvantage seemed to be the high melting point of the sulfolane,[6] which makes it less suitable for industrial purposes. Nevertheless, several reaction conditions were evaluated to test the performance under microreactor conditions. Table 3.3 summarises the results. The first reaction that was performed was at 40 °C at a relative high flow rate, to prevent clogging of the microreactor. Although there were no problems in performance, the conversions were rather disappointing (Table 3.3, entry 5). Since it was noticed that the aldehyde/catalyst did not solidify in sulfolane, when standing at room temperature, a second trial was performed at room temperature conditions at the highest possible residence time. Entry 3 shows

[5] See remark 3 on page 48.

[6] The melting point of sulfolane 99+% is 27.4 - 27.8 °C (Acros).

that the result was very promising, since better results were obtained compared to the reaction in water/1,4-dioxane (v/v 1:1) (Table 3.2, entry 2). Increasing or decreasing the reaction temperature did not give better results (entries 2 and 6). A temperature of 70 °C was tested because of the good results obtained at the reflux temperature of methyl acrylate (76 °C) with DABCO as a catalyst.[248] As mentioned, the mixture of aldehyde and DABCO in sulfolane did not solidify at room temperature. When the temperature was further decreased to 4 °C, there was still no solidification, even after standing for 2 days. However, performing the reaction at 10 °C in the microreactor (according to literature, lower temperatures are beneficial for the Baylis-Hillman reaction[249,250]), almost immediately led to clogging of the microchannels (entry 2). A similar explanation as for the aqueous 1,4-dioxane mixture is suggested (*vide supra*, § 3.2.2.5). Combining methyl acrylate and DABCO also led to solidification however, but now it already occurred in the mixture. Taking all these results into account, a final experiment in sulfolane was done at a higher concentration in order to increase the output. Surprisingly, the conversion and yield of the reaction dropped significantly (entry 1). No decent explanation for this behaviour was found. Although the higher conversion obtained with sulfolane at a 0.05 M concentration of aldehyde, this route was abandoned, since in the case of water/1,4-dioxane (v/v 1:1), a higher output was possible without the extra problems of solidification.

Further attempts to work at decreased temperatures were made by using dichloromethane as a solvent,[182,253] since no solubility problems occurred in this solvent. Unfortunately, the use of dichloromethane showed a severe drop in the actual flow rate during processing.[7] As a consequence, the residence time was not reproducible. When evaluating the reaction mixture, also no Baylis-Hillman adduct was formed, although the residence time was increased due to the lowered flow rates. For these reasons, this route was abandoned. In attempts to work with neat methyl acrylate as a solvent, which proved to

[7] According to the chemical resistance chart of the CYTOS® College System, provided by CPC - Cellular Process Chemistry Systems GmbH, dichloromethane can be used in a limited way because of the low compatibility with some parts of the piston pumps. In this particular case, even after half an hour problems occurred to maintain the flow rate. Therefore, no further experiments were done with dichloromethane.

be advantageous in some cases,[248,254] problems with the pump stability were also observed,[8] so no further experiments were performed.

Table 3.3: Baylis-Hillman reaction of 4-nitrobenzaldehyde and methyl acrylate in continuous mode using DABCO as a catalyst in sulfolane as solvent.[a]

Entry	*4-Nitrobenzaldehyde (M)*	*DABCO (M)*	*Methyl acrylate (M)*	*T (°C)*	*Degree of conversion (mol %)[b]*	*Yield (%)[c]*
1	**0.1**	**0.1**	0.3	RT	23	19
2	**0.05**	**0.05**	0.15	10	--	--
3[d]	**0.05**	**0.05**	0.15	RT	82 (8)	73 (7)
4	0.05	**0.05**	**0.15**	RT	--	--
5[e]	**0.05**	**0.05**	0.15	40	5	5
6	**0.05**	**0.05**	0.15	70	7	6

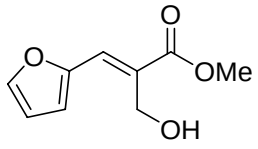
--: Clogging of the microreactor. [a] Residence time: 1 h 58 min; products in bold are mixed together before they enter the microreactor system; concentration of the reagents as in the reactor; reaction quenched with HCl (1 N). [b] Based on the integration signals in the ^{1}H-NMR spectrum. [c] Based on total mass of end product collected in the crude mixture and degree of conversion. [d] In brackets: results collected after the microreactor alone i.e. with a residence time of 3 min. [e] Residence time: 23.5 min.

3.2.3 Generality

The aforementioned optimisation study was used to check the generality of the Baylis-Hillman procedure under microreactor conditions. Several aromatic and aliphatic aldehydes were subjected to these conditions, together with different activated alkenes. The results are presented in Table 3.4. In case of the aldehyde, moderate to good conversions were obtained without any problems. Even the aliphatic propionaldehyde gave a good conversion to the Baylis-Hillman adduct. No side-products were detected in the spectrum with one exception. In the ^{1}H-NMR spectrum of the Baylis-Hillman reaction with furaldehyde **1d**, formation of a side-product was detected. A ratio of Baylis-

[8] No compatibility issues were known about methyl acrylate, according to the chemical resistance chart of the CYTOS® College System.

Hillman adduct **4d** *versus* side-product of 86:14 was calculated. When the reaction time was prolonged, as in the stopped-flow procedure (*vide infra*, § 3.2.4), a further shift towards the side-product was seen (ratio = 58:42), which meant that the Baylis-Hillman adduct was converted to this side-product. Purification by column chromatography and analysis of the different spectra proved that this side-product was methyl (2*E*)-3-furan-2-yl-2-hydroxymethyl acrylate **107** (Figure 3.6). Considering the E- or Z-isomer the following rationale was followed. First of all, it was expected that the E-isomer was formed based on literature data since for Baylis-Hillman esters, mostly the E-isomer was formed in a S_N2' reaction, while this was mostly the Z-isomer in the case of nitrile adducts.[255-257] Secondly, the proton on the double bond has a value of 7.45 ppm. Calculations predict the value of this proton in the E-configuration to be around 7.62 ppm, while the Z-configuration has a far more upfield value of around 7.08 ppm. Moreover, a carbon value of 57 ppm is expected for the methylene protons in the E-configuration, while this is 63 ppm in the other case. The real value (58.2 ppm) is closer to the E-isomer. Finally, some NOE experiments were performed. No Nuclear Overhauser Effect was observed between the methylene protons and the vinylic proton. These facts led to the conclusion that the side-product is the E-isomer. The reason why only in the case of the furaldehyde a side reaction to the S_N2' product was observed, is not clear.

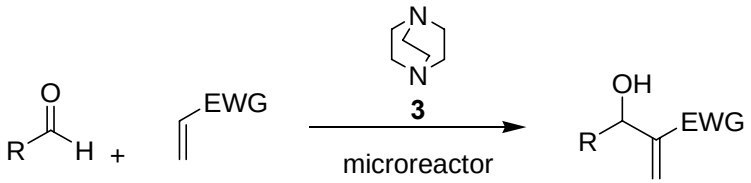


107

Figure 3.6: Methyl (2*E*)-3-(furan-2-yl)-2-hydroxymethyl acrylate **107** as a side-product of the Baylis-Hillman reaction between furaldehyde **1d** and methyl acrylate **2a**.

Generally, it was possible to achieve throughputs of several g/day. In some particular cases, a production rate up to 17 g Baylis-Hillman adduct/day was possible.

Table 3.4: Continuous Baylis-Hillman reaction for different aldehydes and activated alkenes.[a]



1a-f **2a-e** **4a-j**

Entry	*Aldehyde* ***1***	*Alkene* ***2***	*Product*	*Concentration (M)*	*Degree of conversion (mol %)*[b]	*Yield (%)*[c]	*Throughput (g/day)*
1	4-nitrobenzaldehyde	methyl acrylate	**4a**	0.2[d]	93	82	22.4
2	3-nitrobenzaldehyde	methyl acrylate	**4b**	0.2[d]	76	66	18.0
3	2-pyridinecarboxaldehyde	methyl acrylate	**4c**	0.1	97	47	5.2
4	2-furaldehyde	methyl acrylate	**4d**	0.1	52	--	--
5[e]	5-nitro-2-furaldehyde	methyl acrylate	**4e**	0.05	90	52	3.4
6	propionaldehyde	methyl acrylate	**4f**	0.1	68	20	1.7
7	4-nitrobenzaldehyde	acrylonitrile	**4g**	0.2[d]	100	74	17.4
8	4-nitrobenzaldehyde	methyl vinyl ketone	**4h**	0.2[d]	--	13[f]	3.3
9	4-nitrobenzaldehyde	2-cyclohexen-1-one	**4i**	0.2[d]	No reaction		--
10	4-nitrobenzaldehyde	acrylamide	**4j**	0.2[d]	Clogging		--

--: No determination possible. [a] Reaction conditions: ratio aldehyde/DABCO/alkene is 1:1:3; residence time is 1 h 58 min; reaction quenched with HCl (1 N). [b] Based on the integration signals in the ^{1}H-NMR spectrum. [c] Based on total mass of end product collected in the crude mixture and degree of conversion. [d] Aldehyde and DABCO dissolved into a 3:7 (v/v) water/1,4-dioxane mixture; alkene stirred into a 7:3 (v/v) water/1,4-dioxane mixture. [e] Residence time is 26 min. [f] Isolated yield.

Varying the activated alkenes showed a higher variability. In the case of acrylonitrile, a complete conversion was observed and the adduct was obtained without need for further purification. Using methyl vinyl ketone, the end product was detected in the spectra, but due to the presence of various side-products, it was not possible to determine the conversion. After purification by flash chromatography, 13 % of the Baylis-Hillman compound was obtained. With 2-cyclohexen-1-one, no end product was detected at all. Finally, when the reaction was conducted with acrylamide, clogging of the microreactor channels was observed. The reason for this clogging remained unclear. So this procedure is more or less general for a variety of aldehydes, but variation of the alkene was less successful.

3.2.4 Stopped-flow technique

Since the reaction was not completed after the maximal residence time of the microreactor and the reaction profile of the batch process shows that the conversion still increases after 3 h (Figure 3.5), the residence time of the microreactor was increased using the stopped-flow technique. The rationale of this process is to increase the residence time and thus the reaction time, by pausing the pumping at regular time intervals. Recently, other research groups have also successfully applied this technique.[151,158,245,247] To make a decent comparison without making the experiment unnecessarily long, a fivefold increase of the residence time was chosen, so that the ratio of pumping time to pause time had to be 1:4. Also, the pumping interval had to be long enough to ensure a reproducible residence time since the pump does not reach the maximum flow rate immediately. By using a pumping interval of 1 s the influence of the start up of the pump was too big, and a longer residence time occurred due to the lower flow rates (Figure 3.7, upper part). On the other hand, long pause times are disadvantageous because of more diffusion in the longitudinal direction. As a compromise, a pumping interval of 1 min was chosen, to minimise the effect of the startup and to minimise the pause time which was 4 min in this case. Since problems with the reactivity of the methyl acrylate (lower conversions were obtained after 9 h 50 min residence time compared to 1 h 58 min residence time) occurred when the methyl

acrylate-solvent mixture was standing too long before reaction, the mixture was refreshed on a regular basis. Also for previous experiments, the methyl acrylate-solvent mixture needed to be refreshed on a daily basis to avoid lower conversions.

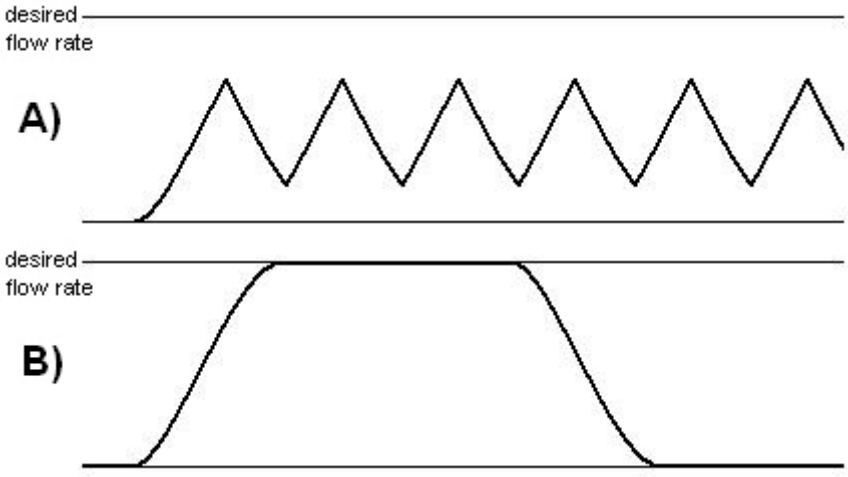


Figure 3.7: Effect of time interval of stop and flow period on the pumping regime (A: suboptimal conditions; B: optimal conditions).

The results of the stopped-flow study are shown in Table 3.5. These data prove that the reactions are still not completed after 2 h of reaction time, since considerable enhancement of conversion and yield can still be achieved. In the case of 3-nitrobenzaldehyde **1b** (entry 2), the conversion to the Baylis-Hillman adduct is doubled at a concentration of 0.05 M. If 2-pyridinecarboxaldehyde **1c** is used (entry 3), even a complete conversion is achieved, although it is obvious that in this case it is not necessary to increase the residence time 5 times since already 97 % conversion is achieved in the normal procedure. Moreover, almost complete conversion is obtained after passing the microreactor alone. The lower conversion in the case of furaldehyde after the stopped-flow is due to the formation of the side-product **107** mentioned in § 3.2.3. When this is taken into account, conversions without or with stopped-flow are respectively 61 and 67 %, which meant only a slight increase.

Thus, by regulating the residence time using the stopped-flow technique, it is possible to drive the Baylis-Hillman reaction to completion in a continuous way. The lower yields are associated with a more difficult work up of the reaction. It must be emphasised that, in this case, this is only a proof-of-concept. Applying these conditions in an industrial scale will not be economically feasible due to the long start up procedure and the lower yield of the experiments. It takes approximately 16 h to reach steady state conditions. A probable solution to the second problem is the use of a 5-way valve and 5 parallel RTUs after the microreactor in order to get a continuous flow instead of a stopped-flow in 80 % of the time (Figure 3.8). Similar solutions are already found in literature.[258]

Table 3.5: Comparison between continuous Baylis-Hillman reaction without or with stopped-flow for different aldehydes.[a]

Entry	*Product*	*Concentration (M)*	*Without stopped-flow*		*With stopped-flow*	
			Degree of conversion (mol %)[b]	*Yield (%)*[c]	*Degree of conversion (mol %)*[b]	*Yield (%)*[c]
1	**4a**	0.2[d]	93	82	99	94
		0.05	57	48	83	87
2	**4b**	0.2[d]	76	66	80	76
		0.05	23	21	45	35
3[e]	**4c**	0.1	97 (66)	47 (30)	100 (89)	51 (50)
4	**4d**	0.1	52	--	39	--

--: Not determined. [a] Reaction conditions: ratio aldehyde/DABCO/methyl acrylate is 1:1:3; residence time is 1 h 58 min without stopped-flow and 9 h 50 min stopped-flow; reaction quenched with HCl (1 N). [b] Based on the integration signals in the ^{1}H-NMR spectrum. [c] Based on total mass of end product collected in the crude mixture and degree of conversion. [d] Aldehyde and DABCO dissolved into a 3:7 (v/v) water/1,4-dioxane mixture; methyl acrylate stirred into a 7:3 (v/v) water/1,4-dioxane mixture. [e] In brackets: results at the microreactor outlet i.e. with a residence time of 3 min (without stopped-flow) or 15 min (with stopped-flow).

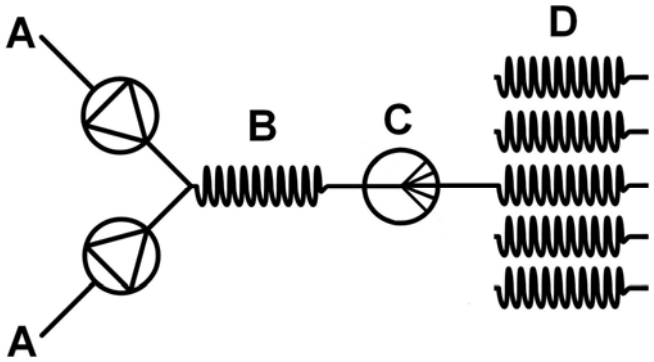


Figure 3.8: Possible setup solution to work with a stopped-flow technique in a continuous way. A = input reagents, B = microreactor, C = 5-way valve, D = parallel RTUs.

3.2.5 Effect of RTU

In many articles it is stated that the high mass transfer in the capillary system is one of the major reasons for the higher reaction rates under microreactor conditions. The question rose if there would be a difference in reaction conversion/output if the system was used as a micromixer instead of as a microreactor. Indeed, if the flow is high enough and the rate small enough, only a small part of the reagents is converted into the end product before leaving the microreactor in the case of a slow reaction. So at higher flow rates, the microreactor only acts as a micromixer while the residence time unit is the real reaction zone of the system. On the contrary, if the flow rate is small enough, mixing and reaction takes place in the microreactor. To check this, it was necessary to select a very fast Baylis-Hillman reaction, because this still takes several minutes to complete. Because the minimum reproducible flow rate of the piston pumps is 0.2 mL/min.pump, the maximum residence time in the microreactor is 3 min. So a reaction which has the biggest increase in conversion between 1 and 5 min was necessary, in order to see the effects. Based on the conditions that were used in the previous chapter, it was found in literature that 5-nitro-2-furaldehyde **1e** reacted very fast with methyl acrylate.[236] To check if this was an appropriate compound to use in this study, a conversion curve was determined. Figure 3.9 shows the result of this

experiment. As shown, complete conversion to the Baylis-Hillman adduct was obtained within 10 min, which made it a suitable reaction to use.

The idea of the experiment was to compare the conversions to the end product with a certain residence time in the microreactor on the one hand and the same residence time in the microreactor and the RTU on the other hand. This meant a flow rate ratio ([microreactor + RTU]/microreactor) of 38.5 was necessary. The results of this study are shown in Figure 3.10.

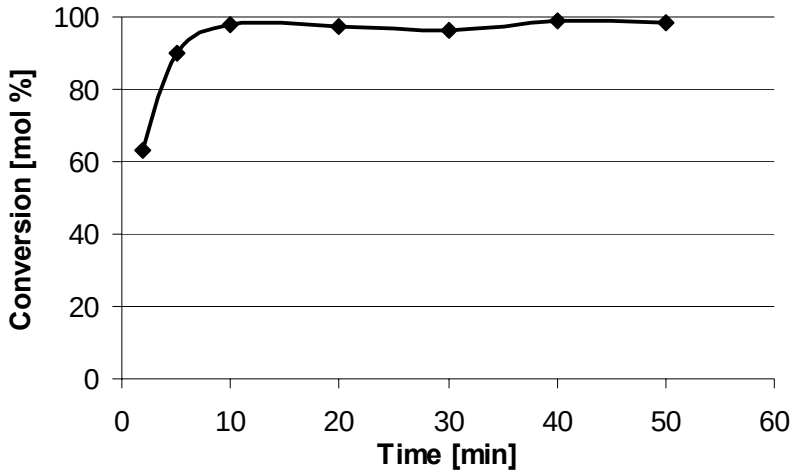


Figure 3.9: Conversion curve of the Baylis-Hillman reaction between 5-nitro-2-furaldehyde **1e** and methyl acrylate **2a** under batch conditions.

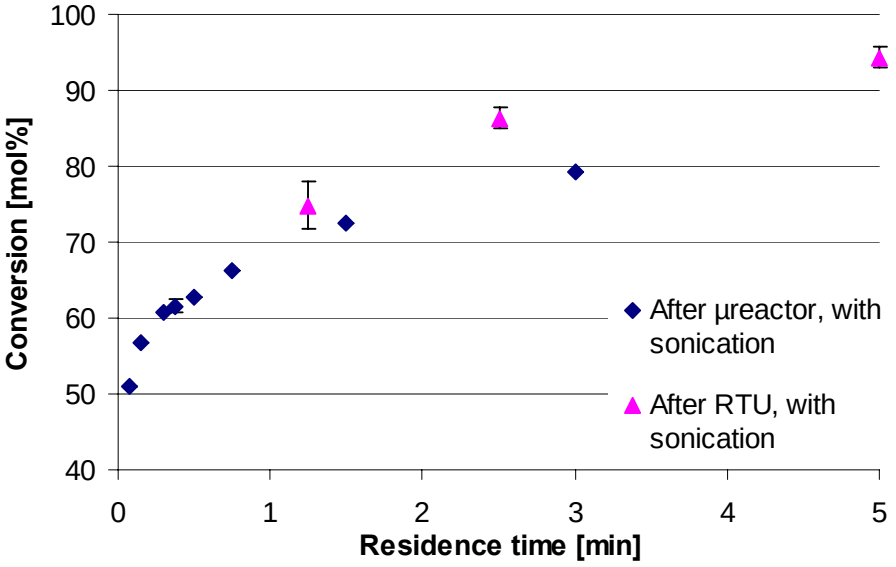


Figure 3.10: Comparison of the conversion to the Baylis-Hillman adduct **4e** with or without the use of the RTU.

In the experiment where the RTU is included, residence times shorter than 1.25 min were not tested because of the high flow rates that are necessary. In the experiments, it is not evident to work accurately at high flow rates and this is seen in the results: higher fluctuations occur in the conversion (see error bars). Furthermore, the results show that there is a difference in conversion between the 2 setups. It was expected that the effect of the microreactor unit would be advantageous, or in the worst case equal, because of two reasons. Firstly, because of the lower flow rate when the experiment was only performed in the microreactor, the reagents stay longer in the microreactor mixing chamber. Secondly, although the flow rate is much higher in the experiment where the RTU is included, there is no expected turbulence (see calculations below). So it was presumed that there will be no extra positive mixing effect and the RTU will only serve to increase the reaction time. However, in the conversion to the Baylis-Hillman adduct, the graph shows opposite results. Indeed, if the RTU is included, the conversion is somewhat higher. Some possible explanations of the opposite phenomenon were suggested, but no decent explanation was found.

1. Effect of turbulence in the RTU.

As already mentioned, there was no expected turbulence in the RTU. As an example, the Reynolds number in the RTU for water as the liquid is calculated (at a temperature of 22 °C, the dynamic viscosity μ_{water} is 0.000955 kg/m.s and the density ϱ_{water} is 997.86 kg/m³). The characteristic properties of 1,4-dioxane are quite close to these of water (at T = 25 °C, $\mu_{1,4\text{-dioxane}}$ = 0.0011795 kg/m.s and $\varrho_{1,4\text{-dioxane}}$ = 1027.97 kg/m³), so it can be assumed that the characteristics of a water/1,4-dioxane (v/v 1:1) mixture are of the same order of magnitude.[259] The RTU consists of a stainless steel tube which is surrounded by another tube wherein the heating or cooling medium flows. Measurement of the tubing gives a total length of approximately 3.14 m. It is known that the inner volume of the RTU is 45 mL. This gives a flow cross-section of approximately 1.43 x 10^{-5} m². The characteristic length L_{char} of a tube is known as the inner diameter of that tube. This gives a L_{char} of 4.27 x

10^{-3} m. The Reynolds numbers at some flow rates are calculated in Table 3.6 according to the following formula:

$$Re = \frac{\varrho \cdot v_s \cdot L_{char}}{\mu} \qquad (3.1)$$

with Re = Reynolds number (-)
ϱ = fluid density (kg/m³)
v_s = mean fluid velocity (m/s)
L_{char} = characteristic length (m)
μ = dynamic fluid viscosity (kg/m.s)

Calculations of the Reynolds number gave a value of around 50 in the case the residence time was around 5 min in the microreactor + RTU (flow rate of 4.7 mL/min.pump). This is far from the turbulence region which starts approximately at a value of 3500 for Re. Moreover, the mixing seems not to be of importance for the Baylis-Hillman reaction (*vide supra*, § 3.2.2.4).

Table 3.6: Estimated Reynolds numbers in the RTU at different flow rates.

Flow rate (mL/min.pump)	*Mean fluid velocity (m/s)*[a]	*Re (-)*
0.2	4.7×10^{-4}	2
0.4	9.3×10^{-4}	4
1.0	2.3×10^{-3}	10
4.7	1.1×10^{-2}	49
9.4	2.2×10^{-2}	98
18.8	4.4×10^{-2}	196

[a] To calculate the mean fluid velocity, the flow rate has to be doubled, since the microreactor has 2 inlets.

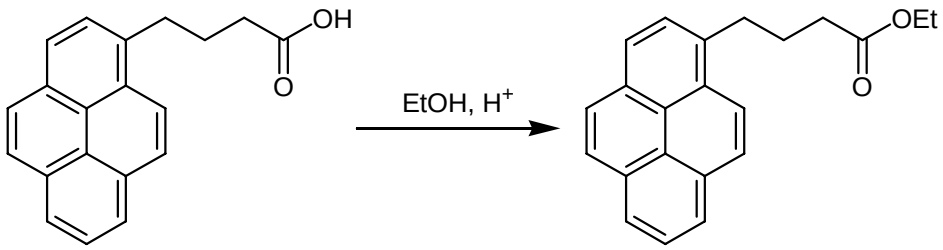
2. Clogging of a part of the microreactor.

It was suggested that if a part of the microreactor was clogged (e.g. 1 of the 4 channels), the pumped volume has to flow through 75 % of the reactor, which means a decrease in residence time by 25 %. In the case of the

microreactor, this means a significant reduction in residence time, while in the case the reaction is flown through both the microreactor and the RTU, there will be only a small difference. According to literature, a difference in channel diameter has only little influence on microreactor performance in a homogeneous reaction.[260] In these calculations however, the assumption was made that the number of channels was large (i.e. more than 30) which is not the case here. Therefore, a similar experiment was performed using the optimised α-aminophosphonate synthesis (*vide infra*, § 3.4.2). No differences occurred here, which proved that this was not a microreactor defect. Interestingly, this also meant that the effect was reaction dependent.

3. Negative surface effect.

Because of the reaction dependence, a surface effect was also considered, conform a positive surface effect already mentioned in the literature. In an acid-catalysed esterification reaction (Scheme 3.5), it was proven that the interaction of the silanol groups of the glass microchip were the reason for the higher and faster conversion observed. The acid was responsible for the activation of the glass surface hydroxyl groups.[261]



108 **109**

Scheme 3.5: Acid-catalysed esterification of 9-pyrenebutyric acid **108**.

In our specific case, the contact area with the surface in the RTU is lower (due to a lower surface-to-volume ratio). Moreover, the conversions in the experiment where the RTU is included are higher. Combining these findings means that if there is a surface effect on the reaction, this should be a negative one. However, intense study of the literature concerning possible

negative effects of the stainless steel inner structure[9] did not bring a possible explanation.

4. Effect of the flow rate.

A final hypothesis included an increase in conversion due to the higher flow rate. However, this is normally due to a better mixing performance.[107,110] The main difference between both setups was the high difference in flow rate. It was suggested that there was a positive influence of the flow rate on the conversion of the Baylis-Hillman reaction, conform positive effects on the selectivity observed by some researchers[108,109]. Unfortunately, this could not be tested due to the static setup of the system.

3.2.6 Comparison of 2 types of microreactor setup

During the last 2 decennia, many different types of microreactors are developed for organic chemistry.[40,46,48,54,107] They all have different properties and some of them are developed for specific purposes like research of microfluidics, optimisation studies or industrial applications to name a few. An overview of some providers of microreactor systems is given in Table 3.7.

Comparisons between microreactors were already made concerning mixing performance[100,262,263] or for selection in a pilot plant[136]. In this chapter, a comparison was made between 2 types of microreactor in their use for the Baylis-Hillman reaction. The first microreactor was the commercially available CYTOS® College System. The second microreactor was a 1-line chip produced at the MESA+ Institute for Nanotechnology at the University of Enschede, Twente, The Netherlands. Some properties of both microreactors are given in Table 3.8.

[9] The stainless steel is from the type 1.4571 (German standard) which has the following composition: 0.08 wt% C, 17 wt% Cr, 12 wt% Ni, 2 wt% Mo, 0.6 wt% Ti.

Table 3.7: Commercially available microreactors.[a]

Supplier	*Material*	*Microreactor types*
Synthacon and Micro-Reactor Systems Provider, Inc. (in collaboration with CPC-Cellular Process Chemistry Systems GmbH)	Stainless steel	CYTOS® Lab System, SEQUOS®, OPTIMOS™
Microinnova Engineering GmbH (in collaboration with IMM)	Stainless steel	Slit Interdigital Mixer, Caterpillar Mixer, Star Laminator
Syrris	Glass	FRX™ system, AFRICA® system
Ehrfeld Mikrotechnik BTS	Stainless steel	Modular microreaction systems
Micronit Microfluidics BV	Glass	Microreactor chips (standard or design)
Dolomite Centre	Glass	Design of devices
INI Power Systems™	Polymer	Laminar Flow Fuel Cell (LFFC®)
ThalesNano, Inc.	Stainless steel	CatCart™, H-Cube™, X-Cube™
Siemens	Stainless steel	SIPROCESS
Systanix, Inc.™	Unknown	SysFlo
Uniqsis Ltd.[b]	Unknown	Unknown

[a] A wide variety of other microreactors is available. Only commercial manufacturers are mentioned in this table. Other research groups specialised in the design of microreactors are e.g. the Forschungszentrum Karlsruhe (FZK), the Department of Chemistry at the University of Hull and the Department of Chemical Engineering at the Massachusetts Institute of Technology. [b] Uniqsis Ltd. was formed in January 2007 by Asynt Ltd. and Grant Instruments Ltd. to develop innovative microreaction technology products for customers in both the research and biopharmaceutical sector. Specific information is not available yet.

Table 3.8: Properties of the 2 microreactors used in this study.

Property	*CYTOS®*	*1-line chip*
Material	Stainless steel	Silicon-glass
Channel width (μm)	200-500	50
Internal volume (mL)	1.2	2.18-2.26 x 10^{-3}
Mixing	Interdigital	Modified Tesla-mixer
Quenching	External	Internal

The same starting reagents were used as in § 3.2.5. Since the experiments in the second type of microreactor were done with an output of 10 μL samples, because otherwise the sampling time was too long, it was necessary to find an appropriate analytical method in order to compare the results. A very convenient method for the reaction follow up is UV spectrometry. Unfortunately, because the absorption maxima of the 2 products were too close to each other (5-nitro-2-furaldehyde **1e**: 301 nm; Baylis-Hillman adduct **4e**: 313 nm), this was not an option. Another method was the use of GC-analysis. Because the reaction was done in a solvent mixture containing water, a preliminary extraction was needed, before analysing the sample.

Some initial experiments using the 1-line chip showed problems of bubble formation in the microchannels. This was not allowed, since no reproducible residence time could be achieved. A procedure to prevent this consists in sonicating the reaction mixture prior to use in the microreactor setup. In literature, some rate enhancement is observed when ultrasound is used while performing the Baylis-Hillman reaction.[180,189] However, this was on the complete reaction mixture instead of the separated reagent mixtures. Although the bubble formation was never observed in the CYTOS® College System[10], it was decided to test if the sonication had an effect. According to the results presented in Figure 3.11, there was an effect noticed in the initial stage of the reaction and at high conversions. Between 60 and 70 % conversion, the ultrasound effect was minimal.

[10] It must be mentioned that in the CYTOS® College System no observation of the inner part of the microreactor is possible. However, there were never bubbles observed in the PTFE tubes at the outlet of the system.

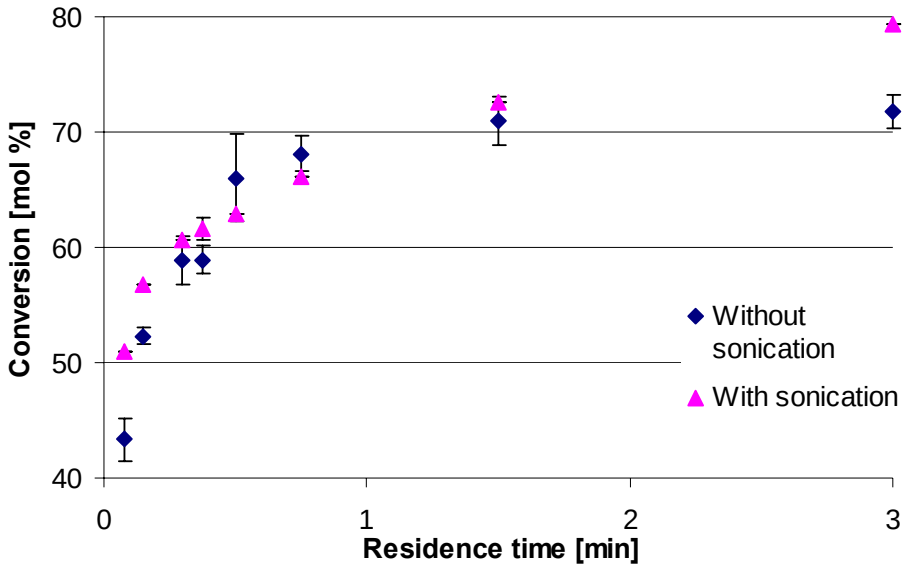


Figure 3.11: Effect of sonication of the reagent solutions on the conversion to the Baylis-Hillman adduct **4e** (CYTOS® College System).

In this and further experiments, 5-nitro-2-furaldehyde **1e** was mixed with methyl acrylate **2a** instead of with the catalyst, as in previous experiments. There were 2 reasons for doing this. Mixing 5-nitro-2-furaldehyde and DABCO provided a dark brownish to black mixture, which made it impossible to see if, in the case of the microreactor chip, clogging occurred or not. Secondly, using ultrasound on the mixture showed already 85 % conversion within 30 seconds in the case DABCO was mixed with 5-nitro-2-furaldehyde and then reacted with methyl acrylate in the microreactor (Figure 3.12), which makes it difficult to compare between the microreactors in further stages, because of the high rates. As previously seen in § 3.2.2.3, mixing methyl acrylate and DABCO was not an option due to the betaine formation and consequently the very low conversion. The only option left was mixing 5-nitro-2-furaldehyde and methyl acrylate. Comparing both figures shows the significant effect of the order of mixing of the reagents, prior to addition to the microreactor, on the conversion. In the case the experiment was repeated, the error bars are added. Calculation of the relative standard deviations showed that, with a few exceptions, this value stayed below 5 %. In the few exceptions, the relative standard deviations also stayed below 10 %. Due to this good reproducibility when performing the same experiment, it was not necessary to repeat every experiment.

Using these reaction conditions, a comparison of the conversion towards the Baylis-Hillman adduct was made between the 1-line chip, the CYTOS® microreactor and the round bottom flask. Some remarkable results were observed (Figure 3.13). The highest reaction rate was observed in the batch procedure. After 15 seconds, already 70 % of the end product was detected. In the microreactors it took between 1 min and 1.25 min to achieve 70 % conversion, with a better performance in the CYTOS® microreactor. Moreover, both microreactors reach a plateau around 70-75 % conversion, while the conversion in the batch procedure further increases.

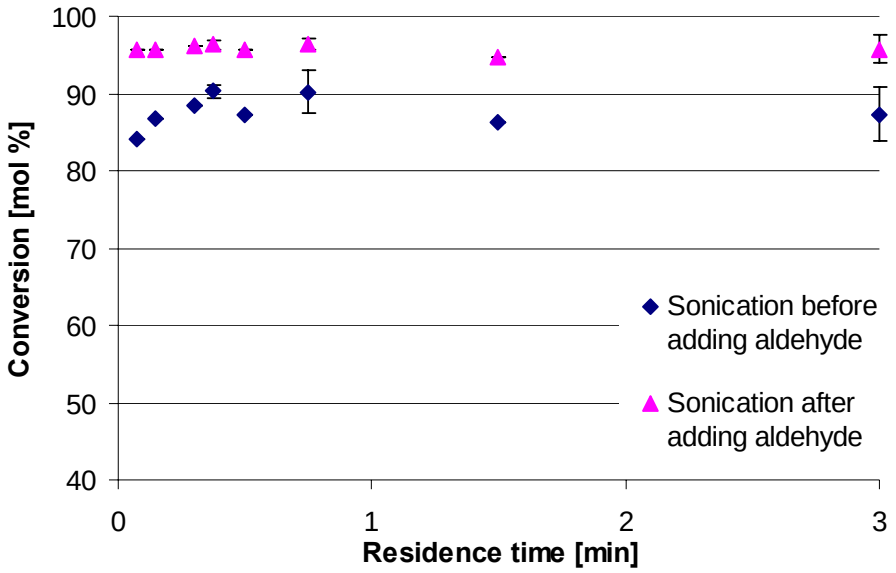


Figure 3.12: Conversion to the Baylis-Hillman adduct **4e** after mixing 5-nitro-2-furaldehyde **1e** with DABCO **3** and using different pre-treatments (CYTOS® College System).

Conversion curves using different reagent ratios in the 1-line chip were also determined (Figure 3.14). As previously seen, the same trends were visible. Without an excess of methyl acrylate, the conversion was significantly low. The switch towards a catalytic amount of DABCO however had an even more pronounced negative effect on the conversion. Interesting to note is the rate enhancement between 0.8 and 1.3 min residence time in the 2 upper curves. This can be seen by the steeper curve. All the experiments have more or less the same initial reaction rate. In the case of the experiment with the

catalytic amount of DABCO, there is a higher probability to form the stable betaine after some time, which leads to a stagnation of the conversion.

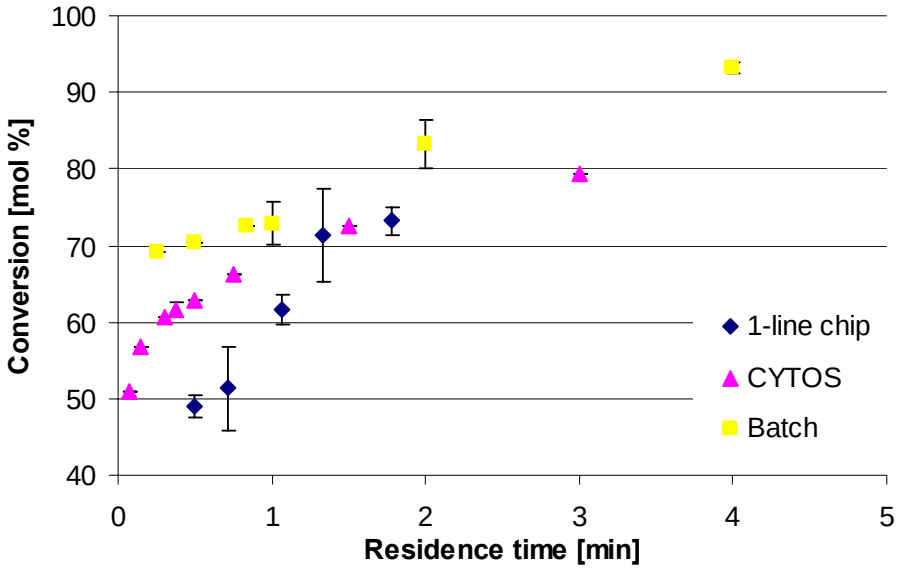


Figure 3.13: Comparison of a conventional batch procedure with 2 different microreactor setups to form Baylis-Hillman adduct **4e**.

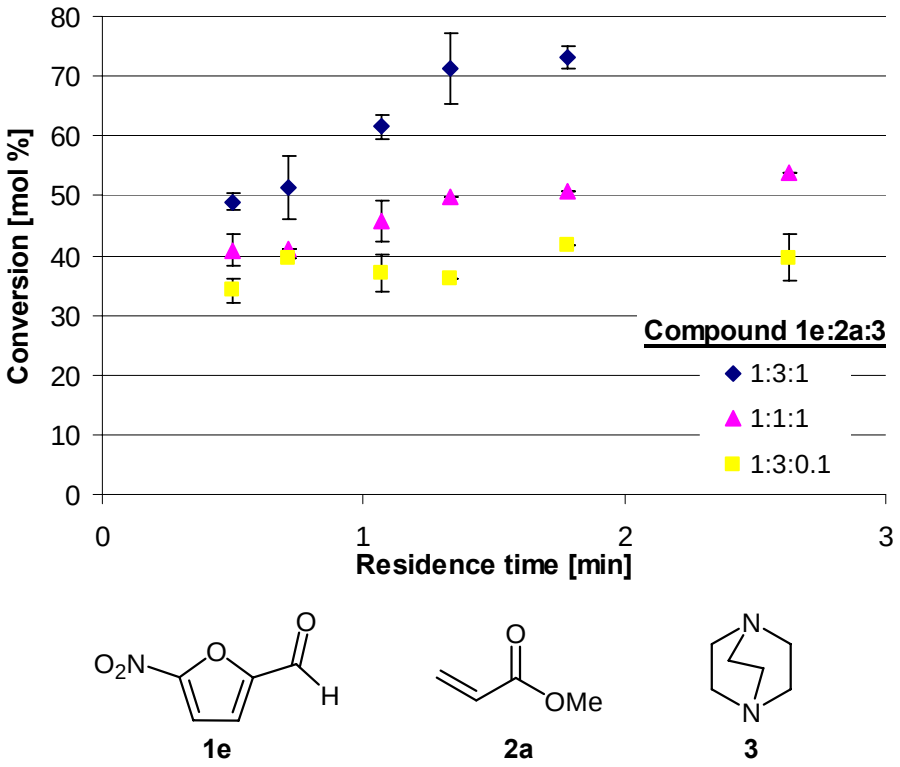


Figure 3.14: Conversion to the Baylis-Hillman adduct **4e** under different reaction conditions using the 1-line microreactor chip.

Thus, after some modifications it was possible to compare 2 types of microreactors with the batch procedure. Although otherwise expected, the reaction performed better under batch conditions. Probably, a similar explanation as in § 3.2.2.4 lies at the basis of these results: the intensity of mixing of the reagents seems not to be important in achieving higher conversions and yields.

3.2.7 Investigation of the aza-Baylis-Hillman reaction

The aza-Baylis-Hillman reaction is even more interesting due to the formation of β-amino-α-methylene functionalised compounds.[207,264-266] This allows the formation of e.g. β-amino acids.[267,268] β-Amino acids occur in nature both in free form and in peptides. The corresponding β-peptides have been thoroughly investigated due to there specific properties, of which the most important ones are the stability of β-peptides towards cleavage by peptidases and to metabolic transformations, their specific folding to form secondary structures in solution with short chain lengths and their possibility to mimic α-peptides in peptide-protein and protein-protein interactions.[269]

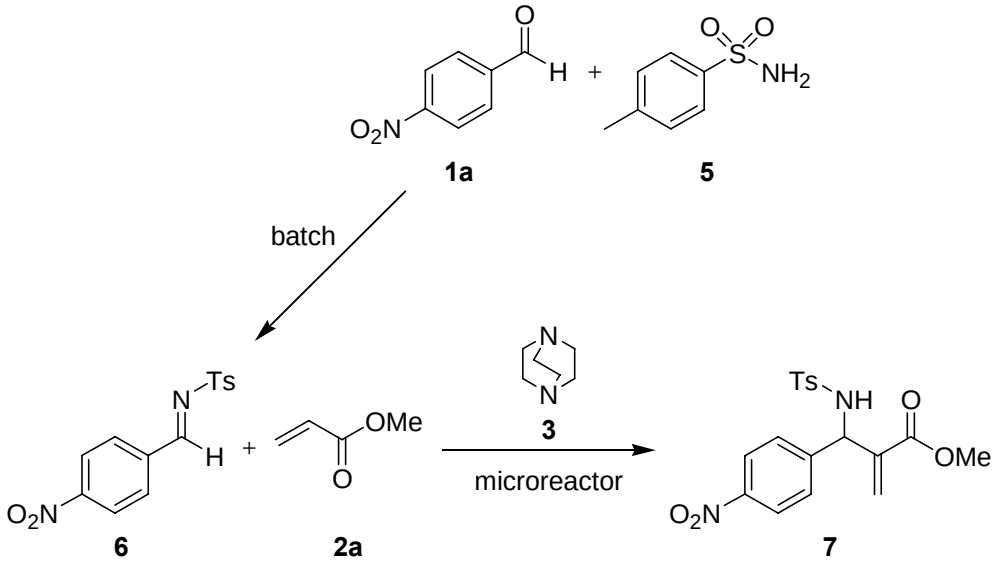
In this doctoral thesis, several attempts were made to optimise a procedure to produce aza-Baylis-Hillman adducts in a continuous manner. Some initial batch experiments were started from a known procedure, which used 2-propanol as the solvent.[268] These initial experiments showed already that 2-propanol could not be used in the microreactor, because of the insolubility of the 4-nitrobenzaldehyde in it, even at very low concentrations. Moreover, the selectivity appeared to be low in the batch reactions, although otherwise mentioned in the literature[269].[11] The selectivity to the aza-Baylis-Hillman adduct *versus* the Baylis-Hillman adduct was around 40-45 % in our experiments. Therefore, further attempts to produce the aza-Baylis-Hillman adducts used the imine compound 4-methyl-N-(4-nitrobenzylidene) benzenesulfonamide **6**, made *via* a known procedure.[270] Several solvents,

[11] Correspondence with the authors learned that in the literature procedure, the aldehyde and the amine were stirred in advance to form the imine. Then the methyl acrylate was added to react to the aza-Baylis-Hillman adduct. This explained the high selectivities of 78 to >99 %.

such as methanol, dichloromethane and DMF, were tested in batch to use in the microreactor procedure. DMF was the solvent of choice since all the reagents were easily dissolved in this solvent and complete conversion occurred after 2 hours of reaction, while in the other solvents there was still 20-30 % of imine left.

Table 3.9 shows the outcome of the aza-Baylis-Hillman adduct formation under microreactor conditions. Several attempts were made and the different tested reaction conditions gave more or less the same result. In the case that the imine **6** was mixed with DABCO before adding to the microreactor (entry 1), a low conversion of 35 % was realised. The unreacted imine was further hydrolysed during the quenching and the work up and both the aldehyde and the amine were detected in the ^{1}H NMR spectrum. In order to increase the conversion to the aza-Baylis-Hillman product, other reaction conditions were tested. Unexpectedly,[249,250] decreasing the temperature to -15 °C had no advantageous effect on the conversion (entry 2). Interesting to note is the fact that there is no decrease in conversion when DABCO is mixed with methyl acrylate (entry 3), although this was expected according to the results obtained in the previous studied Baylis-Hillman reaction (*vide supra*, § 3.2.2.3). In view of the formation of the betaine (Scheme 3.4), which acts as a competing factor for the formation of the Baylis-Hillman adduct, water is needed for the hydrolysis of the ester. In this case however, dry reaction conditions are used, so probably no formation of the stable betaine is possible which could explain why there is no negative effect on the conversion to the aza-Baylis-Hillman adduct. In a final experiment, the highest possible imine concentration in DMF was used (entry 4). This afforded an increase in conversion, but after work up, the yield stayed approximately the same. In all the reactions performed, no Baylis-Hillman product was detected in the reaction mixture using the microreactor procedure, which meant that no hydrolysis of the imine occurred during the reaction. On the contrary, in the batch procedure, performed under the same conditions as entry 1, 5 % Baylis-Hillman adduct was detected.

Table 3.9: Aza-Baylis-Hillman reaction of imine **6** and methyl acrylate in continuous mode using DABCO as a catalyst in dry DMF as solvent.[a]



Entry	*Imine **6** (M)*	*DABCO (M)*	*Methyl acrylate (M)*	*T (°C)*	*Degree of conversion (mol %)*[b]	*Yield (%)*[c]
1	**0.05**	**0.05**	0.15	RT	35	29
2	**0.05**	**0.05**	0.15	-15	31	27
3	0.05	**0.05**	**0.15**	RT	33	30
4	**0.075**	**0.075**	0.225	RT	46	30

[a] Residence time: 1 h 58 min; products in bold are mixed together before they enter the microreactor system; concentration of the reagents as in the reactor; reaction quenched with HCl (1 N). [b] Based on the integration signals in the ^{1}H-NMR spectrum. [c] Based on total mass of end product collected in the crude mixture and degree of conversion.

3.2.8 Conclusions

It was possible to produce comparable results under continuous conditions with those from batch procedures after optimisation. In the specific Baylis-Hillman reaction studied, a reduction of the reaction time by approximately 30 % was accomplished. The best conditions were obtained using water/1,4-dioxane (v/v 1:1) as a solvent at room temperature using a 1:1:3 ratio of aldehyde, DABCO, and methyl acrylate and a concentration of 0.2 M of 4-nitrobenzaldehyde in the microreactor. To work with these high

concentrations, the solvent mixture had to be adjusted properly. In this optimised procedure, a throughput of 22 g/day Baylis-Hillman product was achieved.

Using a stopped-flow regime, the Baylis-Hillman reaction can be forced to completion, although this had as a consequence a significant decrease in output. Further study of this reaction showed that there was an effect of the microreactor setup, which was probably due to a flow rate effect on the Baylis-Hillman reaction. A final comparison between 2 different microreactors and the batch procedure showed that the batch procedure performed best, followed by the CYTOS® College System.

The study of the aza-Baylis-Hillman reaction yielded some disappointing results. Preforming the imine was necessary to avoid competition with the Baylis-Hillman adduct formation and only a maximal conversion of 46 % was achieved.

3.3 IMIDAZOLE SYNTHESIS

3.3.1 Introduction

The imidazole core is an important unit in heterocyclic chemistry.[31] It occurs in different natural products and in a variety of synthetic compounds. Some examples of imidazole-containing compounds in living organisms are the essential amino acid histidine **110** and histamine **111** (Figure 3.15). Different imidazoles show biological activities such as anti-inflammatory activity inhibiting cytokine release or inhibiting the p38 MAP kinase,[271-278] anti-allergic activity[279] and analgesic activity[280]. They are also sensitisers of multi-drug-resistant cancer cells,[281] pesticides,[282-284] antibiotics[285] or sodium-channel modulators[286,287]. Recently, neurodazine **112,** an imidazole that is able to induce neuro-specific activity in mouse myoblasts and in human muscle tissue, was discovered.[288]

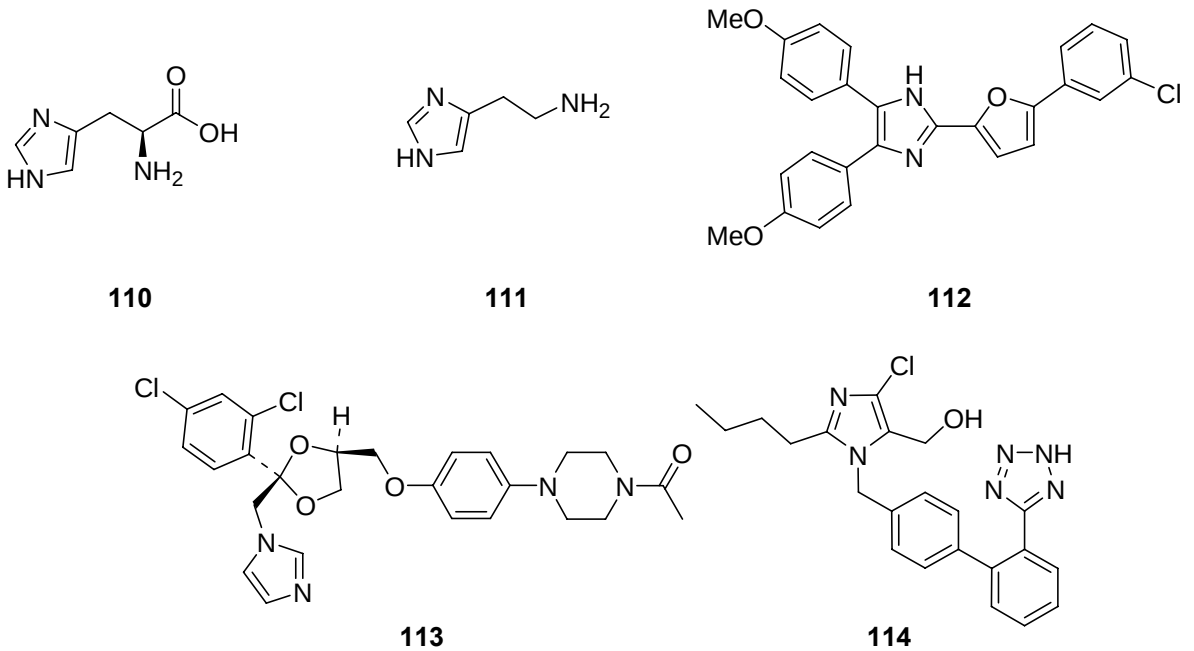
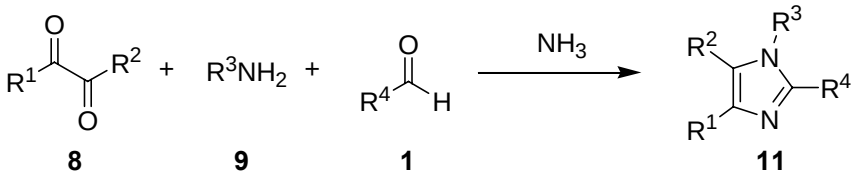


Figure 3.15: Some natural and synthetic imidazole containing compounds.

Known imidazole based drugs are ketoconazole **113**, which has antifungal properties, and losartan **114**, a drug against hypertension (Figure 3.15). More recently, interest in imidazoles is increasing due to applications as green solvents by means of ionic liquids[289,290] and in organometallic chemistry as

N-heterocyclic carbenes[291-295]. Imidazole was firstly prepared in 1858 from glyoxal and ammonia,[296] and the scope was broadened in 1974[297]. Ever since, many procedures have been developed to generate a broad range of differently substituted imidazoles.[298-302]

Although there is a wide variety of synthetic routes towards imidazoles, only a few studies exist for the synthesis of 1,2,4,5-tetrasubstituted imidazoles which are mostly obtained *via* multistep routes[274,276,277,303-308] or *via* a trisubstituted 1*H*-imidazole in which the nitrogen is substituted in the final step[280,309]. Several MCRs have been developed towards the efficient construction of imidazole scaffolds.[281,310-314] However, the reported MCRs often make use of solid-supported reactants which make these procedures not suitable for continuous multigram-scale production under microreactor conditions. Recently, a solution-phase MCR procedure based on a modified[29,30] Radziszewski[32] reaction under microwave conditions has been developed, in which an α-diketone **8**, an amine **9** and an aldehyde **1** react with ammonia to form a tetrasubstituted imidazole **11** (Scheme 3.6). Although a promising approach, scale up of this four-component condensation under microwave conditions is not trivial and multigram production of the desired imidazoles is not straightforward. The similar batch reaction to form tri- or tetrasubstituted imidazoles without microwave heating was very slow,[315] although starting from benzoin, good results were obtained.[316] This led us to study the potential of the microreactor concept towards a continuous production of tetrasubstituted imidazoles.

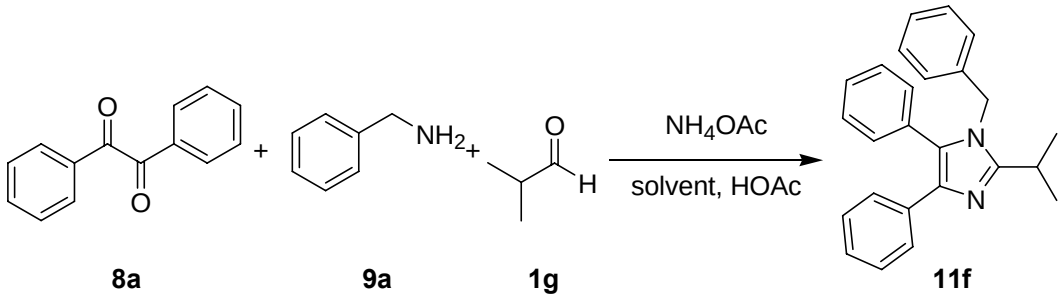


8 **9** **1** **11**

Scheme 3.6: The modified Radziszewski reaction.

3.3.2 Optimisation study using microreactor technology

The one-pot reaction of benzil **8a**, benzylamine **9a**, isobutyraldehyde **1g** and ammonium acetate under acidic conditions to give imidazole **11f** was used to optimise the four-component condensation in the microreactor environment (Scheme 3.7). Similar compounds appeared to have antinociceptive and anti-inflammatory properties.[317] Although the exact reaction mechanism is not yet fully understood, it is believed that the reaction proceeds *via* initial imine formation followed by cyclocondensation-aromatisation with the concomitant loss of two molecules of water (Scheme 3.8).[29] The main side-product produced proved to be the trisubstituted imidazole **11'd** (Figure 3.16), formed by the incorporation of two moles of NH_4OAc (as a source of NH_3) instead of benzylamine.



Scheme 3.7: The modified Radziszewski reaction, used for the optimisation study.

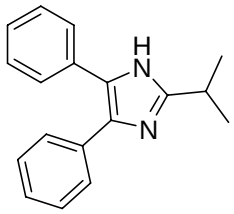
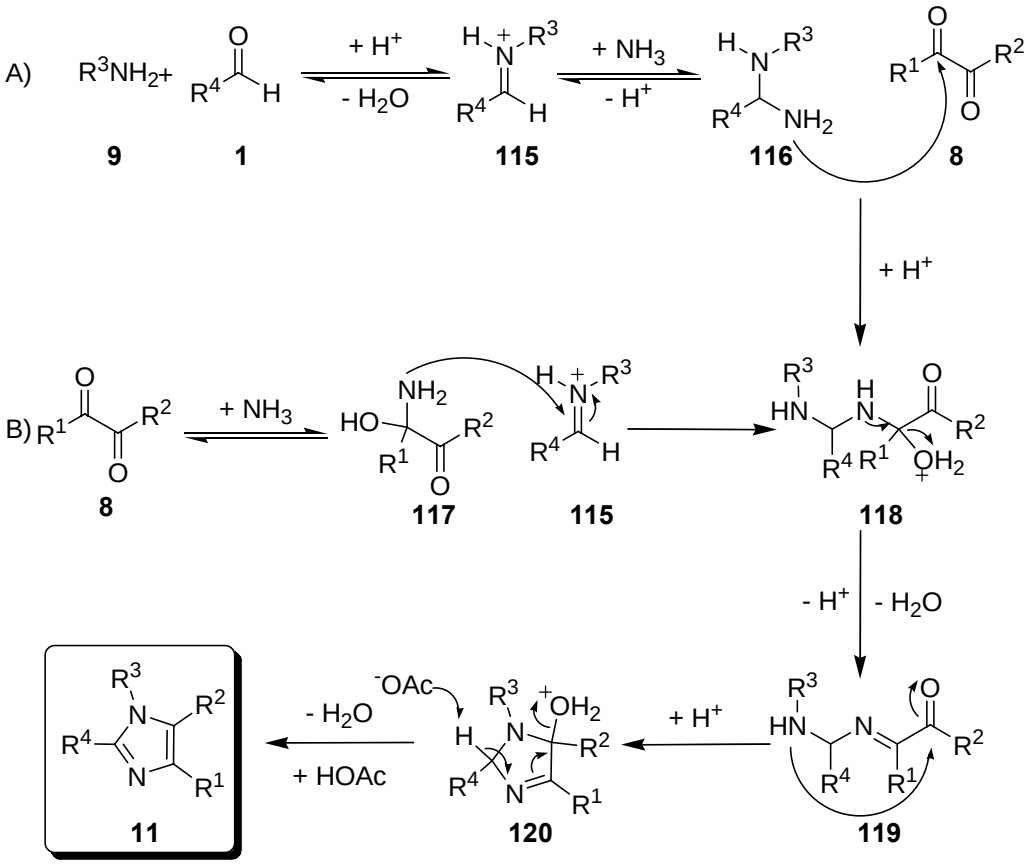


Figure 3.16: The main side-product of the tetrasubstituted imidazole formation.

First, different solvents or solvent mixtures were evaluated, since handling of solids in this type of microreactor is disfavoured. Thus, the maximal concentration of the reagents was dictated by the solubility of NH_4OAc in the reaction solvents, since this was in general the least soluble reactant. The

relative ratios of the reactants were based on the reaction procedure described for the microwave-assisted modified Radziszewski imidazole formation.[29] Since only two inlets are available in the microreactor system, reactants were pre-mixed pair-wise before entering the microreactor. In order to avoid imine formation in advance, which seems essential to the reaction mechanisms, benzil **8a** and isobutyraldehyde **1g** were supplied simultaneously *via* one inlet, while benzylamine **9a** and ammonium acetate were added simultaneously *via* the other inlet.



Scheme 3.8: A proposed mechanism of the 4-CR imidazole synthesis.

Table 3.9 shows the results of this first screening. It must be emphasised that the maximum reaction temperature in a given solvent needs to be 10 °C below the boiling point of the reaction mixture. Otherwise, gas-bubble formation in the system occurs, resulting in unequal residence times. Based on the literature methods,[30,313,318] first acetic acid was chosen as the solvent. Entry 1 shows little conversion and mainly the starting products benzil **8a** and benzylamine **9a** were recuperated. Only an experiment at 50 °C was evaluated

since corrosive effects of HOAc to the stainless steel material of the microreactor could not be fully excluded.[12]

Table 3.9: Distribution of the end products during the screening for the appropriate solvent.[a]

Entry	*Solvent*	*T (°C)*	*Starting material* ***8a*** *(%)*[b]	***11f*** *(%)*[b]	***11'd*** *(%)*[b]	*Selectivity (%)*	*Other (%)*[b]
1	HOAc	50	46	10	0	100	26[f], 12[g]
2[c,d]	DMF/ *n*-butanol	90	26	28	13	68	13[h], 4[i]
3[c,d]	DMF/ *n*-butanol	100	23	34	20	63	11[h], 4[i]
4[c,d]	DMF/ *n*-butanol	120	11	39	28	58	10[h], 2[i]
5[d,j,k]	DMF/ *n*-butanol	120	25	30	17	64	11[h], 4[g], 4[i]
6[c]	DMSO	140	5	29	34	46	6[g], 15[i]
7[c]	DSMO	160	9	25	39	39	8[g], 3[i]
8[c]	DMSO	160	2	21	30	41	31[g], 13[i]
9[e]	DMSO	160	5	26	34	43	27[g]
10[d,e]	DMF/ *n*-butanol	90	28	48	4	92	4[h], 3[i]

[a] Residence time: 118 min; inlet A: 0.5 M of benzil and 0.5 M of isobutyraldehyde; inlet B: 0.5 M of ammonium acetate and 0.6 M of benzylamine. [b] Based on the crude reaction mixture after GC analysis. [c] 2 equiv of acetic acid. [d] Products of inlet A are dissolved in DMF and products of inlet B in *n*-butanol. [e] 10 equiv of acetic acid. [f] Benzylamine. [g] Unidentified product(s). [h] N-benzylformamide. [i] N-(benzylidene) benzylamine. [j] 4 equiv of acetic acid. [k] Use of imine instead of aldehyde and amine.

Then, higher boiling solvents were tested: *n*-butanol (bp = 116-118 °C), DMF (bp = 153 °C) and DMSO (bp = 189 °C). Because benzil **8a** does not dissolve in *n*-butanol and NH_4OAc does not dissolve in DMF, a mixture of these solvents was evaluated. Moreover, it is known that, compared to methanol as the solvent, *n*-butanol and also ethanol have a positive effect on

[12] This was based on the chemical resistance chart of the CYTOS® College System provided by CPC - Cellular Process Chemistry Systems GmbH.

the formation of some imidazoles starting from glyoxal instead of an α-diketone.[319]

Using the solvent systems n-butanol/DMF or DMSO, the effect of the temperature on the conversion was studied (Table 3.9, entries 2-4, 6 and 7). While at 90 °C there is still 26 % of benzil in the reaction mixture, an increase of the temperature to 140 °C shows only 5 % of benzil after 2 h of reaction. A problem occurring in both solvent systems, is the lack of selectivity and a tendency towards the formation of trisubstituted imidazole **11'd** (no substituent on the nitrogen) was observed. This tendency was even stronger when DMSO was used as the solvent. Although previously stated that the working temperature has to be 10 °C lower than the boiling point of the solvent, one experiment was done near the boiling point temperature of *n*-butanol (entry 4). In this experiment, a PRV was placed at the outlet of the microreactor in order to increase the boiling point of the solvent. It was observed that using a PRV in combination with the low flow rate of the pumps (in this case: 0.2 mL/min.pump), the residence time was not maintained. In order to keep the residence time constant, experiments with the PRV were done at higher flow rates, in combination with a stopped-flow regime. In this experiment, a little increase in conversion was observed. However, because the used pumps were not able to handle an increased pressure continuously and because there was only little increase in conversion, no further experiments were performed using this setup.

Since using acetic acid as the solvent (Table 3.9, entry 1) gave no trisubstituted imidazole **11'd**, it was thought that increasing the amount of acetic acid in the reaction mixture would be advantageous towards selectivity. Some experiments were repeated but now with a higher amount of acetic acid, i.e. 10 equivalents instead of 2 equivalents. When these conditions were applied using the DMF/*n*-butanol mixture (e.g. compare entries 2 and 10 of Table 3.9) it was shown that a fivefold increase of the acetic acid concentration gave a sixfold increase in selectivity towards the desired tetrasubstituted imidazole product. The GC-analysis of the crude reaction mixtures shows clearly the effect on the selectivity (Figure 3.17). This effect

on selectivity was already observed at a slight increase of acetic acid (entry 5). An excess of ten equivalents was therefore used for further optimisation. When the same experiment was conducted in DMSO, no selectivity increase occurred however (entry 7 and 9), which meant that besides the acid increase, also the solvent plays an important role in the selectivity issue. In one experiment, the order of mixing was changed: the α-diketone was combined with ammonium acetate, while the amine and the aldehyde were mixed together (entry 8). As a result, a higher amount of side-product formation was observed and the selectivity stayed the same. Further experiments focussed on the mixture of the aldehyde and the α-diketone.

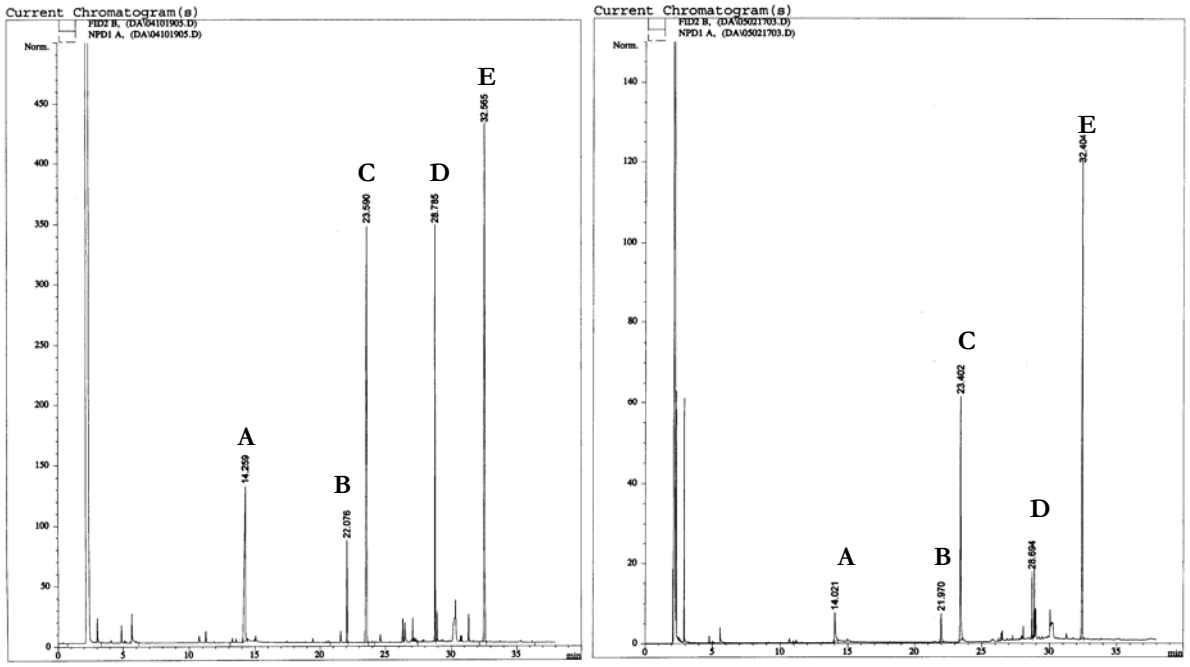


Figure 3.17: GC-analysis showing the effect of the amount of acetic acid on the selectivity towards tetrasubstituted imidazoles (Left: 2 equiv, Right: 10 equiv, A = N-benzylformamide, B = N-(benzylidene)benzylamine, C = benzil, D = trisubstituted imidazole, E = tetrasubstituted imidazole).

Table 3.10: Distribution of the end products of the imidazole MCR during temperature optimisation.[a]

Entry	*Solvent*[b]	*T (°C)*	*Starting material* ***8a*** *(%)*[c]	***11f*** *(%)*[c]	***11'd*** *(%)*[c]	*Selectivity (%)*	*Other (%)*[c]
1	DMF/ *n*-butanol	90	28	48	4	92	4[f], 3[g]
2[j]	DMF/ *n*-butanol	90	42	32	3	91	5[f], 4[g], 5[h]
3[d]	DMF/ *n*-butanol	90	16	53	6	90	11[f], 6[h]
4	**NMP/ *n*-pentanol**	**120**	**10**	**79**	**6**	**93**	**5[h]**
5[d]	NMP/ *n*-pentanol	120	6	75	7	91	4[h], 6[i]
6[e]	NMP/ *n*-pentanol	115-135	11	65	5	93	6[i]
7	NMP/ *n*-hexanol	130	11	74	1	99	6[i]
8	NMP/ *n*-hexanol	140	8	72	5	94	9[i]
9	NMP/ *n*-octanol	160	11	54	7	89	13[i]

[a] Residence time: 118 min; inlet A: 0.5 M of benzil, 0.5 M of isobutyraldehyde and 2.5 M of acetic acid; inlet B: 0.5 M of ammonium acetate, 0.6 M of benzylamine and 2.5 M of acetic acid. [b] Products of inlet A are dissolved in DMF or NMP and products of inlet B in the primary alcohol. [c] Based on the crude reaction mixture after GC analysis. [d] fivefold residence time i.e. 9 h 50 min. [e] Batch procedure (*vide infra*, § 4.4.1). [f] N-benzylformamide. [g] N-(benzylidene)benzylamine. [h] Unidentified product(s). [i] N-benzylacetamide. [j] Use of imine instead of aldehyde and amine.

Table 3.9 and 3.10 also give the major side-products, in addition to the trisubstituted imidazole. Some of the side-products were identified *via* GC-MS analysis. In the case of the DMF/*n*-butanol mixture, N-benzylformamide was detected which is formed from benzylamine and DMF. N-(benzylidene)benzylamine was also frequently detected but the origin of this product is unclear. Probably the benzil was decomposed to benzaldehyde, which in turn was then converted to the imine. Literature procedures of a

photochemical,[320] an electrochemical[321] or a thermal acid-catalysed[322] decomposition of benzil are known. Moreover, in the thermal acid-catalysed procedure, an influence of the reactor wall on the decomposition was observed.[323] The use of a stainless steel reactor resulted in approximately 25 % of single ring decomposition products, such as benzaldehyde.[322] In a quartz-walled reactor, no single ring decomposition products, but only rearrangement products (consisting of 2 aromatic rings) were observed. The difference was attributed to Ni-catalysis in the stainless steel reactor.[323] Thus, since our experiments were also done under acid-catalysed thermal conditions in a stainless steel microreactor, it is possible that the benzil is also decomposed under our experimental conditions.

Because there was a clear temperature effect on the conversion (entries 2-4, 6 and 7 of Table 3.9) and there was still a lot of starting material left in the reaction mixture, attempts were made to increase the conversion by increasing the temperature further. As a consequence, another solvent mixture was required since the boiling temperature of *n*-butanol is 117 °C. DMF was replaced by NMP (bp = 202 °C) and *n*-butanol was replaced by either *n*-pentanol (bp = 136-138 °C), *n*-hexanol (bp = 156-157 °C) or *n*-octanol (bp = 196 °C), depending on the reaction temperature investigated (Table 3.10).

From entry 4 in Table 3.10 it becomes clear that an increase in the temperature of 30 °C leads to a remarkable increase of the conversion and a shift towards the desired imidazole. Additional increase in temperature did not improve the conversion further (entries 7-9). Entries 3 and 5 are the results of a stopped-flow experiment. The residence time, and thus the reaction time, is increased by pausing the pumps at regular time intervals. In contrast to the Baylis-Hillman reaction, no or little differences occur when there is a fivefold increase of the reaction time. After two hours, no significant change of the conversion was observed in this MCR even under extensively extended reaction times, although there was still some α-diketone left in the reaction mixture. This presence of remaining α-diketone is evident, because formation of the trisubstituted side-product consumes two

equivalents of ammonium acetate. As a consequence, as long as there is no complete selectivity towards the tetrasubstituted imidazole, there is not enough ammonium acetate left to allow all the starting α-diketone to react. This was confirmed by a similar batch reaction were at different times a sample was taken and analysed by GC. Figure 3.18 shows these results. Comparing the results of the batch reaction after two hours with the microreactor reaction under similar conditions shows that the conversion is better in the microreactor system (Table 3.10, entries 4 and 6). The batch procedure was performed on 0.05 mol of benzil. Figure 3.18 shows that this gave 65 % conversion to the product after 2 h (equal to the residence time in the microreactor). Further increase was small (20 h: 67 %; 68 h: 71 %). At the given concentration (*vide infra*, § 4.4.1), the microreactor delivers 0.05 mol of benzil in 8 h 20 min with a conversion to the imidazole of 79 %. It must be emphasised that it was possible to stabilise the temperature in the microreactor on 120 °C, while in the batch procedure there was a constant fluctuation between 115 and 130 °C observed during the reaction, although a temperature control system was used.

Some experiments were performed starting from an equimolar amount of preformed imine instead of the aldehyde and an excess of amine. Although otherwise expected, both results of this 3-CR showed a lower conversion compared with the equivalent 4-CR (Table 3.9, entries 4 and 5; Table 3.10, entries 1 and 2).

Table 3.11: Final modification towards optimised production of tri- and tetrasubstituted imidazoles.[a]

Entry	*Benzil (equiv)*	*NH_4OAc (equiv)*	*Starting material **8a** (%)*[b]	***11f** (%)*[b]	***11'd** (%)*[b]	*Selectivity (%)*	*Other (%)*[b]
1	1	1	10	79	6	93	5[d]
2	1	1	3	75	7	91	4[e]
3	0.9	1	9	69	7	91	5[e], 2[f]
4	1	2	20	0	67	--	7[d]

[a] Residence time: 118 min; temperature: 120 °C; inlet A: 0,5 M of isobutyraldehyde, benzil and 2.5 M of acetic acid in NMP; inlet B: ammonium acetate, 0.6 M benzylamine and 2.5 M of acetic acid in *n*-pentanol. [b] Based on the crude reaction mixture after GC analysis. [c] Without benzylamine. [d] Unidentified product(s). [e] N-benzylacetamide. [f] N-(benzylidene) benzylamine.

In a final attempt to force the reaction to completion, a slight excess of all the reagents compared to benzil **8a** was used. Next to the selectivity problem, it was also thought that the low boiling isobutyraldehyde was partially lost due to the high reaction temperature, although no bubble formation was observed at first sight. As shown in Table 3.11, entry 3, this gave no improvement of the conversion. On the contrary, less of the desired imidazole was formed. Entry 2 is an experiment under the same reaction conditions as entry 1 and proves that the reaction is reproducible. Also, a reaction without benzylamine **9a** but with two equivalents of NH_4OAc was performed. This shows that the reaction conditions are also applicable to produce the corresponding trisubstituted imidazoles (entry 4). An important side-product that is formed in the NMP/alcohol mixture is N-benzylacetamide (see Tables 3.10 and 3.11), which is formed from benzylamine and acetic acid.[324]

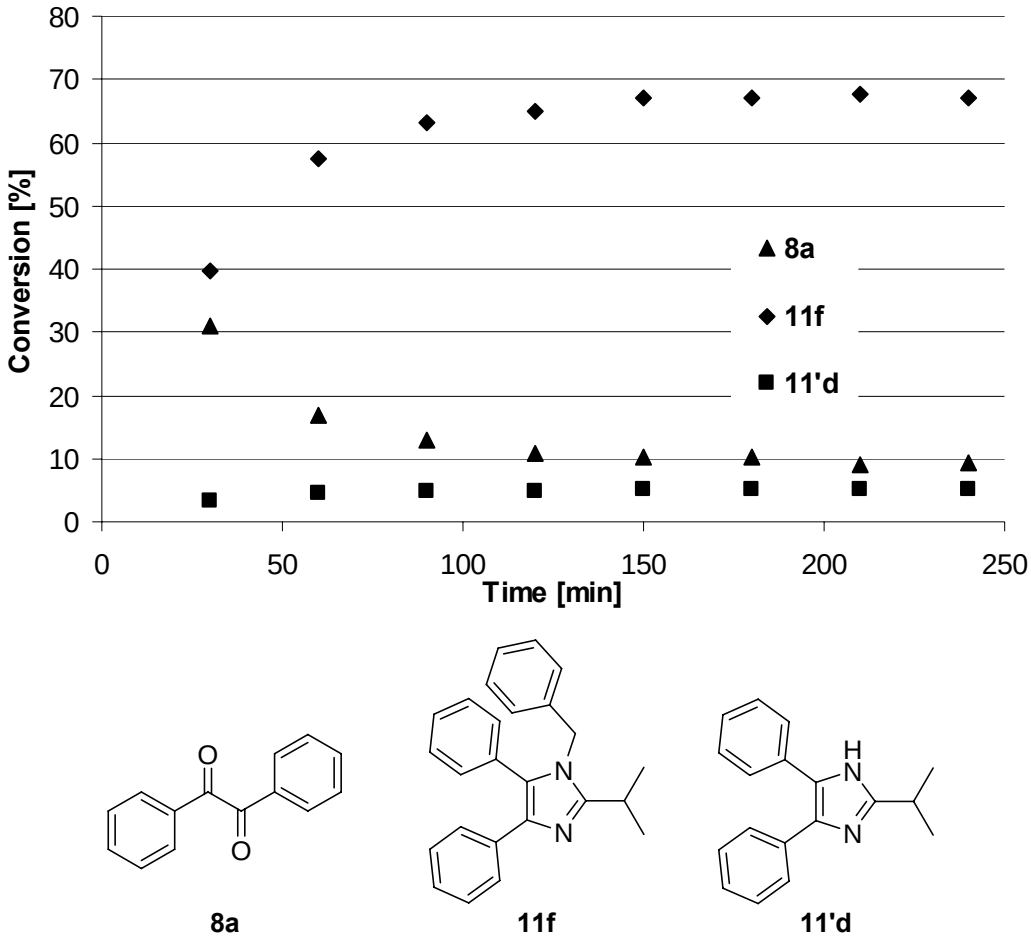


Figure 3.18: Course of the conversion towards the tetrasubstituted imidazole **11f** using conventional batch conditions.

3.3.3 Generality of the optimised reaction

With the optimised conditions known, a variety of α-diketones **8**, primary amines **9** and aldehydes **1** were tested in order to demonstrate the general applicability of microreactor technology to this MCR. The results are summarised in Table 3.12. The yields of the imidazoles, obtained by using the microreactor technology, were compared with those obtained by the microwave-assisted multicomponent reaction reported earlier.[29] The combination with isobutyraldehyde resulted in similar conversions for the microreactor reaction as compared to the microwave-assisted reaction (entries 3, 5, 6 and 8), while in the case of benzaldehyde generally lower conversions were noticed for the microreactor method (entries 1, 2 and 9). One major exception is found in entry 7, in which the conversion is almost doubled, compared to the microwave reaction.

The regioselectivity in entry 8 and 9 proved to be quite similar as in the microwave assisted reaction, with a preference for incorporation of the phenyl group next to the substituted nitrogen. For entry 8, the ratio for R^1(Me:Ph) = 4.6 (compared to 4.0 in reference [29]) and for entry 9, R^1(Me:Ph) = 5.2 (compared to 4.2 in reference [29]). The ratios were determined *via* the crude reaction mixture in GC and GC-MS. The structures of the different regioisomers were characterised by NOE-analysis. As an example, the Nuclear Overhauser Effects for both regioisomers of compound **11h** are given in Figure 3.19. By irradiating the CH_2 of the benzylic group on the 1-position of the imidazole, only in the minor compound, an effect on the methyl group is seen, which proves that in the minor fraction the methyl group is on the 5-position. The microreactor technology is able to generate a variety of imidazoles in moderate to good yields with a throughput between 5.5 and 39.5 g/day depending on the imidazole. Since no purified yields were mentioned in the microwave-assisted reaction, no comparisons on the isolated yields can be made (although the work up is analogous in both setups). The main advantage of the microreactor procedure is the possibility for multigram-scale production of these highly substituted imidazoles. While microwave-assisted reactions are batch procedures mostly on a small scale,

although recently some continuous procedures are developed,[129-132,325] the microreactor now allows to produce these imidazoles in a continuous way.

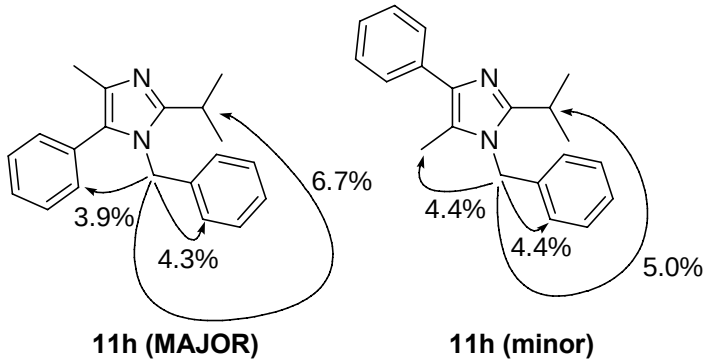
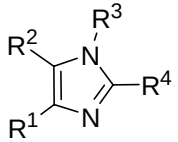


Figure 3.19: Results of the NOE experiments (in percentage) after irradiation of the benzylic CH_2.

3.3.4 Conclusions

In conclusion, it was possible to optimise the four-component condensation towards tri- and tetrasubstituted imidazoles using a microreactor procedure. Using a modified solvent system of NMP/*n*-pentanol (v/v 1:1) at 120 °C, and a 1:1:1:1.2:10 ratio of α-diketone **8**, aldehyde **1**, ammonium acetate, primary amine **9** and acetic acid, respectively, with a final concentration of 0.25 M of the α-diketone in the microreactor, a variety of imidazoles was produced. The use of acetic acid was essential to increase the selectivity towards the tetrasubstituted imidazoles. However, due to the formation of side-products, still a purification step using flash chromatography was necessary, which was the major drawback of this continuous procedure. It was possible to obtain a throughput of up to 40 g imidazole a day.

Table 3.12: General production of tri- and tetrasubstituted imidazoles.[a]



11 ($R^3 \neq H$)
11' ($R^3 = H$)

Entry	*R^1/R^2*	*R^3*	*R^4*	*Product*	*Conversion (%)*			*Selectivity (%)*	*Yield (%)[c]*	*Throughput (g/day)*
					11	***11'***	*[29][b]*			
1	Me	H	Ph	**11'a**	--	64[d]	83	--	29	7.2
2	Me	*i*-Pr	Ph	**11b**	39[d]	nd	61	100	18	5.5
3	Me	Bn	*i*-Pr	**11c**	67[e]	7[e]	66	91	47	15.4
4	Ph	H	*i*-Pr	**11'd**	--	71[f]	85	--	46	17.4
5	Ph	*i*-Pr	*i*-Pr	**11e**	62[f]	10[f]	65	86	37	16.2
6	Ph	Bn	*i*-Pr	**11f**	85[f]	8[f]	90	91	78	39.5
7	Ph	Ph	Ph	**11g**	49[f]	18[f]	30	73	48	25.7
8	Me/Ph	Bn	*i*-Pr	**11h**	89[f]	nd	84	100	47	19.6
9	Me/Ph	Ph	Ph	**11i**	38[f]	8[f]	73	83	24	10.7

--: Not applicable. nd: No trisubstituted imidazole detected. [a] General conditions: residence time: 118 min; temperature: 120 °C; inlet A: 0.5 M of α-diketone, 0.5 M of aldehyde and 2.5 M of acetic acid in NMP; inlet B: 0.5 M of ammonium acetate, 0.6 M of amine and 2.5 M of acetic acid in *n*-pentanol. [b] Conversion based on the MCR under microwave conditions. [c] After purification *via* flash chromatography. [d,e,f] Conversion based on analysis of crude reaction mixture in GC and GC-MS: calculated on residual aldehyde,[d] amine[e] or α-diketone[f].

3.4 α-AMINOPHOSPHONATE SYNTHESIS

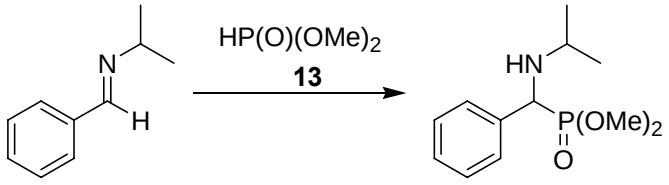
3.4.1 Introduction

α-Aminophosphonates are considered as important compounds, with several biological activities[35-37] due to their structural analogy with the corresponding α-amino acids. The most important example is glyphosate. Traditionally, α-aminophosphonates can be formed *via* two pathways. The most interesting reaction pathway is *via* a three-component reaction in which an aldehyde, an amine and a di- or trialkyl phosphite react together in a one-pot setup. This method is better known as the Kabachnik-Fields reaction.[326,327] However, this procedure suffers from moderate yields and a limited scope. A second method, known as the Pudovik reaction, starts initially from the preformed imine.[328-330] In fact, this is a two-stage process, in which the dialkyl phosphite is added to the imine in the second step. Both methods are very well investigated, both from a mechanistic point of view[326,327,331] as well as towards optimisation studies[332,333]. Mostly, the use of catalysts is necessary for the 3-CR.[334-339] However, in 1952 Fields already produced α-aminophosphonates under solvent and catalyst free conditions.[340,341]
For the optimisation of α-aminophosphonate formation under microreactor conditions, we initially started from the Fields' procedure which was modified to be suitable for the microreactor setup.

3.4.2 Optimisation study using microreactor technology

The aldimines used in this study were synthesised by treatment of the aldehyde with a primary amine in dichloromethane in the presence of anhydrous magnesium sulfate. After filtration and evaporation, the imines were isolated in almost quantitative yields. Fields' two-component reaction is fast, high-yielding and moreover has a 100 % atom efficiency.[340] Since the microreactor has two inlets, this reaction seemed applicable to switch to a continuous process, except for the solvent-free conditions. Because of the high viscosities of the end products and the risk of crystallisation (the end

products were mainly crystalline), a solvent is needed to switch to a microreactor synthesis, in order to prevent clogging of the capillary tubes. Therefore, the initial step concerned the selection of an appropriate solvent in which the reaction proceeds rapidly since the maximum residence time of the microreactor utilised is approximately two hours. Complete conversion is required in this time in order to prevent laborious separation of the end product and reagents. The benzylidene-isopropylamine **12a** was used for optimisation of the reaction conditions (Scheme 3.9).



12a **14a**

Scheme 3.9: Formation of α-aminophosphonate **14a** starting from the preformed imine.

In literature, the most common solvent utilised for this type of addition is dichloromethane. This solvent gave, however, unsatisfactory results as compared to the solvent-free conditions (Table 3.13). The reaction proceeded much slower and moreover, the reaction did not go to completion. When other solvents (acetonitrile, diethyl ether, methanol[342] and toluene[343]) were screened, methanol seemed to give the fastest reaction, without formation of any side-products. Diethyl ether gave almost no reaction and acetonitrile resulted in the formation of side-products. Toluene provided reasonable results while MeOH obviously was the solvent of choice. Under batch conditions, four hours of reflux in methanol, which still is longer than the maximal residence time of the microreactor, still left 6 % of starting imine in the reaction mixture.

Monitoring the reaction by ^{31}P-NMR, a dramatic drop of the reaction rate was noticed at the end of the reaction when reagents become limiting. Therefore, two equivalents of phosphite were used, decreasing the reaction time considerably to 80 min with 100 % conversion, which was now below the residence time of the microreactor. Distilling the excess of phosphite

from the reaction mixture was not successful, resulting in a partially breakdown of the product. Moreover, it proved to be hard to remove the excess phosphite completely. Finally, an acid base-extraction after evaporation of the methanol *in vacuo* resulted in the total removal of the phosphite and the α-aminophosphonate **14a** was recovered in high yield (94 %).

Table 3.13: Solvent optimisation in the batch formation of α-aminophosphonate **14a**.

Entry	*Solvent*	*Conversion after 1.5 h (mol %)*[a]	*Conversion after 22 h (mol %)*[a]
1	Neat	91	--
2	Dichloromethane	2	73
3	Acetonitrile	14	58[b]
4	Diethyl ether	1	32
5	Methanol	90	94[c]
6	Toluene	76	95

--: Not determined. [a] Determined by ^{31}P-NMR. [b] Formation of side-products. [c] No change after 3.5 h.

The reaction was further tested to a variety of aldehydes, amines and phosphites and seemed to be generally applicable (74-97 % yield).[38] Only in the case of diisopropyl phosphite, somewhat lower yields were observed. The reaction was further tested using purified methanol and dialkyl phosphite, to check the need for acid catalysis. During mechanistic studies, it was suggested that acid catalysis *via* a small degree of hydrolysis of phosphite reagent occurred.[344] However, yields and purities were comparable with previous experiments, which proved that no acid catalysis was necessary. In further experiments, no purification of the reagents was done.

The next step of the research comprised the evaluation of the α-aminophosphonate synthesis in the microreactor. Therefore, reaction parameters such as the residence time, the amount of phosphite, the temperature and the concentration have been varied. There are, however, some restrictions concerning the temperature and the concentration. The reaction temperature is limited by the boiling point of the solvent in order to avoid cavitation effects in the reactor which gives undeterminable residence

times and uncontrollable reaction conditions. The concentration on the other hand is limited in order to prevent crystallisation of the end product which could cause clogging of the capillary tubes.

First, the optimised batch conditions were tested (Table 3.14, entry 1), which resulted in a complete conversion and a comparable yield. Entries 2 to 4 show attempts to diminish the amount of phosphite. However, no complete conversion could be achieved, even when higher residence times were applied. When a higher concentration was applied in the reactor, a higher production rate of α-aminophosphonate could be achieved with less solvent consumption. However, increasing the concentration to 40 mass% resulted in incomplete conversion, whereas a 20 mass% concentration seemed to be optimal (entries 5 and 6). In the case of 40 mass% imine, this meant an input concentration of the imine of 80 mass% (or 0.875 mL/mL). The dialkyl phosphite input was a neat solution. A possible explanation of the lower conversion is that the higher viscosity diminishes the diffusion process which is an important feature in the small channels of the microreactor. Also the flow was doubled to study this influence (entry 7), but this resulted also in incomplete conversion.

Because of the low boiling point of methanol, it was difficult to increase the temperature. As an alternative, higher alcohols were tested as a solvent in order to evaluate the influence of the temperature (entries 8-11) and to obtain lower residence times for a higher output. With *n*-butanol as a solvent, the residence time could be diminished to 26 minutes with 100 % conversion, but due to transesterification side-products were formed. Analysing the ^{31}P NMR spectrum of entry 8 showed 3 peaks in the dialkyl phosphite region (δ = 11.1 (59 %), 9.8 (37 %) and 8.4 (4 %) ppm) and 3 peaks in the α-aminophosphonate region (δ = 26.8 (91 %), 25.7 (6 %) and 24.2 (3 %) ppm). The main peaks were the dimethyl phosphite and the desired α-aminophosphonate, respectively. The peak at 8.4 ppm accounted for di-*n*-butyl phosphite, which proved that some transesterification of the phosphite occurred during the reaction. In literature, the ^{31}P shift between dimethyl and di-*n*-butyl (*N*-benzyloxycarbonylamino)(4-nitrophenyl)-methylphosphonate

was 2.5 ppm.[345] Related compounds showed a similar shift. The ^{31}P peak of the *n*-butyl methyl compound was found between the other two peaks.[346] Based on these findings, it was assumed that the other 2 products formed were the α-aminophosphonates with the different alkyl chains. Decreasing the reaction time did not result in a loss of the side-products. About 9 to 12 % of the conversion resulted in the transesterified side-products. Since the goal was to obtain only the dimethyl α-aminophosphonate, further experiments were performed to optimise the procedure. It must be emphasised however that, if the alkyl substituent on the phosphorus does not matter (e.g. if the product is hydrolysed in a further step), it is possible to use these conditions and thus obtain higher throughputs. In a final optimisation experiment, a switch was made to *sec*-butanol, because it was believed to reduce the transesterification due to a higher steric hindrance. Unfortunately, in this case even more transesterification was observed (there was 100 % conversion, but only 82 % was converted to the dimethyl α-aminophosphonate).

Table 3.14: Optimisation of the α-aminophosphonate **14a** formation in the microreactor.

Entry	*Mass % in MR*	*Residence time (min)*	*Solvent*	*T (°C)*	*Dimethyl phosphite (equiv)*	*Conversion (mol %)*	*Yield (%)*[a]
1	10	78	MeOH	50	2	100	85
2	10	78	MeOH	50	1.5	94	83
3	10	78	MeOH	50	1.6	94	82
4	10	78	MeOH	50	1.75	95	89
5	**20**	**78**	**MeOH**	**50**	**2**	**100**	**82**
6	40	78	MeOH	50	2	67	24
7	10	44	MeOH	50	2	93	83
8	10	44	*n*-BuOH	100	2	100	[b]
9	10	26	*n*-BuOH	100	2	100	[b]
10	10	17	*n*-BuOH	100	2	94	[b]
11	10	26	*sec*-BuOH	85	2	100	[b]

[a] Yield after acid base extraction. [b] Side-products due to transesterification.

3.4.3 Generality of the procedure

Again the generality of this method was investigated by varying the amine and the aldehyde. As can be seen in Table 3.15, the continuous process allowed us to synthesise more than 10 grams α-aminophosphonate per hour (or more then 250 g per day) without having the risk of handling big amounts of unpleasant chemicals in the lab. Several derivatives can be produced without alteration of the method, simply by switching of the aldimine.

Table 3.15: Continuous synthesis of different α-aminophosphonates under optimised conditions in the microreactor.[a]

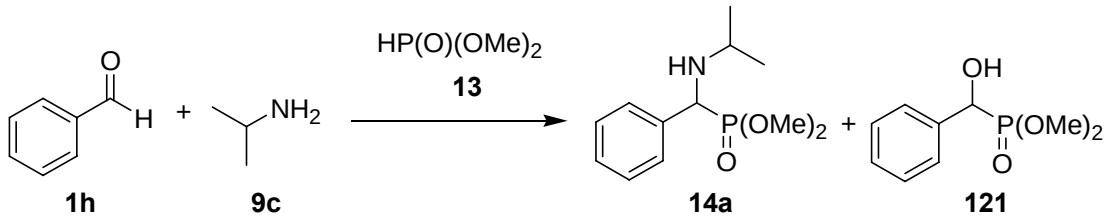
Entry	*Product*	*R¹*	*R²*	*R³*	*Yield (%)*	*Throughput (g/day)*
1	**14a**	Ph	*i*-Pr	Me	82	247.2
2	**14b**	2-phenylethenyl	*i*-Pr	Me	91	256.8
3	**14c**	*c*-Hex	*i*-Pr	Me	78	232.8
4	**14d**	*i*-Pr	Bn	Me	68	196.8
5	**14e**	2-furyl	allyl	Me	72	225.6

[a] Conditions: 20 mass% imine, 2 equiv phosphite, residence time of 78 min.

3.4.4 Switch to the 3-CR

In a second stage, attempts were made to perform the three-component reaction in a microreactor setup (Scheme 3.10). In preliminary studies, it was already seen that aldimine formation was possible in the given residence time range. The results of these experiments are listed in Table 3.16. A first experiment was based on the optimised conditions of the Pudovik type reaction (Table 3.16, entry 1). In order to prevent as much as possible the competition between the phosphite addition to the aldehyde and to the imine, the phosphite was always mixed with the amine. Secondly, the amounts of aldehyde and amine were calculated to obtain 20 mass% imine in the microreactor, which is the same as in the optimised procedure. The molar aldehyde/amine ratio was 1:1. Investigating the crude reaction mixture of the first experiment by ^{1}H NMR showed that no benzaldehyde or imine was left. In the ^{31}P spectrum, 4 peaks were observed, of which one was the excess of

dimethyl phosphite. The peak at 26.9 ppm was the α-aminophosphonate. Another peak (δ = 24.4 ppm) appeared to be the dimethyl-(phenylhydroxymethyl)phosphonate **121**.[347,348] Based on both spectra, a ratio of 35:65 in disfavour of the α-aminophosphonate was calculated. After acid base extraction, about 20 % of the α-aminophosphonate was retained. The fourth peak in the ^{31}P spectrum at 6.6 ppm remained unclear. To further improve the outcome of the reaction, an orthoester was added in an equimolar amount. It was believed that the orthoester could promote the imine formation by capturing the water and thus promoting the addition of phosphite to the imine instead of to the aldehyde. An increase of the yield was observed, which became bigger with longer reaction times. Unfortunately, a maximum yield of 49 % was obtained. The crude spectrum of entry 3 still showed the formation of the side-product **121**. However, the ratio was increased to 83:17, which shows that the addition of the orthoester indeed promotes the imine formation.



Scheme 3.10: The α-aminophosphonate 3-CR.

Table 3.16: The 3-CR reaction with formation of α-aminophosphonates in the microreactor.[a]

Entry	*Residence time (min)*	*Solvent*	*T (°C)*	*Dialkyl phosphite*	*Trialkyl orthoformate*	*Yield (%)*[b]
1	78	MeOH	50	Me	No	20
2	78	MeOH	50	Me	Yes (Me)	39
3	118	MeOH	50	Me	Yes (Me)	49
4	118	EtOH (96 %)	70	Et	Yes (Et)	48
5	118	EtOH (abs)	70	Et	Yes (Et)	28

[a] Conditions: 20 mass% aldehyde and amine, 2 equiv phosphite. [b] Yield after acid base extraction.

Final attempts were made to increase the yield by using ethanol to work at higher temperatures (entry 4 and 5). In order to prevent the transesterification observed in previous experiments, diethyl phosphite and triethyl orthoformate were used instead of the dimethylated products. While in previous cases no imine was observed anymore, in these experiments, about 10 mol% imine was not converted to the α-aminophosphonate. Also in this case, the addition side-product was observed. Strangely, working with absolute ethanol gave even the worst results.

3.4.5 Conclusions

Based on a known procedure in batch conditions, the two-component reaction between an imine (that was formed in batch conditions) and phosphite was evaluated for working under microreactor conditions. After some optimisation steps, of which the solvent optimisation was the most important, it was possible to produce several α-aminophosphonates with an outcome that was higher than 190 g/day. A further conversion of the sequential batch imine formation and the continuous phosphite addition towards a three-component Kabachnik-Field reaction failed due to a combination of low conversions and a lack of selectivity towards the α-aminophosphonate.

3.5 ISOCHROMENONE SYNTHESIS

3.5.1 Introduction

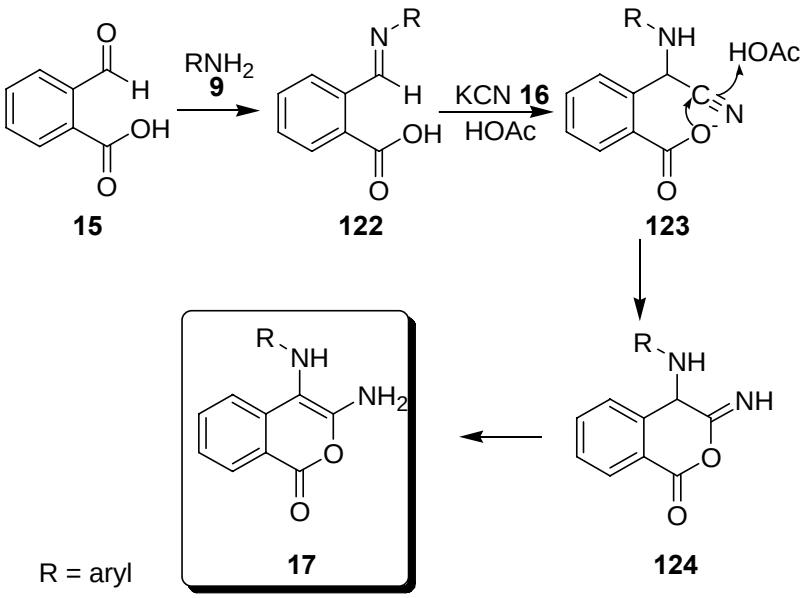
An interesting MCR recently described the production of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones **17** (Scheme 3.11). This type of isocoumarin is of great interest due to the possibility of forming base pairs with guanine due to the 'donor-acceptor' similarity with cytosine.[39] Unfortunately, the reaction proceeds *via* a modified Strecker reaction, in which the highly toxic hydrogen cyanide is needed. In order to avoid large quantities of HCN, the idea of using microreactor technology for the production of this isochromen-1-one was proposed. In the past, specialised microreactor systems were already assembled to synthesise HCN *via* the Andrussov process, an industrial process to produce large quantities of HCN by reacting methane and ammonia in the presence of oxygen (*vide supra*, § 2.4.3).[40,349] Until now, there is no literature known about the *in situ* production of HCN in a microreactor system for further reaction in the microreactor.

The MCR to form the 3-amino-4-(arylamino)-1*H*-isochromen-1-ones **17** consists of a Strecker reaction-intramolecular nucleophilic addition-tautomerisation sequence. First, the cyanide anion is added to the imine **122**, followed by an attack of the carboxy group onto the nitrile to form an O-acyl imidate **124**. This compound tautomerises towards the final structure **17**. The *in situ* generation of the hydrogen cyanide results from the addition of acetic acid to potassium cyanide.

3.5.2 Optimisation study using microreactor technology

As stated in earlier chapters, the optimisation of a reaction under microreactor conditions always contains a number of important steps: the order of mixing of the starting materials, the residence time (flow rate), the concentration of the reagents and the solvent choice are of major importance

to get a good production of the desired compound. Table 3.17 summarises the results of this optimisation.

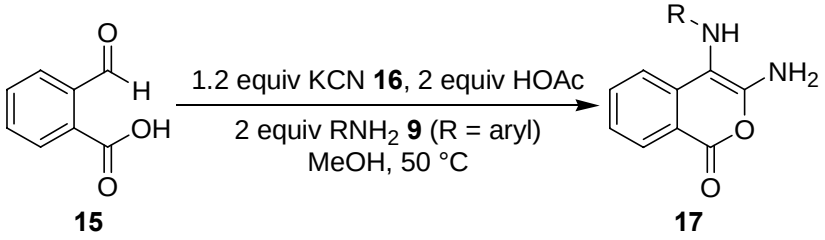


Scheme 3.11: Mechanism of the 3,4-diamino-1*H*-isochromen-1-ones **17** formation.

A primary experiment was based on the reaction conditions provided by Opatz and Ferenc (Table 3.17, entry 1).[39] Some changes had to be made, however, to fit the microreactor setup:

1. The reaction temperature was lowered from 65 to 50 °C, since temperatures approaching the boiling point of the solvent (less than 10 °C under the boiling point) provide irregular residence times due to partial evaporation of the solvent (in this case methanol).
2. The concentration of the reagents in the microreactor was lowered by 50 % due to the limited solubility of KCN (the maximum solubility of KCN in methanol at room temperature is approximately 0.48 M). Moreover, other solvents could not be used because of the low solubility of KCN in these solvents.
3. The maximum residence time of the system (approximately 2 h) was used instead of 3 h. For safety reasons and in order to generate HCN only *in situ*, the potassium cyanide and the acetic acid were pumped separately into the microreactor.

Table 3.17: Optimisation of the production of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones **17** under microreactor conditions.[a]



15 **17**

Entry	*Residence time (min)*	*Concentration of **15** (M)*[b]	*Yield (%)*[c]	*Output (g/day)*
1	118	0.2	Clogging[d]	--
2	118	0.15	Clogging	--
3	118	0.1	67	9.8
4	39.2	0.2	Clogging	--
5	**39.2**	**0.15**	**43-66**	**28.1-43.2**
6[e]	29.3	0.2	49	56.9
7	19.6	0.2	46-54	80.2-94.1
8[f]	5	0.2	48	13.9
9[f]	0.83	0.2	51	88.8

--: Not applicable. [a] Temperature: 50 °C; inlet A: 2-formyl benzoic acid and 2 equiv acetic acid in methanol; inlet B: 1.2 equiv potassium cyanide and 2 equiv amine in methanol; the residence time was calculated according to equation (4.1). [b] Concentration of the reagents in the reactor. [c] After crystallisation. [d] By 'clogging' the formation of crystals in the tubes and the subsequent blockage of the tubes is indicated. [e] Partial clogging occurred after the first sample. [f] The sample was taken at the end of the microreactor.

This experiment gave no good results because crystals of the end product were formed in the tubing at the end of the reactor which led to clogging of the system. Since the crystallisation only occurred at the end of the tubing, it can be explained by a combination of a high product concentration and a saturation effect. Because the microreactor output was flushed with nitrogen for safety reasons (removal of traces of HCN), the solvent was partially removed at the end of the system due to evaporation. This initiated crystallisation due to saturation and led after some time to crystals appearing everywhere in the end tubing. In an attempt to solve this problem, the setup was changed by submerging the end tubing in the solvent with or without the use of an ultrasound bath to prevent nucleation in the tube. Both alternatives appeared to be insufficient, although putting the end tubing in the solvent

meant that slower crystallisation occurred. The use of ultrasound gave only smaller crystals: more nucleation and less growth, which seemed to be in accordance with the literature.[350] A decrease to a concentration of 0.10 M of starting material was finally enough to prevent blocking of the system (Table 3.17, entry 3). In order to increase the amount of product produced in a certain time, a combination of residence time decrease and concentration increase was tested. In the case of 0.20 M of starting material, the residence time had to be lowered to one-sixth of the maximal residence time to prevent clogging (entry 7). A reduction to approximately 30 min gave no initial crystallisation in the tubing, but after a longer run, partial blocking of the system was observed (entry 6). Final tuning of the reaction conditions to 0.15 M of starting material and a residence time of approximately 40 min gave a maximum yield of 66 % (entry 5). Although some daily outputs (g/day) were higher in other cases, this optimal setup was chosen because of the higher yields.

Next to these results, a different setup was applied. Since no crystallisation occurred after the microreactor, a HPLC pump was installed between the microreactor and the RTU by means of a T-junction (Figure 3.20). Through this pump an immiscible perfluorated solvent, Fluorinert® FC-70, was introduced to the reaction flow. This method created plugs of the reaction mixture, which was mixed in the microreactor, separated from each other by the immiscible solvent, with lengths depending on the flow rates of the pumps.[351] Preliminary tests showed that the ratio of flow rates of the reaction solution and the Fluorinert® FC-70 input were of importance. Using a flow rate of the HPLC pump that was too high or too low gave a flow in the direction of the microreactor or the Fluorinert® FC-70 input respectively, instead of in the direction of the RTU. Indeed, during some preliminary tests, whereby an aqueous methylene blue solution was used instead of the reaction mixture, a flow in the direction of the Fluorinert® FC-70 was observed at flow rates of the HPLC pump lower than 0.5 mL/min, irrespective of the flow rate of the piston pumps (between 0.4 mL/min and 12.8 mL/min). If the flow rate of the HPLC pump was above 5 mL/min, a pressure built up (> 6 bar) was observed and the pump was automatically switched off. At these

high flow rates, the Fluorinert® FC-70 flow was also directed to the microreactor, which gave these high pressures due to the pumping of the piston pumps in the opposite direction.

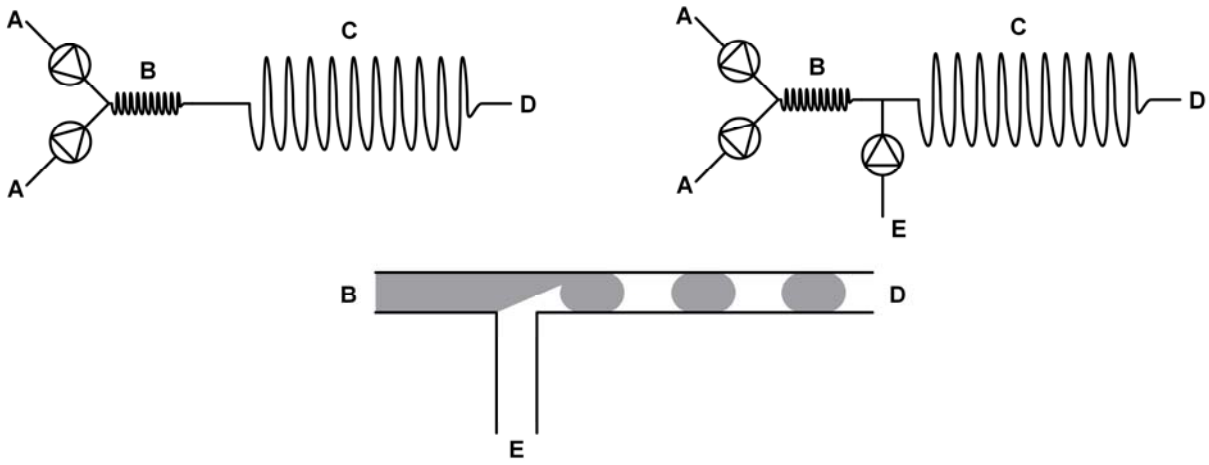


Figure 3.20: Reaction setup of the microreactor system: (above left) normal setup; (middle) plug formation; (above right) adjusted setup. A = input reagents, B = microreactor, C = RTU, D = output reaction mixture, E = input Fluorinert® FC-70.

Based on the research of Ismagilov and coworkers,[123,137,352] the idea was proposed that the immiscible solvent will drive the product further through the system, even if there was crystallisation in the plugs itself. Table 3.18 shows the results of this setup. Although installation of the pump directly after the mixing zone of the microreactor is a better method to study the effect of the plug formation, this was practically impossible due to the specific construction of the microreactor. So it must be emphasised that already some reaction (but no crystallisation) takes place before the plug formation. The results show that the yields in this particular setup are lower than in the normal setup (Table 3.17, entry 5). However, it must be emphasised that, even at those high concentrations, no clogging was observed in the tubes. It was even possible to work at higher concentrations of reaction product and longer residence times without the problem of crystallisation in the tubing system (Table 3.17, entry 4 and Table 3.18, entry 1). The immiscible solvent forms an oily layer between the wall of the microreactor and the plug, which prevents the crystals accumulating on the walls of the reactor.[123,352] Figure 3.21 shows the formation of plugs in the tubes. An additional advantage is

that, owing to the immiscibility and, moreover, the rapid separation of the solvent, the quite expensive Fluorinert® FC-70 can be reused directly *via* a loop by simple separation from the reaction mixture.

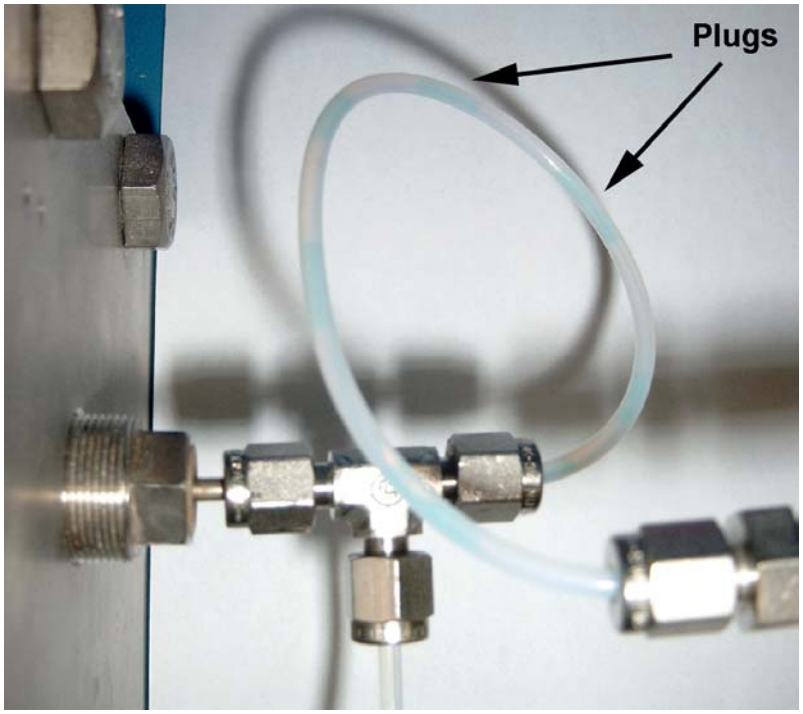


Figure 3.21: Example of the plug formation after the microreactor (blue plugs: aqueous methylene blue solution).

From an economical point of view, Table 3.18, entry 1 provides the best conditions since it has the highest yield and the lowest consumption of Fluorinert® FC-70 (highest *rmf*, Equation 3.2). The reaction mixture fraction (*rmf*) is the fraction of the microreactor output that comes from the reaction mixture. The *rmf* is calculated as follows:

$$rmf\ (\text{-}) = \frac{V_{\text{reaction mixture}}}{V_{\text{reaction mixture}} + V_{\text{Fluorinert}}} \tag{3.2}$$

with $V_{\text{reaction mixture}}$ = volume of the reaction mixture in the sample (mL)
$V_{\text{Fluorinert}}$ = volume of Fluorinert® FC-70 in the sample (mL)

The only disadvantage is the somewhat higher residence time which leads to a longer start up procedure. Due to the additional flow of the Fluorinert® FC-

70, the residence time τ of the system was also calculated in a different manner, given by Equation 3.3:

$$\tau\,(\text{min}) = \frac{V_{\text{microreactor}}}{r_{\text{total}}} + \frac{V_{\text{RTU}}}{r_{\text{total}} + r_{\text{HPLC}}} \quad \text{with } r_{\text{total}} = 2\, r_{\text{piston pump}} \tag{3.3}$$

with $V_{\text{microreactor}}$ = inner volume of the microreactor (mL)
V_{RTU} = inner volume of the RTU (mL)
r_{total} = total flow rate of the 2 piston pumps (mL/min)
$r_{\text{piston pump}}$ = flow rate of the piston pump (mL/min)
r_{HPLC} = flow rate of the HPLC pump (mL/min)

Table 3.18: Production of 3-amino-4-(arylamino)-1*H*-isochromen-1-one **17** under microfluidic plug flow conditions.[a]

Entry	*Residence time (min)*[b]	*Reaction mixture fraction (rmf)*[c]	*Yield (%)*[d]	*Output (g/day)*
1	**50**	**0.71**	**50**	**25.7**
2	30	0.20	42	6.2
3	23	0.33	44	10.6

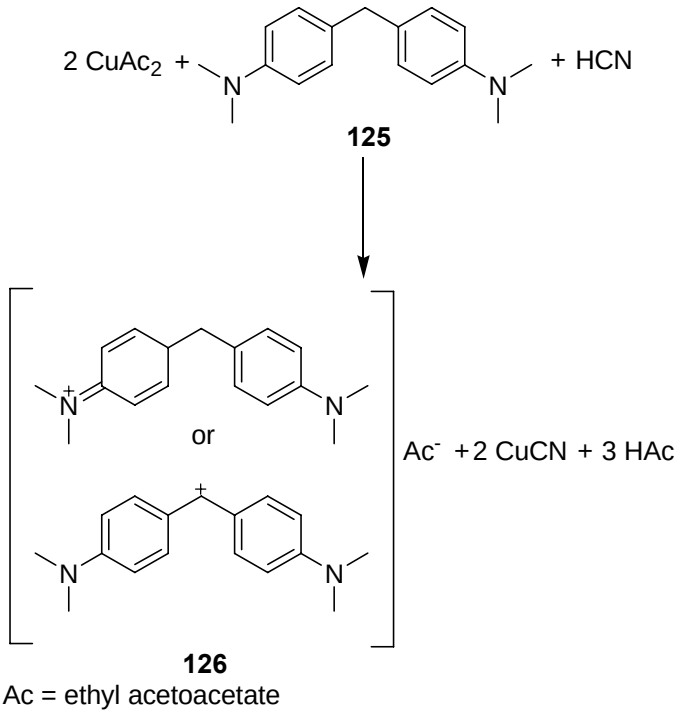
[a] Temperature: 50 °C; inlet A: 0.4 M of 2-formyl benzoic acid and 0.8 M of acetic acid in methanol; inlet B: 0.48 M of potassium cyanide and 0.8 M of amine in methanol; the residence time was calculated according to Equation 3.3. [b] The *rmf* was calculated according to Equation 3.2. [c] After crystallisation.

3.5.3 Safety of the procedure

As mentioned in the introduction, one of the important advantages of microreactor technology is the possibility of using in a safe way toxic reagents which cannot be used in a conventional reaction setup without considerable safety risks. Because of the small dimensions of the microreactor (2 mL), only minor amounts of the toxic reagent are formed. It is obvious that there will always be a HCN release in the original setup due to the excess of KCN used in the procedure. In this particular case, it was supposed that no hydrogen cyanide was released at the end of the reaction setup, in the case that

equimolar (or lower) quantities of KCN were used. In order to test this, first a hydrogen cyanide spot test was used.[353,354] The colour reaction is based on the oxidation of 4,4''-methylenebis(N,N-dimethylaniline) **125** in the presence of HCN and copper ethylacetoacetate. The salts of these cations **126** formed, give a blue colour, while the starting base is colourless (Scheme 3.12). However, this test provides only qualitative results.

In both the batch and the microreactor system, coloration of the reagent was detected in the headspace of the crude reaction mixture, which proved that HCN was released. The only difference between both setups was a slower colouration in the case of the microreactor setup. It was supposed that in the case of the microreactor setup, less HCN was released during the reaction since the cyanide had more time to react (and thus to disappear) before being released to the environment, while in the batch procedure there is a constant exposure to the air.



Scheme 3.12: Reaction that induces a blue colour when HCN is present.

Therefore, it was necessary to develop a suitable, easy and economic method to measure the amount of HCN that was released during the reaction. Among the different potentiometric, fluorescent and colorimetric procedures to

measure HCN, such as e.g. the use of an acridinium salt[355] or the oxidation of CN^- to CN^+,[356,357] a procedure based on the measurement of free (non-complexed) cyanide and HCN in water solutions was used. The original method is a standard procedure used by the U.S. Environmental Protection Agency (EPA) for measuring free (non-complexed) cyanide and HCN in drinking water, natural surface waters, domestic and industrial wastewaters and in soil extracts.[358] In order to get the CN^- ions in the correct form to quantify them (i.e. in an aqueous solution), another modification of a standard procedure of the EPA was applied.[359]

To measure the output of HCN gas and also for safety reasons, the outlet of the RTU is set under nitrogen atmosphere. This gas solution is then put in a 1 N NaOH solution to absorb the HCN of the system *via* neutralisation and salt formation. The final concentration of cyanide ions is then measured using the modified EPA method.

The calculation of the possible theoretical minimum (due to the excess of HCN) and maximum (if no conversion at all to the end product is achieved) amount of HCN released at the end of the microreactor in the optimised procedure (Table 3.17, entry 5) gave values of 0.162-0.972 mg/mL (162-972 mg/L) aqueous solution. This was based on a 25 min collection of sample at steady state conditions. Based on these theoretical results, it was decided to use the titration method and not the colorimetric method for the HCN measurement. This titration method is used for cyanide concentrations exceeding 0.1 mg/L. The titration is based on the following reaction:

$$Ag^+ + 2\ CN^- \rightarrow [Ag(CN)_2]^-$$

When all the CN^- ions are complexed, an excess of $AgNO_3$ gives complexation of the silver ions with the rhodanine indicator. This results in a change of colour from yellow to pink and further on to brownish-pink.

To check the reliability of the modified procedure, different tests were performed. First of all, a solution of KCN in water or in a NaOH solution was made and titrated with $AgNO_3$. This experiment was repeated 3 times and all the titrations gave an outcome of 99-102 % KCN. This showed that

the titration procedure is reliable. It must be emphasised that the colour change was not easily visible and some experience was necessary to detect the end point of the titration.
In a second experimental setup, a solution of acetic acid in methanol was added slowly to KCN. The final solution was stirred for 3 h at 50 °C to imitate the final experimental batch setup. This was set under nitrogen atmosphere and the gas solution was put in a NaOH-scrubber. Titration of the NaOH solutions, gave 83-88 % of the theoretical maximum outcome. Since the titration itself gave excellent results, this meant there was no complete HCN conversion or some loss of HCN during the scrubbing procedure. The use of 50 mL of 0.25 N NaOH as a scrubber solution gave somewhat lower HCN capture than a solution of 125 mL of 1 N NaOH. Probably this was due to a tenfold higher amount of NaOH combined with a higher volume of scrubber solution, so there was more time and opportunity for the HCN in the gas to react with the NaOH. Therefore, it was decided to work with the second scrubber solution. Since in both batch and continuous experiments the same procedure for HCN capture will be used, these results will have no effect on the final conclusions. It only has to be stated that the final results will give an underestimation of approximately 15 % of the actual HCN release.

In the microreactor procedure, different fractions were collected: the start up fraction (i.e. before steady state), 2 steady state fractions and the shutdown fraction (i.e. when the reagent solutions at the inlet are changed back to the solvent to clean the microreactor). Table 3.19 shows the results of the samples at steady state conditions.

For the batch reaction, the HCN capture method was slightly modified. It was supposed that a continuous flow of nitrogen would flush away the HCN immediately, giving the cyanide no time to react with the 2-formyl benzoic acid **15**. Therefore, the solution of 2-formyl benzoic acid, aniline and KCN in methanol was first put under a nitrogen atmosphere for half an hour. After the nitrogen flow was switched off, the acetic acid was slowly added to the reaction mixture by means of a syringe pump at a flow of 10 mL/h. The

reaction mixture was then refluxed for 3 h. Finally, the reaction mixture was again flushed for half an hour with nitrogen to remove the residual amount of HCN in the solution. The amount of HCN in the scrubber solution was determined in the same way as for the microreactor setup. The results are also given in Table 3.19.

It can clearly be noted that there is a difference in performance between the batch and microreactor conditions. The amount of HCN released in the environment is at least 2 orders of magnitude higher in the batch reaction. This means that the system under microreactor conditions is much safer.

Also, in the batch procedure there is a considerable difference in HCN release at the different scales as can be seen from Table 3.19. The amount of HCN released at the scale of 250 mL is relatively lower than the release at 25 mL. In this particular case, this tenfold scale up has a positive effect. This clearly shows that scaling up under batch conditions has an effect on the reaction conditions, while this is not the case under microreactor conditions. Once the microreactor procedure is started up, which means running at steady state conditions, the system constantly runs at the same conditions. A tenfold increase in scale (from 25 to 250 mL), e.g. by numbering up (i.e. the number of reactors is increased instead of the volume of the reactor) the optimised conditions, just means a tenfold increase in HCN release.

Table 3.19: HCN release during microreactor and batch conditions.

	Batch		*Microreactor*		
Scale (mL)	*Amount HCN (mg)*	*% of theoretical amount*	*Amount HCN (mg)*	*% of theoretical amount*	*Ratio (batch/micro-reactor)*
25	17-20	14-17	0.04-0.08	0.04-0.06	213-500
250	73	6	0.40-0.80	0.04-0.06	91-183

Another interesting part of this research was the follow up of the HCN release during a total cycle of a continuous procedure, i.e. the start up, the steady state and the shutdown. In Figure 3.22, the outcome of the experiment is shown. This clearly shows that the start up and the shutdown of a continuous procedure have effects on the quality of the product outcome. As can be seen in the figure, there are big fluctuations in HCN release between 2

different experiments in the start up and shut down fraction. This is probably due to the non steady state conditions during these two periods, wherein the concentrations of the product are constantly changing. Only under steady state a relatively constant release of HCN is measured in one experiment and also between the experiments. The relative standard deviation for the steady state measurements is around 5 %.[13]

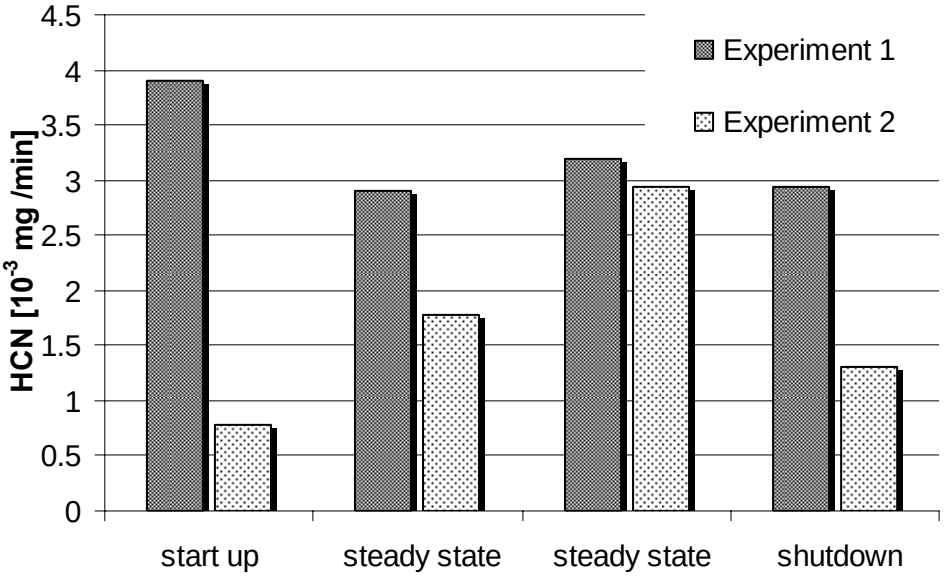


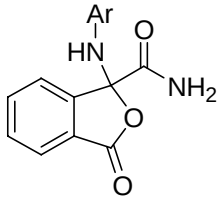
Figure 3.22: HCN release during a continuous microreactor cycle.

3.5.4 Degradation

The 3-amino-4-(arylamino)-1*H*-isochromen-1-one **17** appeared to be unstable in solution. Several solvents (chloroform, DMSO, methanol, acetone) were tested and led to degradation after some days. DMSO gave degradation after one week towards the starting product and 3-oxo-1-(arylamino)-1,3-dihydroisobenzofuran-1-carboxamide **127** (Figure 3.23).[360] The other solvents gave complex mixtures of degradation products. This led to the fact that during the sample collection and evaporation of the solvent, a nitrogen atmosphere was necessary to prevent degradation of the end product. Once the crystals were separated and dried, the 3-amino-4-(arylamino)-1*H*-

[13] This value is calculated if the first steady state measurement of experiment 2 is seen as an outlier. If not, a relative standard deviation of 23 % is obtained.

isochromen-1-ones **17** are stable, even in open air. The bottleneck of the procedure was the purification of the end product which led to the testing of several methods to purify the end product. Direct evaporation of the reaction mixture gave formation of a mixture of end product, amine and side-products. Using an extraction of the mixture gave too much amine in the final extract, so that the end product was not able to crystallise. Attempts were made to develop an extraction procedure which removes the excess of amine out of the mixture, prior to crystallisation, based on a known purification method for primary, secondary and tertiary amines by adjustment of the pH.[361] This was without any success, since in all the trials, still too much amine was left. Therefore, the purification was finally based on evaporation under nitrogen, followed by a filtration and drying of the crystals. The results of Table 3.17, 3.18 and 3.20 are based on this purification procedure.



127

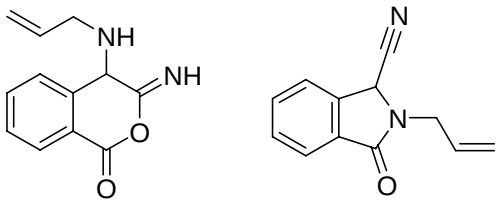
Figure 3.23: Side-product of 3-amino-4-(arylamino)-1*H*-isochromen-1-one **17** that is formed in the presence of DMSO.

3.5.5 Scope of the reaction

Finally, the optimised procedure was tested for different amines. When anilines were used, moderate to good yields were achieved (Table 3.20, entry 1-4). Allylamine was converted mostly to the Strecker product **128** (37 %), while 4-allylamino-3-iminoisochroman-1-one **124h** was only produced in 6 % yield (Figure 3.24). Apparently, when non-aromatic amines are used the imino tautomer is more stable than the corresponding enamine tautomer.

A production rate higher than 60 g/day was achieved for some adducts. When comparing the yields of the batch procedure and the microreactor procedure, higher yields in most batch procedures were observed. This is easy

to explain, since in the batch procedure crystallisation occurs in the round-bottom flask during the reaction, which promotes a shift towards the formation of the end product. In the microreactor procedure, crystallisation needs to be avoided due to clogging problems. Nevertheless, scale up of this reaction is more advantageous in the case of the microreactor procedure. The most important reason is that more severe precautions are needed due to the formation of high concentrations of HCN in the scale up of the batch reaction, while in the case of the microreactor procedure this is possible by simple numbering up without changing the reaction conditions. Furthermore, the procedure is continuous, which guarantees a more constant quality of the end product in comparison to different batch reactions.



124h **128**

Figure 3.24: The non-tautomerised end product **124h** and the Strecker product **128** when allylamine is used as the amine compound.

Table 3.20: Production of different 3-amino-4-(arylamino)-1*H*-isochromenones **17** using the CYTOS® College System. [a]

Entry	*Amine* ***9***	*Product*	*Yield (%)*[b]	*Yield (%)*[c]	*Output (g/day)*
1	Aniline	**17a**	66	82	43.2
2	3-Methoxyaniline	**17b**	75	88	54.7
3	3-Methylaniline	**17c**	69	60	47.5
4	4-Methoxyaniline	**17d**	62	78	45.4
5	4-Methylaniline	**17e**	91	82	62.6
6	4-Fluoraniline	**17f**	89	--	62.4
7	*N*-Methylaniline	**17g**	49	64	33.8
8	Allylamine	**124h**	6[d]	--	3.4

--: Not described. [a] Residence time: 39.2 min; temperature: 50 °C; inlet A: 0.3 M of 2-formyl benzoic acid and 0.6 M of acetic acid in methanol; inlet B: 0.36 M of potassium cyanide and 0.6 M of amine in methanol. [b] Microreactor procedure, after crystallisation. [c] Batch procedure, after crystallisation[39]. [d] No crystallisation occurred and the reaction mixture was subjected to column chromatography which gave product **124h**.

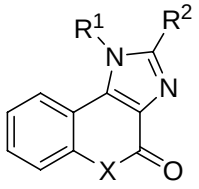
3.5.6 Conclusions

A multicomponent reaction was studied and optimised to produce 3-amino-4-(arylamino)-1*H*-isochromen-1-ones *via in situ* generation of HCN. This is the first chemical reaction in a microreactor system in which HCN is generated and further reacted in the microreactor. Moderate to good yields were achieved, which gave an outcome of up to 60 g/day of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones. To avoid that crystallisation occurred in the system, 2 types of solutions were possible. The first and most obvious one was a decrease in residence time together with a decrease in concentration of the starting materials. A second approach was based on an alternative and easy setup, using plug flow, and allowed to work at higher concentrations. When using an aliphatic amine, the final tautomerisation towards the end product did not proceed and a competition with the appropriate Strecker reaction was seen. Finally, a qualitative and quantitative comparison was made between the batch and microreactor setup for the safe use of HCN. It was concluded that the release of HCN in the air was approximately 2 orders of magnitude smaller in the case microreactor technology was used.

3.6 SYNTHESIS OF 1*H*-ISOCHROMENO[3,4-*d*]IMIDAZOL-5-ONES

3.6.1 Introduction

Using the previously formed 3,4-diamino-1*H*-isochromen-1-ones **17** under microreactor conditions with *in situ* formation of hydrogen cyanide, a ring closure of the vicinal amino groups was evaluated in order to attach an imidazole core to the molecule. Until now, this skeleton was only detected once in a side reaction for the production of 3*H*-indeno[2,1-*d*]imidazol-8-ones **135** starting from the addition of N-substituted amidines **131** to ninhydrin **130** (Scheme 3.13).[362] These compounds **135** are members of the indenoimidazoles, which show biological effects such as analgesic, anti-inflammatory and anticonvulsive activity.[363,364] Some related compounds, which contain the chromenone instead of the isochromenone structure (Figure 3.25), are known to have an interesting biological activity as phosphodiesterase inhibitor for the treatment of allergic or immunity-associated diseases[365] and as central nerve system depressants[366].



129

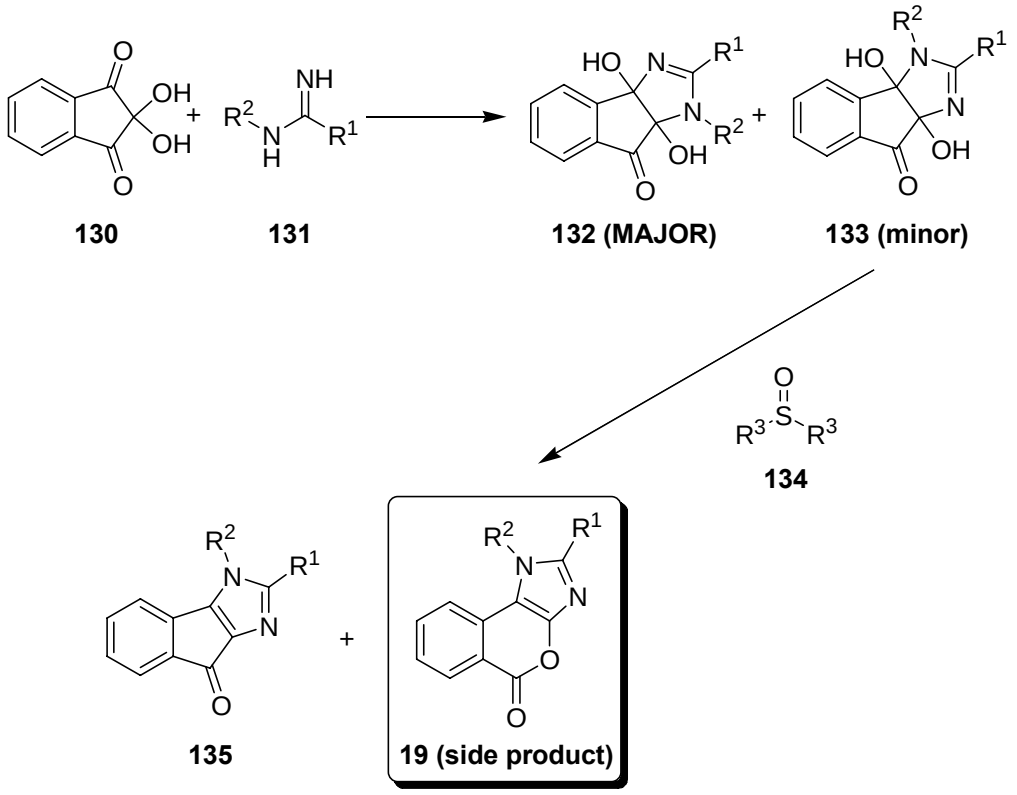
R^1 = H, alkyl, (hetero)aryl
R^2 = H, alkyl
X = O, S

Figure 3.25: 1*H*-(thio)chromeno[3,4-*d*]imidazol-4-ones **129**, as an example of compounds with a chromenone structure showing biological activity.

3.6.2 Optimisation study using microreactor technology

After the microreactor synthesis and the isolation of the starting 3-amino-4-(arylamino)-1*H*-isochromen-1-one **17**, a subsequent microreactor

modification was envisaged to decorate the scaffold *via* the synthesis of a physiologically interesting imidazole moiety.



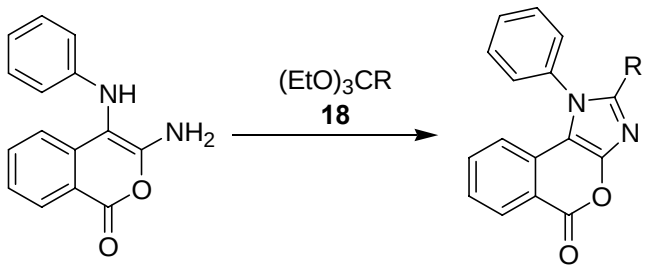
R^1,R^2 = Ph,Me; Ph,*c*-Hex; Ph,Bn; Ph,Ph; $(CH_2)_3$; $(CH_2)_4$; $(CH_2)_5$
R^3 = Cl, 1-imidazolyl, $N(CH_3)_2$, $N(C_2H_5)_2$, $N(i\text{-}Pr)_2$

Scheme 3.13: Formation of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19** as a side-product during the synthesis of 3*H*-indeno[2,1-*d*]imidazol-8-ones **135**.

The initial part of the research consisted of the search for compatible reaction conditions for the ring closure in the microreactor. Scheme 3.14 displays the ring closure using orthoesters. A set of different reaction conditions based on known ring closures to imidazole structures[367-369] was evaluated in batch to find suitable parameters for the implementation to microreactor conditions. Table 3.21 summarises the results of the optimisation of the reaction.

In these initial batch studies, three different acids, either in catalytic or in equimolar amounts, were tested to obtain the ring closed product. The acid was necessary to activate the orthoester. In the case of ethyl orthoformate $(EtO)_3CH$ **18a**, a catalytic amount of p-TsOH was enough to push the

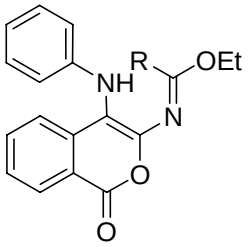
reaction to completion (entry 1). An analogue procedure with HCl (entry 2) yielded the end product also in quantitative amounts, but much faster. In both these procedures, the orthoester was used as a solvent. In the case TFA was used as the acid catalyst (entry 3), almost quantitative yields were obtained. In this reaction setup, dichloromethane was utilised as solvent. All these batch procedures resulted in solubility problems of the starting compound, which needed to be overcome before testing the reaction under microreactor conditions. When dichloromethane was used as solvent, it was possible to dissolve the 3-amino-4-phenylamino-1*H*-isochromen-1-one **17a** only in small amounts (less than 0.1 M). In case the orthoester itself served as solvent, even worse results were obtained. Since this concentration is too low to perform a continuous reaction with a reasonable output, other solvents were tested. It appeared that only DMF and related solvents were suitable to dissolve larger amounts of the starting compound.



17a **19a (R = H)** **19i (R = CH_3)**

Scheme 3.14: Formation of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19**.

If ethyl orthoacetate $(EtO)_3CCH_3$ **18b** was used as orthoester, only an intermediate product was formed in the case of HCl (entry 4) and p-TsOH (entry 5). It seemed that the cyclisation with $(EtO)_3CCH_3$ **18b** was more demanding.[367] It was seen that the reaction did not go to completion and based on the spectral data it was assumed that ethyl N-(1-oxo-4-phenylamino-1H-isochromen-3-yl)acetimidate **136i** was isolated as the intermediate (Figure 3.26). Only in the case TFA was used as the catalyst, complete cyclisation was obtained in excellent yields (entry 6).



136a (R = H)
136i (R = CH_3)

Figure 3.26: Ethyl N-(1-oxo-4-phenylamino-1H-isochromen-3-yl)acetimidate **136i** formed as an intermediate.

Table 3.21: Ring closure to 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19** under batch conditions.

Entry	*Orthoester*	*Conditions*	*Reaction time (h)*	*Yield (%)*[c]
1	$(EtO)_3CH$	A	3	quantitative
2	$(EtO)_3CH$	B	0.5	quantitative
3	$(EtO)_3CH$	C	2	97
4	$(EtO)_3CCH_3$	A	6	intermediate **136i**
5	$(EtO)_3CCH_3$	B	2.5	intermediate **136i**
6	$(EtO)_3CCH_3$	C	2	96

A: 1 mmol of compound **17a** and 0.1 mmol of p-toluenesulfonic acid monohydrate (p-TsOH) were added to 10 mL of the orthoester **18a** or **18b** at room temperature.[367] B: 1 mmol of compound **17a** and 1 mmol of 12.1 N HCl were added to 5 mL of the orthoester **18a** or **18b** at room temperature.[367] C: 1 mmol of compound **17a**, 0.5 mmol of trifluoro acetic acid (TFA) and 5 mmol of the orthoester **18a** or **18b** were added to 10 mL of dichloromethane at room temperature.[368]

To optimise the reaction under microreactor conditions, different parameters were analysed: solvent, reaction time, temperature, concentration and the ratio of start product **17**, catalyst and orthoester **18**. The optimisation was started based on the reaction conditions of the p-TsOH catalysed ring closure. Due to the low solubility of the start product **17a**, DMF was the solvent of choice. Table 3.22 shows the optimisation efforts. As can be seen from the table, the optimal reaction temperature was room temperature (entry 2). Both an increase or a decrease of the reaction temperature led to worse results. In the case of 0 °C (entry 1), the final reaction mixture contained only starting

product and end product, while at 100 °C (entry 4) the intermediate was detected together with the end product. Increasing the catalytic amount of p-TsOH gave rise to the formation of trace amounts of a side-product. After analysis of the ^{1}H-NMR spectrum, it became clear that the side-product was ethyl p-toluene sulfonate (p-TsOEt, entries 5 and 6). If the excess of orthoester was increased, similar effects occurred (entries 7 and 8). In the case of a 50:50 solvent mixture (orthoester/DMF, entry 9), no complete conversion was achieved and the amount of p-TsOEt increased even to 11 mol% in the mixture.
The concentration of the starting product was finally doubled to 0.2 M with a similar outcome as entry 2 (entry 10). A final optimisation step resulted in the decrease of the residence time (entries 11-13). It was possible to decrease the residence time to approximately half an hour. Further decrease resulted in incomplete conversion. The optimised conditions were: 0.2 M starting product **17a** in DMF was mixed at room temperature in the microreactor with a mixture of 0.1 equivalents of p-TsOH and 5 equivalents of $(EtO)_3CH$ **18a** in DMF with a total residence time in the microreactor and RTU of 30 min.

Although complete conversion and reasonable yields were already obtained after the RTU with the initial reaction conditions (entry 2), the further optimisation tests were performed in order to achieve a complete conversion after the microreactor unit (i.e. after 5 min of reaction instead of 118 min). Comparison of the conversion results after the microreactor and after the RTU, showed that in most cases complete conversion was easily obtained in the latter case, which is obvious due to the prolonged reaction time. On the other hand, after the microreactor a mean conversion of only 50 % was achieved. However, the different optimisation steps were not successful in order to get a complete conversion. The best result was obtained in the case of a twenty-fivefold excess of $(EtO)_3CH$ **18a** (81 %, entry 8). In all reaction samples taken after the microreactor, traces of the intermediate **136a**, p-TsOEt or both were detected.

Table 3.22: Optimisation of the ring closure of **19a** under microreactor conditions.[a]

Entry	*T (°C)*	*p-TsOH (equiv)*	*$(EtO)_3CH$ (equiv)*	*After microreactor*		*After RTU*	
				Conversion (%)[b]	*Yield (%)*[c]	*Conversion (%)*[b]	*Yield (%)*[c]
1	0	0.1	5	41	24	78	58
2	RT	0.1	5	58	28	100	86
3	50	0.1	5	52	19	100	87
4	100	0.1	5	0	0	67	27
5	RT	0.2	5	52	29	100	78
6	RT	0.5	5	60	28	100	82
7	RT	0.1	10	46	22	100	79
8	RT	0.1	25	81	50	100	76
9	RT	0.1	60	19	14	90	67
10[d]	RT	0.1	5	54	43	100	82
11[d,f]	RT	0.1	5	--	--	100	80
12[d,f]	**RT**	**0.1**	**5**	**--**	**--**	**100**	**88**
13[d,g]	RT	0.1	5	--	--	97	43

--: Not measured. [a] Inlet A: 0.1 M of **17a** in DMF; inlet B: $(EtO)_3CH$ **18a** and p-TsOH in DMF; residence time after microreactor: 5 min; residence time after RTU: 118 min. [b] Based on the integration signals in the ^1H NMR spectrum. [c] Based on the total mass of end product collected from the rough mixture and the degree of conversion. [d] Inlet A: 0.2 M of **17a** in DMF. [e] Residence time after RTU: 59 min. [f] Residence time after RTU: 29.5 min. [g] Residence time after RTU: 19.6 min.

A final attempt to achieve complete conversion at the end of the microreactor resulted from stopped-flow experiments in previous work (*vide supra*, § 3.2.4 and 3.3.2).[151,158,247] Based on the optimised results for the output after the microreactor in Table 3.22 (which gave a conversion of around 50 %, entry 2), it was decided to double the residence time in the microreactor twice: one time to achieve a theoretically 100 % conversion and a second time as a safety margin. This led to a flow period of 1 min alternated with a pump stop period of 3 min. Table 3.23 shows the results of this study. Entry 1 shows that this setup did not result in complete conversion. An increase of the residence time by increasing the stop period (entry 3) gave even a lower conversion. Longer

residence times were not examined since it is not interesting from a practical point of view due to the very low flow rates resulting in a low output per time unit. A final attempt was made by increasing the excess of orthoester since this gave better results in the optimisation procedure (Table 3.22, entry 8). In this case, it gave only similar results. So, it was not possible to get complete conversion after the microreactor.

Table 3.23: Use of the stopped-flow technique in the optimisation of the reaction output at the microreactor outlet.[a]

Entry	*Stop-flow (min-min)*	*Residence time (min)*	*$(EtO)_3CH$ (equiv)*	*After microreactor*	
				Conversion (%)[b]	*Yield (%)*[c]
1	3-1	20	5	84	61
2	3-1	20	25	87	59
3	5-1	30	5	60	35

[a] Inlet A: 0.2 M of **17a** in DMF; inlet B: $(EtO)_3CH$ **18a** and 0.02 M of p-TsOH in DMF; room temperature; stopped-flow technique. [b] Based on the integration signals in the ^1H NMR spectrum. [c] Based on the total mass of end product in the crude mixture and the degree of conversion.

The goal to achieve complete conversion after the microreactor was to combine the reaction with a continuous extraction in the RTU, since initial tests with a continuous extraction gave better performances in product recovery. An optimised work up procedure had to be evaluated, since DMF is difficult to remove from the reaction mixture.

Several work up conditions were tested such as a basic extraction in the presence of $NaHCO_3$ and different acidic work ups (HCl, acetic acid) in batch mode and also *via* a micro-extraction[14] in basic medium. Under batch conditions, several extraction steps were necessary to remove all DMF in both basic and acid extractions, which resulted in a loss of approximately 20 % of the product. The HCl-based extraction gave the best performance in

[14] During the micro-extraction, the reaction mixture was dissolved in an equal amount of CH_2Cl_2 and was pumped *via* one inlet of the microreactor, while the extraction medium was pumped *via* the other inlet (successively 60 mL of H_2O, 60 mL of $NaHCO_3$ solution and 60 mL of H_2O).

DMF removal, while the acetic acid based extraction was the worst. Since the microreactor used in this study is made of stainless steel, no continuous HCl extraction was possible, so only the basic extraction was tested in the micro-extraction procedure. This gave a recovery of 97 % of the end product. The main disadvantage here was the lower performance in DMF removal. After extraction, the mixture still existed for approximately 50 % of DMF. Unfortunately, although good recovery results were obtained, this micro-extraction was not applicable due to the incomplete conversion achieved after the microreactor. All the previous results were therefore worked up using the HCl-based batch extraction procedure.

3.6.3 Generality of the reaction

Finally, the generality of the optimised conditions were tested. This was accompanied by some additional problems. The results are shown in Table 3.24. Entries 2 and 4 already indicate that the optimised reaction conditions are not general for all starting materials. However, after elongation of the residence time to approximately 2 h, all the end products without substituent on the 2-position were completely converted to the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19** (entry 3 and entry 7-9). The only exception was the 3-tolyl substituted compound **17c** that was only converted in 48 % to the end product after the maximal residence time of 2 h (entry 5).

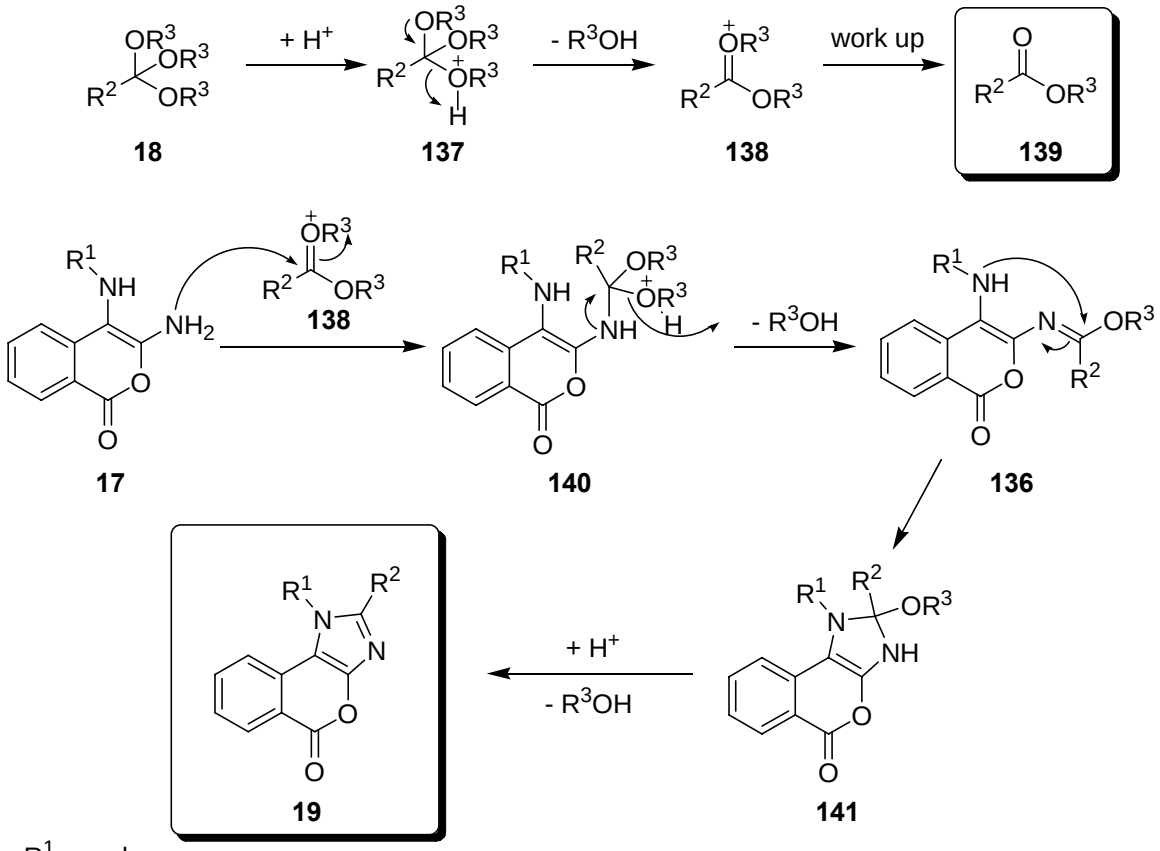
In the case of more sterically demanding orthoesters, such as triethyl orthoacetate **18b**, trimethyl orthovalerate **18c** and trimethyl orthobenzoate **18d**, it was not possible to obtain a complete conversion at the end of the RTU under the given conditions. Since under batch conditions, the reaction to achieve ring closure was faster with TFA (Table 3.21), it was decided to check this harsher procedure under microreactor conditions for the reactions that did not proceed or proceeded only partially. It had to be taken into account that there was no known effect of the TFA concentration on the

inside of the microreactor.[15] In the case of the 3-tolyl substituted 1*H*-isochromen-1-one **17c**, it was possible to obtain a complete conversion of the reaction (entry 6). For the other substituents, it was only possible to obtain a partial conversion (entries 11-13). This was due to the bulky substituent that had to be incorporated which lowered the reaction rate.

A possible reaction mechanism for the formation of the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19** is presented in Scheme 3.15. In the reaction mixture to produce the phenyl substituted compound (entry 13), a large amount of methyl benzoate was detected. When investigating the ^{1}H NMR spectrum of the crude mixture of the *n*-butyl substituted compound (entry 12), there were also some peaks detected which could lead to the corresponding methyl pentanoate. No ester formation is possible during the reaction itself, since no water is present. So it is suggested that the intermediate product **138** formed during the reaction is converted to the ester **139** during the quenching of the reaction and the subsequent work up. Reinvestigating the spectra of the reactions with triethyl orthoacetate **18b**, showed also a small amount of ethyl acetate.

In the case of complete conversion to the end products, no extra purification was necessary. But when only partial conversion was obtained, the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19** were further purified by crystallisation. Using the method optimised in this study, it was possible to produce a small library of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19** applying microreactor technology.

[15] Oral communication with the manufacturers of the microreactor device learned that there was no knowledge about the effect of TFA on stainless steel 1.4571 (German Standard). It was decided to work under very dry conditions, using fresh DMF.



Scheme 3.15: Suggested reaction mechanism of the ring closure towards the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19** and the formation of side-products.

The ideal procedure would be a two step sequence formation of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones initially starting from 2-formyl benzoic acid **15** without the need for intermediary work up. Unfortunately, as already stated in the discussion, the 3-amino-4-(arylamino)-1*H*-isochromen-1-ones had the tendency to crystallise in methanol once they were produced in a reasonable amount. Similar to other research,[157] a solvent switch, and a simultaneous purification, between both reactions was necessary before the ring closing reaction could be performed. This was a disadvantage of the procedure. Attempts were made to produce the 1*H*-isochromeno[3,4-*d*]imidazol-5-one in a one step procedure starting from 2-formyl benzoic acid, but without any success.

Table 3.24: Optimised conditions to produce 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **19** in the microreactor.[a]

Entry	*R¹*	*R²*	*Product*	*Conversion (%)*[b]	*Yield (%)*[c]	*Output (g/day)*
1[d]	Ph	H	**19a**	100	88	53.0
2[d]	3-Methoxyphenyl	H	**19b**	46	7	4.8[g]
3[e]	3-Methoxyphenyl	H	**19b**	100	55	9.4
4[d]	3-Tolyl	H	**19c**	34	8	5.0[g]
5[e]	3-Tolyl	H	**19c**	48	27	4.3[g]
6[f]	3-Tolyl	H	**19c**	100	69	11.0
7[e]	4-Methoxyphenyl	H	**19d**	100	75	12.7
8[e]	4-Tolyl	H	**19e**	100	78	12.5
9[e]	4-Fluorophenyl	H	**19f**	100	92	14.9
10[e]	Ph	CH_3	**19i**	0	0	0
11[f]	Ph	CH_3	**19i**	52	36	5.8[g]
12[f]	Ph	C_4H_9	**19j**	27	18	3.4[g]
13[f]	Ph	Ph	**19k**	2	1	0.2[g]

[a] General conditions: inlet A: 0.2 M of **17** in DMF; inlet B: acid and 1.0 M of **18** in DMF; room temperature, sampling at the RTU outlet. [b] Based on the integration signals in the ^{1}H NMR spectrum. [c] Based on the total mass of end product collected from the rough mixture and the degree of conversion. [d] Residence time: 29.5 min, acid: 0.02 M p-TsOH. [e] Residence time: 118 min, acid: 0.02 M p-TsOH. [f] Residence time: 118 min, acid: 0.1 M TFA. [g] Purification *via* crystallisation.

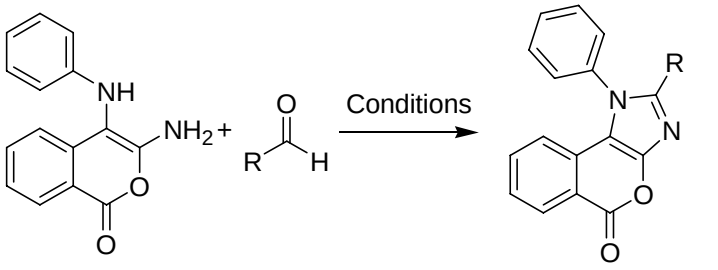
3.6.4 Other ring closing methods

Next to the previous optimised procedure, attempts were made to broaden the scope of the reaction including other substituents on the 2-position of the imidazole moiety, because of the small variability of the orthoesters. Among a wide variety of ring closing methods of diamino aryl compounds, a lot of procedures were rejected, because of problems related to the compatibility with the microreactor system.[370-377] A method using silica treated with thionyl chloride for the formation of benzimidazoles was not feasible due to the solid nature of the reagents.[370] Other methods using solids,[371,372] such as a

manganese dioxide mediated tandem oxidation process[371] and a L-proline mediated benzimidazole synthesis[372] were also not applicable. The use of a 2-step procedure was also not suitable.[373,374] In the first procedure, 1,2-diphenylamines reacted with an aldehyde to the corresponding benzimidazolines. These require an oxidative step with aerial oxygen or elemental sulphur to obtain the benzimidazole.[373] The other 2-step procedure involved a condensation reaction of the 1,2-diphenylamines with carboxylic acid under 1-propane phosphonic cyclic anhydride catalysis, followed by dehydratation towards the end product.[374] An efficient procedure using (bromodimethy)sulfonium bromide was not evaluated because of the corrosive effect of the bromine ions on the stainless steel microreactor,[375] other procedures using chlorine likewise[376,377].

Finally, three literature procedures, using acetic acid as dehydratation compound,[378] or 1,4-benzoquinone[379,380] or Oxone®[381] as oxidation agent were tested first on a batch process to produce compound **191**, but only the last procedure gave good results (Table 3.25). Using the Oxone® mediated procedure, a variety of imidazoles were produced in batch conditions. A major problem to implement this procedure to a microreactor setup was the rapid precipitation of the Oxone® when put in contact with DMF. Also the end product precipitated during the reaction. To prevent this in the microreactor, the goal was to use a similar setup as in the 1*H*-isochromen-1-one synthesis: a 2-phasic system with Fluorinert® to prevent contact of the precipitate with the microreactor wall was evaluated. Therefore, the Fluorinert® was added at the microreactor inlet were the Oxone® solution was injected. A scheme of the reaction setup is given in Figure 3.27. Initial experiments were made using only the Oxone® solution (so without any other reagent) to test the procedure. Unfortunately, it was seen that, after a short period of normal flow, clogging of the microreactor occurred. Even by changing the solution to a higher water content or by lowering the concentration of Oxone®, precipitation occurred with subsequent clogging as a consequence. Therefore, this method for 1*H*-isochromeno[3,4-*d*]imidazol-5-one synthesis was not further evaluated.

Table 3.25: Different methods for the ring closure towards the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones.



17a **1**

19k (R = Ph)
19l (R = 4-nitroPh)
19m (R = *i*-Pr)
19n (R = *c*-Hex)

Entry	*Conditions*	*Product*	*Yield (%)*	*Reference*
1	10 equiv **1a**, 5 % HOAc in DMA, 120 °C	**19l**	No reaction	[378]
2	1 equiv **1a**, 1 equiv 1,4-benzoquinone, DMF, reflux	**19l**	Complex reaction mixture	[379,380]
3	1.1 equiv **1a**, 0.65 equiv Oxone®, DMF/water (30:1), RT	**19l**	58 (25[a])	[381]
4	1.1 equiv aldehyde, 0.65 equiv Oxone®, DMF/water (30:1), RT	**19k**	31	[381]
5	1.1 equiv aldehyde, 0.65 equiv Oxone®, DMF/water (30:1), RT	**19m**	43	[381]
6	1.1 equiv aldehyde, 0.65 equiv Oxone®, DMF/water (30:1), RT	**19n**	56	[381]

[a] After crystallisation.

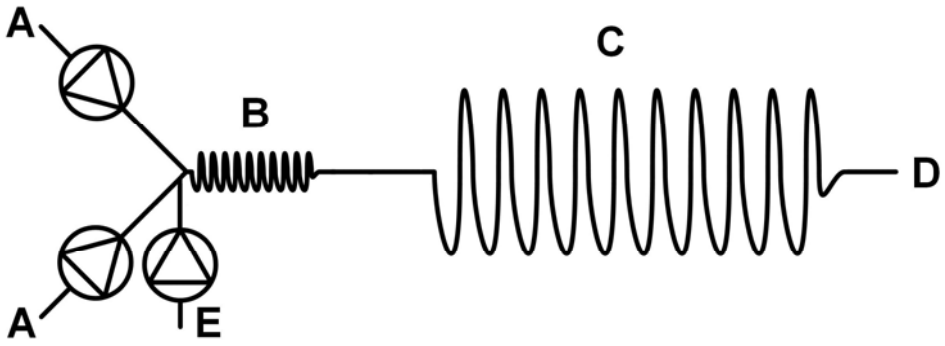


Figure 3.27: Setup for the Oxone® mediated reaction. A = input reagents (input Oxone® *via* the T-junction with E), B = microreactor, C = RTU, D = output reaction mixture, E = input Fluorinert® FC-70.

3.6.5 Conclusions

Starting from 3-amino-4-(arylamino)-1*H*-isochromen-1-ones, produced under microreactor conditions, different procedures were tested to ring close the vicinal amino groups towards an imidazole moiety. Only one procedure, which used orthoesters, proved to be suitable under microreactor conditions. This reaction was further optimised. Attempts to completely convert the 3-amino-4-(arylamino)-1*H*-isochromen-1-ones towards the 1*H*-isochromeno [3,4-*d*]imidazol-5-ones in the microreactor itself, failed. After optimisation, it was possible to apply this method under microreactor conditions leading to a small library of compounds with a new 1*H*-isochromeno[3,4-*d*]imidazol-5-one skeleton. Moderate to good yields were obtained and in the case of complete conversion of the reaction, a continuous output of up to 53 g/day of end product was achieved. However, depending on the substrate, some extra adjustments were necessary during the generalisation.

Chapter 4 - Experimental Procedures

4.1 GENERAL EQUIPMENT

4.1.1 NMR spectrometry

^{1}H NMR spectra (300 MHz), ^{13}C NMR spectra (75 MHz), ^{31}P NMR spectra (121 MHz) and ^{19}F NMR spectra (282 MHz) were recorded on a *Jeol Eclipse FT 300 NMR* spectrometer. The compounds were diluted in deuterated solvents and peaks are relative to tetramethylsilane (TMS) as internal standard. Peak assignments were accomplished by using COSY, DEPT, HSQC and HMBC spectra.

4.1.2 Infrared spectrometry

Infrared spectra were measured with a *Perkin-Elmer Spectrum One FT-IR* spectrophotometer. For liquid samples, spectra were recorded by putting a small drop of product between two sodium chloride plates. For crystalline products, a small amount was mixed with potassium bromide and pressed to a transparent potassium bromide plate.

4.1.3 Mass spectrometry

Low resolution mass spectra of pure compounds were recorded *via* direct injection on an *Agilent 1100 Series LC/MSD type SL* mass spectrometer with Electron Spray Ionisation geometry (ESI 70 eV) and using a Mass Selective Detector (quadrupole). If crude reaction mixtures were analysed, the mass spectrometer was preceded by a HPLC reversed phase column with a diode array UV/VIS detector. High resolution mass spectra were obtained on a *Finnigan MAT 95 XPAPI-GC-Trap tandem Mass spectrometer* system.

4.1.4 Gas chromatography

Gas chromatography analysis was performed on an *Agilent 6890 Series*. The column that was used was of the type Alltech EC-5 with a film thickness of 0.25 μm (length 30.0 m, i.d. 250 μm) with helium as the carrier gas. The GC was connected to a FID detector (H_2 gas).

4.1.5 Melting point

Melting points of crystalline products were measured with a *Büchi B-540* apparatus and are uncorrected.

4.1.6 Column chromatography

For purification of crude reaction mixtures, column chromatography was applied. For the packing of the column, silica gel (*Acros Organics*, particle size 0.035-0.070 mm, pore diameter ca. 6 nm) was used. Solvent systems were obtained *via* thin-layer chromatography (TLC) analysis (*Merck*, Kieselgel $60F_{254}$, precoated 0.25 mm). UV light, adsorption with iodine vapours or colouration with $KMnO_4$ were used for detection of the compounds on the silica plates.

4.1.7 Reagents

The reagents were used without prior purification, unless otherwise stated. Fluorinert® FC-70 was purchased from *Acros Organics*.

4.1.8 Elemental analysis

Elemental analysis was performed with a *Perkin Elmer 2400 Series 2 Elemental Analyser*.

4.1.9 Microreactor system

The microreactor used in this study is a CYTOS® College System provided by *CPC-Cellular Process Chemistry Systems GmbH* (Figure 3.1).[176] The CYTOS® College System microreactor consists of several stacked plates with microstructures in the sub-millimeter range (width approximately 100 μm). The internal volume of the microreactor itself is 2 mL ($V_{microreactor}$) and that of the RTU is 45 mL (V_{RTU}) so the total volume (V_{total}) of the system is 47 mL. For the moving of reaction mixtures or solvents, pumping was pressure-driven *via* 2 valveless rotary piston dispensing pumps (pump: *Ismatec®*, REGLO-CPF Digital, pump head: *Fluid Metering Inc.*, FMI 005, ceramic piston, 5-50μL/stroke). Cooling or heating of the system was provided by an external circuit *via* a circulation thermostat (*Peter Huber Kältemaschinenbau GmbH*, Huber Unistat Tango).

4.2 GENERAL MICROREACTOR SETUP

Unless otherwise stated, the general procedure for a reaction under microreactor conditions was as follows. First, the system was cooled or heated at the desired temperature using the thermostat. The pumps were calibrated at the desired flow rate ($r_{piston\ pump}$), according to the desired residence time τ, using the solvent of the reaction. The residence time τ was calculated by the following formula:

$$\tau\,(\text{min}) = \frac{V_{total}}{r_{total}} \text{ with } r_{total} = 2\ r_{piston\ pump} \qquad (4.1)$$

with V_{total} = inner volume of the microreactor and RTU (mL)
r_{total} = total flow rate of the 2 piston pumps (mL/min)
$r_{piston\ pump}$ = flow rate of the piston pump (mL/min)

Meanwhile, both solutions with the appropriate reagents were prepared in a measuring cylinder. Care has to be taken that no solid particles were present

in the solutions. The reagent solutions were connected to the inlets of the microreactor system. The pumps were started and the flow rate was controlled by measuring both incoming and outcoming volume per time unit. At the outlet, the end product was collected at steady state conditions, i.e. after minimal 1.6 τ. When enough sample volume was taken, the reaction mixtures at the inlet were replaced again by the solvent and the system was flushed with at least 2 times the inner volume of the device. The sample was finally analysed according to the procedure mentioned in the experiments.

4.3 BAYLIS-HILLMAN STUDY

4.3.1 General procedure in batch mode (Table 3.1, entry 1)

For the Baylis-Hillman reaction in batch mode, the procedure of Yu *et al.*[236] was followed. In a round-bottom flask, 4-nitrobenzaldehyde (151 mg, 1 mmol), DABCO (112 mg, 1 equiv), and methyl acrylate (272 μL, 3 equiv) were mixed in 10 mL of water/1,4-dioxane (v/v 1:1). The solution was stirred for different time intervals (see Figure 3.5) after which the mixture was partitioned with 150 mL of *tert*-butyl methyl ether and 80 mL of water. The organic phase was washed with 2 times 50 mL of brine, dried with $MgSO_4$ and filtered, and the solvent was evaporated. A ^{1}H-NMR spectrum of the crude mixture was recorded. The degree of conversion was calculated using the integration of the signals in the ^{1}H-NMR spectrum. The yield of the reaction was calculated from the total mass of end product collected and the degree of conversion. The other results were obtained in the same way, except for minor changes such as concentration and the lack of stirring the mixture.

4.3.2 General procedure using the microreactor (Table 3.2)

For entry 1, a solution of 0.2 M 4-nitrobenzaldehyde and 0.2 M DABCO in a water/1,4-dioxane (v/v 1:1) mixture was prepared and transferred in a measuring cup. Another solution of 0.6 M methyl acrylate was prepared in the

same solvent mixture and transferred to a second measuring cup. Both measuring cups were connected to the CYTOS® College System and the ***general microreactor setup*** was followed. At the outlet, about 10 mL sample was quenched with 10 mL of 1 N HCl and collected for analysis. The work up of the reaction mixture was performed using the procedure of Yu *et al.* (*vide supra*, § 4.3.1).[236] The degree of conversion and the yield were calculated in the same way as in the batch procedure. The other results in Table 3.2 were obtained in the same way, except for changes such as concentration, ratio of reagents, mixing of reagents, temperature, flow rate, catalyst, as stated with the experiments.

For the results of Table 3.3, reagents were dissolved in sulfolane and a different work up procedure was used.[187] The 10 mL sample was diluted with 20 mL of water and extracted with 3 times 30 mL of diethyl ether. The combined organic layers were washed with brine, dried with $MgSO_4$ and filtered, and the solvent was evaporated. The degree of conversion and the yield were calculated in the same way as in the batch procedure.

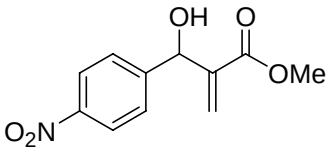
In Table 3.4, the aldehyde and alkene were varied. A ratio for aldehyde/DABCO/alkene of 1:1:3 was maintained and the further procedure was in accordance with the general procedure in the microreactor. In the case of concentrations above 0.1 M aldehyde, the aldehyde and DABCO were dissolved in a 3:7 (v/v) mixture of water and 1,4-dioxane. The alkene was added to a 7:3 (v/v) water/1,4-dioxane mixture and was continuously stirred to have a homogeneous solution.

4.3.3 Stopped-flow technique (Table 3.5)

In the experiments with the stopped-flow technique, the same conditions were used as in the ***general microreactor setup***. The goal was a fivefold increase in residence time. A flow time of 1 min was chosen, so the stop time was 4 min. With a total volume of 47 mL and a flow rate of 0.2 mL/min.pump, this led to a total residence time increase from 1 h 58 min to 9 h 50 min.

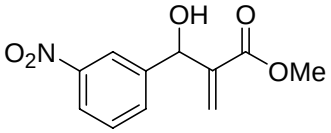
Compounds **4a,g,h**,[382] **4b-e**,[236] and **4f**[383] are known compounds, and their spectroscopic data matched those reported in the literature.

Methyl 2-[hydroxy-(4-nitrophenyl)-methyl]acrylate 4a



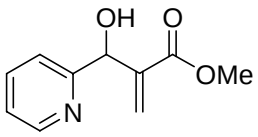
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.29 (1 H, d, *J* = 6.3 Hz, OH), 3.75 (3 H, s, OCH_3), 5.64 (1 H, d, *J* = 6.1 Hz, C*H*OH), 5.87 (1 H, s, C=CH_2), 6.40 (1 H, s, C=CH_2), 7.58 (2 H, d, *J* = 8.8 Hz, arom. H), 8.21 (2 H, d, *J* = 8.8 Hz, arom. H).

Methyl 2-[hydroxy-(3-nitrophenyl)-methyl]acrylate 4b



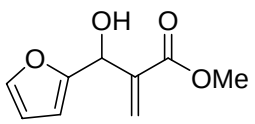
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.00-3.80 (1 H, br s, OH), 3.69 (3 H, s, OCH_3), 5.67 (1 H, s, C*H*OH), 5.98 (1 H, s, C=CH_2), 6.42 (1 H, s, C=CH_2), 7.53 (1 H, t, *J* = 8.0 Hz, arom. H), 7.76 (1 H, d, *J* = 7.7 Hz, arom. H), 8.12 (1 H, m, arom. H), 8.25 (1 H, d, *J* = 1.7 Hz, arom. H).

Methyl 2-[hydroxy-pyridin-2-yl-methyl]acrylate 4c



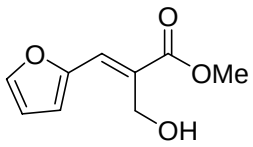
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.74 (3 H, s, OCH_3), 4.83 (1 H, d, *J* = 5.2 Hz, OH), 5.62 (1 H, d, *J* = 3.9 Hz, C*H*OH), 5.97 (1 H, br s, C=CH_2), 6.36 (1 H, br s, C=CH_2), 7.22 (1 H, ddd, *J* = 7.5, 5.0, 1.1 Hz, arom. H), 7.42 (1 H, d, *J* = 8.0 Hz, arom. H), 7.68 (1 H, td, *J* = 7.7, 1.7 Hz, arom. H), 8.55 (1 H, d, *J* = 4.7 Hz, arom. H).

Methyl 2-[furan-2-yl-hydroxymethyl]acrylate 4d



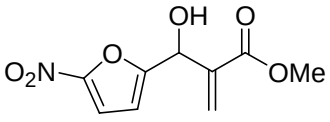
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.25 (1 H, br s, OH), 3.77 (3 H, s, OCH_3), 5.60 (1 H, t, *J* = 1.1 Hz, C*H*OH), 5.96 (1 H, br s, C=CH_2), 6.26 (1 H, br s, =CH), 6.33 (1 H, dd, *J* = 3.2, 1.9 Hz, =CH), 6.39 (1 H, br s, C=CH_2), 7.38 (1 H, m, CHO).

Methyl (2*E*)-3-(furan-2-yl)-2-hydroxymethyl acrylate 89



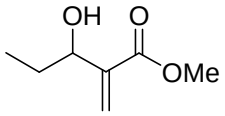
IR (KBr, cm^{-1}): ν_{max} = 3505, 1685 (C=O), 1644, 1439, 1374, 1271, 1218, 1093, 1015, 775. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.52 (1 H, br s, OH), 3.84 (3 H, s, OCH_3), 4.79 (2 H, s, CH_2), 6.52 (1 H, dd, *J* = 3.6, 1.7 Hz, C=CH), 6.73 (1 H, d, *J* = 3.6 Hz, =CH), 7.45 (1 H, s, C*H*=CCH_2), 7.58 (1 H, d, *J* = 1.7 Hz, CHO). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 52.3 (OCH_3), 58.2 (CH_2), 112.5 (C=*C*H), 117.7 (=CH), 126.8 (*C*C=O), 127.5 (*C*H=CCH_2), 145.5 (CHO), 150.7 (CO), 168.5 (C=O). LRMS (70 eV, ES^+): m/z = 165 ($M - OH^-$). Elem. anal.: calculated for $C_9H_{10}O_4$: C, 59.34 %, H, 5.53 %, O, 35.13 %, found: C, 59.19 %, H, 5.50 %, O, 35.31 %. Brown oil. R_f (PE/EA 70:30) =0.17.

Methyl 2-[hydroxy-(5-nitrofuran-2-yl)-methyl]acrylate 4e



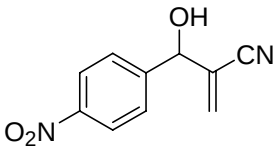
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.55 (1 H, br s, OH), 3.80 (3 H, s, OCH_3), 5.58 (1 H, br s, C*H*OH), 6.07 (1 H, d, *J* = 0.8 Hz, C=CH_2), 6.50 (1 H, br s, C=CH_2), 6.57 (1 H, dd, *J* = 3.9, 0.8 Hz, arom. H), 7.29 (1 H, d, *J* = 3.9 Hz, arom. H).

Methyl 3-hydroxy-2-methylene-pentanoate 4f



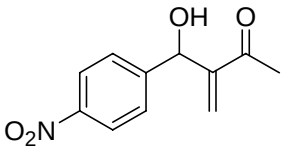
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.95 (3 H, t, *J* = 7.4 Hz, CH_3), 1.61-1.70 (2 H, m, CH_2), 3.70 (1 H, br s, OH), 3.79 (3 H, s, OCH_3), 4.35 (1 H, t, *J* = 6.3 Hz, C*H*OH), 5.81 (1 H, br s, C=CH_2), 6.25 (1 H, br s, C=CH_2).

2-[Hydroxy-(4-nitrophenyl)-methyl]acrylonitrile 4g



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.59 (1 H, br s, OH), 5.47 (1 H, br s, C*H*OH), 6.12 (1 H, d, *J* = 1.1 Hz, C=CH_2), 6.20 (1 H, d, *J* = 1.4 Hz, C=CH_2), 7.62 (1 H, d, *J* = 8.5 Hz, arom. H), 8.28 (1 H, d, *J* = 8.8 Hz, arom. H).

3-[Hydroxy-(4-nitrophenyl)-methyl]but-3-en-2-one 4h



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.36 (3 H, s, CH_3), 3.54 (1 H, br s, OH), 5.69 (1 H, br s, C*H*OH), 6.08 (1 H, d, *J* = 1.1 Hz, C=CH_2), 6.28 (1 H, br s, C=CH_2), 7.55 (1 H, d, *J* = 8.3 Hz, arom. H), 8.17 (1 H, d, *J* = 8.8 Hz, arom. H).

4.3.4 Effect of RTU

4.3.4.1 Description of the 1-line chip

The chip used in this experiment was a 1-line chip (Figure 4.1), with 2 reagent inlets, 1 quenching inlet and 1 product outlet. The quenching of the reaction was internal. The chip was fabricated using standard microfabrication processes. The channels were formed in 4 inch silicon wafers by deep reactive ion etching (BOSCH-type process) using a mask of photoresist. Inlet holes were fabricated using powder-blasting. The silicon wafer was bonded to Pyrex glass by anodic bonding (T = 400 °C, U_{max} = 1000 V, t = 20 min) and then diced into separate chips. The use of only (oxidised) silicon and glass makes the chip compatible with a wide range of organic solvents and reaction temperatures. Channel dimensions are 50 μm x 51 μm (width x depth). The geometry of the reaction chamber was approximately 50 μm x 50 μm x 90 m. The mixer was a small modification (increase of the number of segments, decrease of mixer area) of an in-plane passive microfluidic mixer with modified Tesla structures.[98]

4.3.4.2 Experiment with the 1-line chip (Figure 3.13)

In the first solution (0.2 M of 5-nitro-2-furaldehyde and 0.2 M of methyl acrylate), 1.41 g (10 mmol) of 5-nitro-2-furaldehyde and 2.73 mL (30 mmol) of methyl acrylate were mixed together in a 50 mL mixture of water/1,4-dioxane (v/v 1:1). The solution was sonicated for 30 minutes. The methyl acrylate was added after the sonication in order to prevent reaction. For the

second solution (0.2 M DABCO), 1.12 g (10 mmol) of DABCO was added to a 50 mL mixture of water/1,4-dioxane (v/v 1:1). The solution was also sonicated for 30 minutes. The quenching reagent was a 1 N solution of HCl. This solution was degassed overnight with N_2.

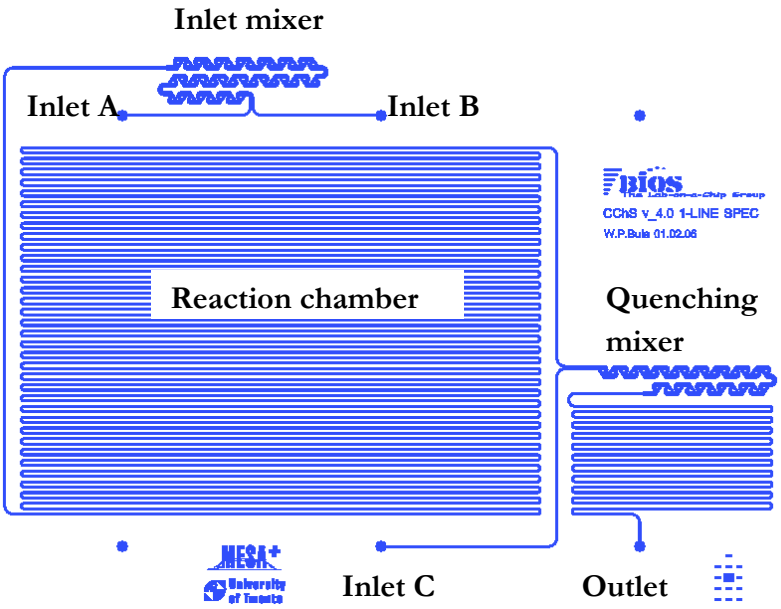


Figure 4.1: Scheme of the 1-line chip.

Before filling the inlet syringes with the reaction solution or quenching solution, the solution was filtered through a Millipore filter (Millex® GV 0.22 µm) to avoid particles to enter the chip. Care had to be taken that no bubbles were present in the syringes to avoid non-reproducible residence times. The syringes were connected to the chip *via* silicon capillaries (i.d. 100 µm). The experiment was started at an initial flow rate of 2.0 µL/min.syringe. After a preflushing stage to reach steady state conditions, 2 samples of approximately 15 µL were collected. Then the flow rate was adjusted to 1.5 µL/min.syringe and the same procedure was followed. This was repeated for the following flow rates: 1.0, 0.8, 0.6 and 0.4 µL/min.syringe. From the collected samples, 10 µL was taken to perform an extraction. To the reaction mixture, 10 µL of water and 30 µL of *tert*-butyl methyl ether were added. The mixture was vigorously stirred by using a vortex mixer. The phases separated in 2 layers and a 1 µL sample of the upper layer was injected in the GC. Calculations of the conversions were based on the peak areas of starting aldehyde **1e** and Baylis-Hillman adduct **4e**, relative to *n*-nonane.

4.3.4.3 Experiment with the CYTOS® College System (Figure 3.10 and 3.13)

The procedure was somewhat different from the ***general microreactor setup***. Following solutions were prepared.

For the first solution (0.2 M of 5-nitro-2-furaldehyde and 0.2 M of methyl acrylate), 2.54 g (18 mmol) of 5-nitro-2-furaldehyde was mixed in a 90 mL mixture of water/1,4-dioxane (v/v 1:1). The mixture was sonicated for 30 min. Then, 4.89 mL (54 mmol) of methyl acrylate were added and the solution was shortly stirred to obtain a homogeneous mixture. In the second solution (0.2 M DABCO), 2.02 g (18 mmol) of DABCO was added to a 90 mL mixture of water/1,4-dioxane (v/v 1:1) and subjected to 30 min sonication. Since the quenching was external, no degassing of the quenching reagent, which was a 1 N solution of HCl, was necessary.

The solutions were connected to the inlet of the CYTOS® microreactor system. The experiment was started at an initial flow rate of 0.2 mL/min.pump. After a preflushing stage to reach steady state conditions, a sample of approximately 10 mL were collected in a 10 mL solution of the quenching reagent. The sample was taken immediately after the microreactor device. Then the flow rate was adjusted to 0.4 mL/min.pump and the same procedure was followed. This was repeated for the following flow rates: 0.8, 1.2, 1.6, 2.0, 4.0 and 8.0 mL/min.pump. For the samples after the RTU, the experiment was performed at a flow rate of 4.7, 9.4 and 18.8 mL/min.pump. From the collected samples, 100 μL was taken to perform an extraction: to every reaction mixture, 100 μL of water and 300 μL of *tert*-butyl methyl ether were added. The mixture was vigorously stirred using a vortex mixer. The phases separated in 2 layers and a 1 μL sample of the upper layer was injected in the GC. Calculations of the conversions were based on the peak areas of starting aldehyde **1e** and Baylis-Hillman adduct **4e**, relative to *n*-nonane.

4.3.4.4 Experiment in batch (Figure 3.13)

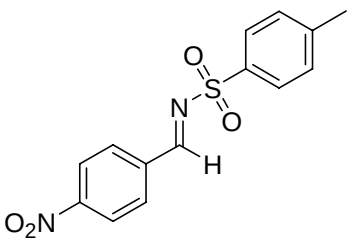
A 10 mL sample of both solutions prepared in § 4.3.4.3 was put together and vigorously stirred. A sample of 50 μL was taken after 15 s, 30 s, 50 s, 1 min, 2 min and 4 min. The samples were worked up and analysed according to a similar procedure as previously mentioned.

All other experiments were obtained in a similar way as the methods described above, with some minor changes such as the mixing of compounds or the use of sonication.

4.3.5 The aza-Baylis-Hillman reaction

4.3.5.1 Synthesis of 4-methyl-N-(4-nitrobenzylidene)benzenesulfonamide 6

The synthesis of **6** was based on a known procedure.[270,384] Generally, 1.51 g 4-nitrobenzaldehyde **1a** (10 mmol) and 1.71 g p-toluenesulfonamide **5** (1 equiv, 10 mmol) were heated under reflux in 70 mL of toluene with a Dean-Stark apparatus. Reflux was continued overnight, with azeotropic removal of water. The mixture was allowed to cool, followed by evaporation of the solvent under reduced pressure. Recrystallisation of the product in chloroform/petroleum ether yielded a light yellow solid in 90 % yield. Spectral data were in accordance with literature data.[385]



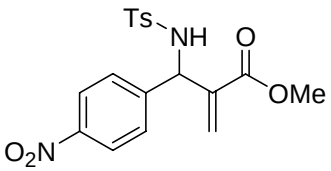
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.46 (3 H, s, CH_3), 7.39 (2 H, d, *J* = 8.3 Hz, arom. H), 7.91 (2 H, d, *J* = 8.3 Hz, arom. H), 8.12 (2 H, d, *J* = 8.8 Hz, arom. H), 8.33 (2 H, d, *J* = 8.8 Hz, arom. H), 9.11 (1 H, s, N=CH).

4.3.5.2 Reaction setup in the microreactor (Table 3.9)

For entry 4, a solution of 0.15 M 4-methyl-N-(4-nitrobenzylidene) benzenesulfonamide **6** and 0.15 M DABCO in DMF was prepared and transferred in a measuring cup. Another solution of 0.45 M methyl acrylate was prepared in the same solvent and transferred to a second measuring cup. Both measuring cups were connected to the CYTOS® College System and the ***general microreactor setup*** was followed. At the outlet, about 10 mL sample was collected for analysis. The reaction mixture was diluted with 50 mL of ethyl acetate and was subsequently washed with 50 mL 0.1 N HCl, 50 mL saturated $NaHCO_3$ and 50 mL brine. The organic phase was dried with $MgSO_4$ and the solvent was evaporated after filtration. A ^{1}H-NMR spectrum of the crude mixture was recorded. The degree of conversion was calculated using the integration of the signals in the ^{1}H-NMR spectrum. The yield of the reaction was calculated from the total mass of end product collected and the degree of conversion. The other results were obtained in the same way, except for minor changes.

Methyl 2-[4-nitrophenyl(toluene-4-sulfonylamino)methyl]acrylate 7

Spectral data were in accordance with literature data.[386]



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.41 (3 H, s, CH_3), 3.63 (3 H, s, OCH_3), 5.36 (1 H, d, *J* = 9.4 Hz), 5.82 (1 H, s, =CH_2), 5.94 (1 H, d, *J* = 9.6 Hz), 6.24 (1 H, s, =CH_2), 7.25 (2 H, d, *J* = 8.5 Hz, arom. H), 7.40 (2 H, d, *J* = 9.1 Hz, arom. H), 7.67 (2 H, d, *J* = 8.3 Hz, arom. H), 8.10 (2 H, d, *J* = 8.5 Hz, arom. H).

4.4 IMIDAZOLES

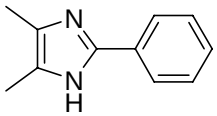
4.4.1 General procedure in batch mode (Table 3.10, entry 6 and Figure 3.18)

In a round-bottomed flask, benzil (10.5 g, 50 mmol), isobutyraldehyde (3.6 g, 1 equiv), ammonium acetate (3.86 g, 1 equiv), benzylamine (6.42 g, 1.2 equiv) and acetic acid (30.0 g, 10 equiv) were mixed and diluted to 200 mL with a NMP/*n*-pentanol (1:1 v/v) solvent mixture. The temperature was controlled at 120 °C with an IKA® ETS-D4 electronic thermometer. At regular time intervals an aliquot of the mixture was taken for GC analysis.

4.4.2 General procedure in the microreactor (Table 3.12, entry 6)

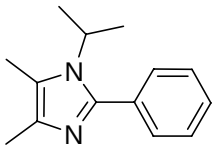
For the optimised production of 1-benzyl-2-isopropyl-4,5-diphenyl-1*H*-imidazole **11f**, a mixture of 0.5 M benzil, 0.5 M isobutyraldehyde and 2.5 M acetic acid in NMP was prepared and transferred to a measuring cup. In a second measuring cup a mixture of 0.5 M NH_4OAc, 0.6 M benzylamine and 2.5 M acetic acid in *n*-pentanol was prepared. Both measuring cups were connected to the CYTOS® College System and the ***general microreactor setup*** was followed. At the outlet, about 10 mL of sample was collected for analysis. An aliquot of the crude reaction mixture was taken for GC and GC-MS analysis. The work up of the reaction mixture consisted of the removal of the solvent mixture of *n*-pentanol, NMP and acetic acid by high-vacuum distillation. Afterwards, the residue was dissolved in 25 mL of CH_2Cl_2 and the organic fraction was washed one time with 100 mL of saturated $NaHCO_3$ and two times with 100 mL of water. The organic fraction was dried with $MgSO_4$ and after filtration the solvent was evaporated. The product was purified through flash chromatography (PE/EA 70:30). All the entries in Table 3.12 were obtained following the same procedure. Instead of 0.5 M NH_4OAc and 0.6 M amine, 1.0 M of NH_4OAc is used in entries 1 and 4. Flash chromatography varied in the used solvent mixtures (see R_f values).

4,5-Dimethyl-2-phenyl-1*H*-imidazole 11'a



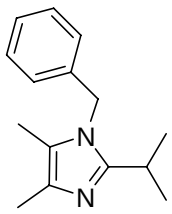
IR (KBr, cm^{-1}): ν_{max} = 3700-3300 (NH), 2355, 2343 (NH), 1624, 1454, 1404 (C=C and C=N). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.19 (6 H, s, 2 x C*H*$_3$), 7.24-7.37 (3 H, m, arom. H), 7.78-7.82 (2 H, m, arom. H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 10.9 (2 C, CH_3), 124.8 (2 C, $CH_{arom.}$), 128.0 ($CH_{arom.}$), 128.3 (2 C, C_q), 128.8 (2 C, $CH_{arom.}$), 130.6 (C_q), 144.2 (C=N). LRMS (70 eV, ES^+): m/z = 173 ($M + H^+$). HRMS: calculated for $C_{11}H_{12}N_2 + H^+$: 173.1073, found: 173.1070. Mp (°C): 222. Light brown crystals. R_f (PE/EA 30:70) = 0.17.

1-Isopropyl-4,5-dimethyl-2-phenyl-1*H*-imidazole 11b



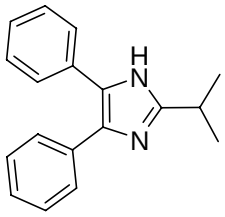
IR (NaCl, cm^{-1}): ν_{max} = 1639, 1595, 1462, 1446 (C=C and C=N), 1393, 1371, 1287 (C-N and $CH(CH_3)_2$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.45 (6 H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 2.19 (3 H_a, s, C*H*$_3$), 2.32 (3 H_b, s, C*H*$_3$), 4.57 (1 H, septet, *J* = 6.9 Hz, $CH(CH_3)_2$), 7.33-7.49 (5 H, m, arom. H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 11.0 (C_bH_3), 12.5 (C_aH_3), 22.2 ($CH(CH_3)_2$), 48.3 ($CH(CH_3)_2$), 122.6 (C_q), 128.4 (2 C, $CH_{arom.}$), 128.5 (C_{para}), 129.6 (2 C, $CH_{arom.}$), 132.2 (C_q), 134.4 (C_q), 146.2 (C=N). LRMS (70 eV, ES^+): m/z = 215 ($M + H^+$). HRMS: calculated for $C_{14}H_{18}N_2 + H^+$: 215.1543, found: 215.1541. Brown oil. R_f (EA 100) = 0.15.

1-Benzyl-2-isopropyl-4,5-dimethyl-1*H*-imidazole 11c



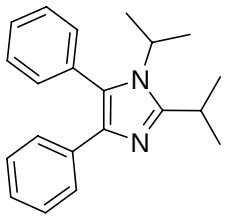
IR (KBr, cm^{-1}): ν_{max} = 1653, 1607, 1496, 1432 (C=C and C=N), 1357, 1324, 1306 (C-N and $CH(CH_3)_2$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.24 (6 H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 1,98 (3 H, s, C*H*$_3$), 2.18 (3 H, s, C*H*$_3$), 2.88 (1 H, septet, *J* = 6.9 Hz, $CH(CH_3)_2$), 5.01 (2 H, s, CH_2), 6.91 (2 H, d, *J* = 6.6 Hz, arom. H), 7.21-7.33 (3 H, m, arom. H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 8.9 (CH_3), 12.8 (CH_3), 22.1 ($CH(CH_3)_2$), 26.3 ($CH(CH_3)_2$), 46.4 (CH_2), 121.6 (C_q), 125.6 (2 C, $CH_{arom.}$), 127.5 (C_{para}), 128.9 (2 C, $CH_{arom.}$), 131.7 (C_q), 137.3 (C_q), 151.5 (C=N). LRMS (70 eV, ES^+): m/z = 229 ($M + H^+$). HRMS: calculated for $C_{15}H_{20}N_2 + H^+$: 229.1699, found: 229.1703. Mp (°C): 104. Brown crystals. R_f (PE/EA 50:50) = 0.32.

2-Isopropyl-4,5-diphenyl-1*H*-imidazole 11'd



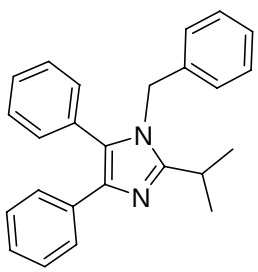
IR (KBr, cm^{-1}): ν_{max} = 3700-3300 (NH), 2369, 2362, 2341 (NH); 1620, 1519, 1444, 1426 (C=C and C=N). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.41 (6 H, d, *J* = 7.1 Hz, CH(C*H*$_3$)$_2$), 3.16 (1 H, septet, *J* = 7.1 Hz, C*H*(CH$_3$)$_2$), 7.20-7.39 (8 H, m, arom. H), 7.59 (2 H, d, *J* = 7.1 Hz, arom. H), 8.75 (1 H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 21.8 (2 C, CH(*C*H$_3$)$_2$), 28.4 (*C*H(CH$_3$)$_2$), 127.2 (2 C, CH$_{arom.}$), 127.8 (4 C, CH$_{arom.}$), 128.6 (4 C, CH$_{arom.}$), 133.2 (2 C, C$_q$), 153.2 (C=N), 2 quaternary carbons were not detected. LRMS (70 eV, ES$^+$): m/z = 263 (M + H$^+$). HRMS: calculated for $C_{18}H_{18}N_2$ + H$^+$: 263.1543, found: 263.1541. Mp (°C): 241. White powder. R_f (PE/EA 70:30) = 0.24.

1,2-Diisopropyl-4,5-diphenyl-1*H*-imidazole 11e



IR (KBr, cm^{-1}): ν_{max} = 1601, 1508, 1462, 1446 (C=C and C=N), 1389, 1375, 1357, 1302, 1270 (C-N and CH(CH$_3$)$_2$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.39 (6 H, d, *J* = 7.1 Hz, NCH(C*H*$_3$)$_2$), 1.46 (6 H, d, *J* = 6.9 Hz, CCH(C*H*$_3$)$_2$), 3.18 (1 H, septet, *J* = 6.9 Hz, CC*H*(CH$_3$)$_2$), 4.30 (1 H, septet, *J* = 7.1 Hz, NC*H*(CH$_3$)$_2$), 7.03-7.16 (3 H, m, arom. H), 7.31-7.45 (7 H, m, arom. H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 22.7 (2 C, CCH(*C*H$_3$)$_2$), 22.9 (2 C, NCH(*C*H$_3$)$_2$), 27.8 (C*C*H(CH$_3$)$_2$), 47.2 (N*C*H(CH$_3$)$_2$), 125.8 (CH$_{arom.}$), 126.8 (2 C, CH$_{arom.}$), 127.4 (1 C, C), 128.0 (2 C, CH$_{arom.}$), 128.5 (CH$_{arom.}$), 128.8 (2 C, CH$_{arom.}$), 131.9 (2 C, CH$_{arom.}$), 132.8 (C$_q$), 135.3 (C$_q$), 136.6 (C$_q$), 152.6 (C=N). LRMS (70 eV, ES$^+$): m/z = 305 (M + H$^+$). HRMS: calculated for $C_{21}H_{24}N_2$ + H$^+$: 305.2012, found: 305.2009. Mp (°C): 172. White powder. R_f (PE/EA 70:30) = 0.50.

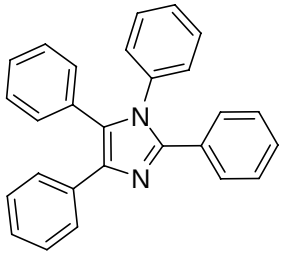
1-Benzyl-2-isopropyl-4,5-diphenyl-1*H*-imidazole 11f



IR (KBr, cm^{-1}): ν_{max} = 1602, 1509, 1496, 1454, 1417 (C=C and C=N), 1362, 1335, 1320 (C-N and CH(CH$_3$)$_2$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.33 (6 H, d, *J* = 6.9 Hz, CH(C*H*$_3$)$_2$), 2.90 (1 H, septet, *J* = 6.9 Hz, C*H*(CH$_3$)$_2$), 4.99 (2 H, s, C*H*$_2$), 6.89-6.93 (2 H, m, benzylic. H$_{ortho}$), 7.07-7.35 (11 H, m, arom. H), 7.48-7.52 (2 H, m, arom. H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 22.1 (2 C, CH(*C*H$_3$)$_2$), 26.7 (*C*H(CH$_3$)$_2$), 46.8 (CH$_2$), 125.8 (2 C, benzylic CH$_{ortho}$), 126.1 (CH$_{arom.}$), 127.0 (2 C, CH$_{arom.}$), 127.5 (CH$_{arom.}$), 128.1 (2 C, CH$_{arom.}$), 128.3 (C$_q$), 128.4 (CH$_{arom.}$),

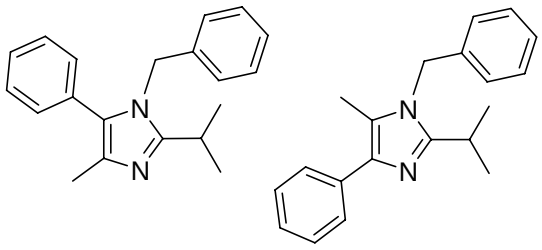
128.8 (2 C, $CH_{arom.}$), 128.9 (2 C, $CH_{arom.}$), 131.1 (2 C, $CH_{arom.}$), 131.5 (C_q), 135.1 (C_q), 136.8 (C_q), 137.7 (C_q), 153.3 (C=N). LRMS (70 eV, ES^+): m/z = 353 ($M + H^+$). HRMS: calculated for $C_{25}H_{24}N_2 + H^+$: 353.2012, found: 353.2011. Mp (°C): 129. White crystals. R_f (PE/EA 70:30) = 0.52.

1,2,4,5-Tetraphenyl-1*H*-imidazole 11g



IR (KBr, cm^{-1}): ν_{max} = 1597, 1497, 1480, 1441 (C=C and C=N), 1396, 1375 (C-N). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.03-7.06 (2 H, m, arom. H), 7.12-7.15 (2 H, m, arom. H), 7.19-7.31 (12 H, m, arom. H), 7.42-7.45 (2 H, m, arom. H), 7.59-7.63 (2 H, m, arom. H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 126.7 ($CH_{arom.}$), 127.5 (2 C, $CH_{arom.}$), 128.1 ($CH_{arom.}$), 128.2 (2 C, $CH_{arom.}$), 128.3 (2 C, $CH_{arom.}$), 128.4 (2 C, $CH_{arom.}$), 128.4 (2 C, $CH_{arom.}$), 128.5 (2 C, $CH_{arom.}$), 129.1 (2 C, $CH_{arom.}$), 129.2 (2 C, $CH_{arom.}$), 130.6 (C_q), 130.8 (C_q), 131.0 (C_q), 131.2 (2 C, $CH_{arom.}$), 134.6 (C_q), 137.2 (C_q), 138.4 (C_q), 147.0 (C=N). LRMS (70 eV, ES^+): m/z = 373 ($M + H^+$). HRMS: calculated for $C_{27}H_{20}N_2 + H^+$: 373.1699, found: 373.1712. Mp (°C): 216. Transparent crystals. R_f (PE/EA 70:30) = 0.50.

1-Benzyl-2-isopropyl-4-methyl-5-phenyl-1*H*-imidazole (*MAJOR*) + 1-Benzyl-2-isopropyl-5-methyl-4-phenyl-1*H*-imidazole (*minor*) 11h

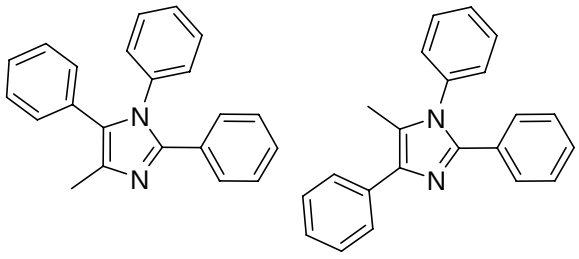


MAJOR **minor**

IR (*Major* KBr, *Minor* NaCl, cm^{-1}): ν_{max} = *MAJOR* 1607, 1497, 1465, 1450, 1425 (C=C and C=N), 1354, 1317 (C-N and $CH(CH_3)_2$). *minor* 1658, 1606, 1512, 1497, 1455 (C=C and C=N), 1381, 1357, 1337 (C-N and $CH(CH_3)_2$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = *MAJOR* 1.27 (6 H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 2.24 (3 H, s, CH_3), 2.84 (1 H, septet, *J* = 6.9 Hz, $CH(CH_3)_2$), 5.02 (2 H, s, CH_2), 6.89 (2 H, d, *J* = 6.6 Hz, arom. H), 7.16-7.36 (8 H, m, arom. H). *minor* 1.31 (6 H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 2.25 (3 H, s, CH_3), 2.95 (1 H, septet, *J* = 6.9 Hz, $CH(CH_3)_2$), 5.12 (2 H, s, CH_2), 6.97 (2 H, d, *J* = 6.6 Hz, arom. H), 7.20-7.41 (6 H, m, arom. H), 7.65-7.68 (2 H, m, arom. H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = *MAJOR* 13.4 (CH_3), 22.1 (2 C, $CH(CH_3)_2$), 26.5 ($CH(CH_3)_2$), 46.9 (CH_2), 125.7 (2 C, $CH_{arom.}$), 127.5 ($CH_{arom.}$), 127.7 ($CH_{arom.}$), 128.1 (C_q), 128.6 (2 C, $CH_{arom.}$), 128.8 (2 C, $CH_{arom.}$), 130.3 (2 C, $CH_{arom.}$), 130.9 (C_q), 133.9 (C_q), 137.9 (C_q), 152.8 (C=N). *minor* 10.3 (CH_3), 22.1 (2 C, $CH(CH_3)_2$), 26.6

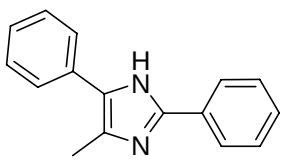
(*C*H(CH$_3$)$_2$), 46.5 (CH$_2$), 122.9 (C$_q$), 125.7 (2 C, CH$_{arom.}$), 126.1 (CH$_{arom.}$), 127.5 (2 C, CH$_{arom.}$), 127.7 (CH$_{arom.}$), 128.4 (2 C, CH$_{arom.}$), 129.0 (2 C, CH$_{arom.}$), 135.8 (C$_q$), 136.4 (C$_q$), 137.0 (C$_q$), 152.6 (C=N). LRMS (70 eV, ES$^+$): m/z = *MAJOR* 291 (M + H$^+$). *minor* 291 (M + H$^+$). HRMS: *MAJOR* calculated for $C_{20}H_{22}N_2$ + H$^+$: 291.1856, found: 291.1860. *minor* calculated for $C_{20}H_{22}N_2$ + H$^+$: 291.1856, found: 291.1861. Mp (°C): *MAJOR* 116. Light brown crystals. R$_f$ (PE/EA 70:30) = 0.27. *minor* Brown oil. R$_f$ (PE/EA 70:30) = 0.41.

4-Methyl-1,2,5-triphenyl-1*H*-imidazole (*MAJOR*) + 5-Methyl-1,2,4-triphenyl-1*H*-imidazole (*minor*) 11i



IR (KBr, cm^{-1}): ν_{max} = *MAJOR* 1596, 1493, 1465, 1441 (C=C and C=N), 1397, 1382, 1364 (C-N). *minor* 1597, 1494, 1471, 1444 (C=C and C=N), 1400, 1382 (C-N). ^{1}H NMR (300 MHz, CDCl$_3$, ppm): δ = *MAJOR* 2.38 (3 H, s, C*H*$_3$), 7.00-7.07 (4 H, m, arom. H), 7.18-7.30 (9 H, m, arom. H), 7.32-7.35 (2 H, m, arom. H). *minor* 2.26 (3 H, s, C*H*$_3$), 7.14-7.31 (7 H, m, arom. H), 7.37-7.49 (6 H, m, arom. H), 7.78-7.81 (2 H, m, arom. H). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): δ = *MAJOR* 13.6 (CH$_3$), 127.2 (CH$_{arom.}$), 128.1 (6 C, CH$_{arom.}$), 128.3 (2 C, CH$_{arom.}$), 128.9 (2 C, CH$_{arom.}$), 129.2 (2 C, CH$_{arom.}$), 130.3 (2 C, CH$_{arom.}$), 130.4 (C$_q$), 130.6 (C$_q$), 130.7 (C$_q$), 135.8 (C$_q$), 137.6 (C$_q$), 146.1 (C=N). *minor* 11.3 (CH$_3$), 126.3 (C$_q$), 126.5 (CH$_{arom.}$), 127.4 (2 C, CH$_{arom.}$), 128.0 (CH$_{arom.}$), 128.2 (2 C, CH$_{arom.}$), 128.3 (2 C, CH$_{arom.}$), 128.5 (4 C, CH$_{arom.}$), 128.8 (1 C, CH$_{arom.}$), 129.7 (2 C, CH$_{arom.}$), 130.8 (C$_q$), 135.3 (C$_q$), 137.6 (C$_q$), 137.8 (C$_q$), 146.3 (C=N). LRMS (70 eV, ES$^+$): m/z = *MAJOR* 311 (M + H$^+$). *minor* 311 (M + H$^+$). HRMS: *MAJOR* calculated for $C_{22}H_{18}N_2$ + H$^+$: 311.1543, found: 311.1540. *minor* calculated for $C_{22}H_{18}N_2$ + H$^+$: 311.1543, found: 311.1543. Mp (°C): *MAJOR* 206. White powder. R$_f$ (PE/EA 70:30) = 0.32. *minor* 123. Brown crystals. R$_f$ (PE/EA 70:30) = 0.47.

4(5)-Methyl-2,5(4)-diphenyl-1*H*-imidazole 11'j



IR (KBr, cm^{-1}): ν_{max} = 3210 (NH), 2355, 2333 (NH), 1657, 1591, 1498, 1463 (C=C and C=N), 1400, 1379 (C-N). ^{1}H NMR (300 MHz, CDCl$_3$, ppm): δ = 2.40 (3 H, s, C*H*$_3$), 7.20-7.40 (6 H, m, arom. H), 7.56-7.59 ppm (2 H, m, arom. H), 7.83-7.86 (2 H, m, arom. H). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): δ = 12.7 (CH$_3$), 125.2 (2 C, CH$_{arom.}$), 126.8 (CH$_{arom.}$), 126.8 (2 C, CH$_{arom.}$), 128.1 (C$_q$),

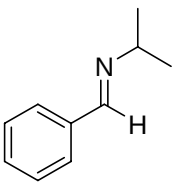
128.6 ($CH_{arom.}$), 128.7 (2 C, $CH_{arom.}$), 128.9 (2 C, $CH_{arom.}$), 130.0 (2 C, C_q), 133.1 (C_q) , 145.0 (C=N). LRMS (70 eV, ES^+): m/z = 235 ($M + H^+$). HRMS: calculated for $C_{16}H_{14}N_2 + H^+$: 235.1230, found: 235.1228. Mp (°C): 55. Yellow powder. R_f (PE/EA 70:30) = 0.20.

4.5 α-AMINOPHOSPHONATES

4.5.1 Synthesis of aldimines

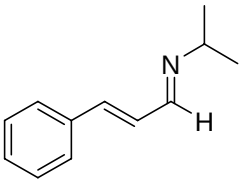
Unless otherwise stated, the aldimines were prepared as follows. A mixture of aldehyde (10 mass%) with an equimolar amount of amine were dissolved in dichloromethane. If the amine was volatile, a slight excess was used. Magnesium sulfate was added and the mixture was stirred overnight. After filtration of the $MgSO_4$, the dichloromethane was evaporated and the aldimine was obtained in high yield and purity.

Benzylidene-isopropylamine 12a



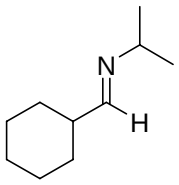
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.27 (6 H, d, *J* = 6.3 Hz, CH_3), 3.53 (1 H, septet, *J* = 6.3 Hz, NCH), 7.39-7.41 (3 H, m, arom. H), 7.70-7.72 (2 H, m, arom. H), 8.31 (1 H, s, N=CH).

Isopropyl-(3-phenylpropenylidene)amine 12b



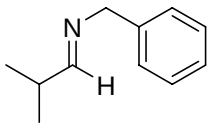
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.23 (6 H, d, *J* = 6.3 Hz, CH_3), 3.41 (1 H, septet, *J* = 6.3 Hz, NCH), 6.91 (1 H, d, *J* = 2.2 Hz, =CH), 6.92 (1 H, s, =CH), 7.26-7.38 (3 H, m, arom. H), 7.44-7.48 (2 H, m, arom. H), 8.05 (1 H, dd, *J* = 5.5, 3.0 Hz, N=CH).

(Cyclohexylmethylidene)isopropylamine 12c



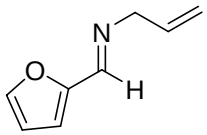
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.13 (6 H, d, *J* = 6.3 Hz, CH_3), 1.10-1.40 (5 H, m, cHexyl), 1.60-1.85 (5 H, m, cHexyl), 2.05-2.20 (1 H, m, cHexyl), 3.22 (1 H, septet, *J* = 6.3 Hz, NCH), 7.47 (1 H, d, *J* = 5.8 Hz, N=CH).

Benzyl-isobutylidene-amine 12d



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.11 (6 H, d, *J* = 6.9 Hz, CH_3), 2.42-2.58 (1 H, m, CH), 4.56 (2 H, s, NCH_2), 7.20-7.38 (5 H, m, arom. H), 7.66 (1 H, d, *J* = 5.0 Hz, N=CH).

Allyl-(furan-2-ylmethylidene)amine 12e



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 4.23 (2 H, dd, *J* = 6.1, 1.4 Hz, NCH_2), 5.10-5.28 (2 H, m, $=CH_2$), 5.95-6.10 (1 H, m, $CH=CH_2$), 6.46-6.49 (1 H, m, =CH), 6.75-6.77 (1 H, d, =CH), 7.52 (1 H, br s, =CHO), 8.10 (1 H, br s, N=CH).

4.5.2 Synthesis of α-aminophosphonates

4.5.2.1 General batch procedure for α-aminophosphonate synthesis

A mixture of aldimine (5 mmol) and dialkyl phosphite (10 mmol) in methanol was refluxed for one to three hours (depending on the type of the imine). After reaction, the solvent was evaporated *in vacuo* and the residue was dissolved in 10 mL of dichloromethane and extracted with 10 mL of 1 N HCl. The aqueous phase was washed 2 times with 10 mL of dichloromethane. Afterwards, the aqueous phase was basified using 1 N NaOH and was extracted 3 times with 10 mL of dichloromethane. The combined organic fractions were dried over $MgSO_4$. After filtration and evaporation the α-aminophosphonates were obtained in high purity.

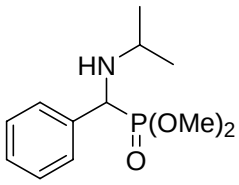
4.5.2.2 General microreactor procedure starting from the imine (Table 3.15)

In the optimised procedure, MeOH was added to 28.0 g of imine (40 mass%) to obtain a 70 mL solution in the measuring cup. In the second measuring cup, MeOH was added to 2 equivalents of dimethyl phosphite to create a 70 mL solution. Both measuring cups were connected to the CYTOS® College System and the ***general microreactor setup*** was followed. At the outlet, about 10 mL was collected for analysis. The work up of the reaction mixture was performed by means of the same acid base extraction as in the batch procedure. The conversion was calculated from the ^{1}H-NMR spectrum of the reaction mixture before work up.

4.5.2.3 General procedure starting from the aldehyde and amine (Table 3.16, entry 3)

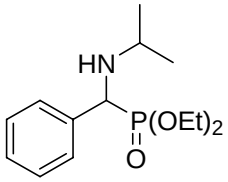
In the optimised procedure, a solution of benzaldehyde (20.2 g, 0.19 mol, 28.9 mass%) and trimethyl orthoformate (20.2 g, 1 equiv, 0.19 mol, 28.9 mass%) was transferred to a measuring cup and adjusted to 70 mL with MeOH. In a second measuring cup, another solution was made, containing isopropylamine (11.2 g, 1 equiv, 0.19 mol, 16 mass%) and dimethyl phosphite (41.9 g, 2 equiv, 0.38 mol, 59.9 mass%), which was adjusted to 70 mL with MeOH. Both measuring cups were connected to the CYTOS® College System and the ***general microreactor setup*** was followed. At the outlet, about 10 mL was collected for analysis. The work up of the reaction mixture was performed by means of the acid base extraction, similar as in the batch procedure. The conversion was calculated from the ^{1}H-NMR spectrum of the reaction mixture before work up. Spectral data were in accordance with literature.[38]

Dimethyl isopropylaminophenylmethyl phosphonate 14a



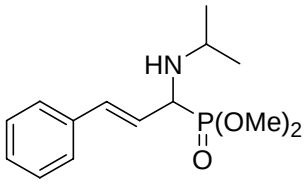
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.99 (3 H, d, J = 6.1 Hz, CH_3), 1.02 (3 H, d, J = 6.3 Hz, CH_3), 1.84 (1 H, br s, NH), 2.68 (1 H, septet, J = 6.3 Hz, NCH), 3.51 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 3.78 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 4.17 (1 H, d, J_{HP} = 22.3 Hz, CHP), 7.27-7.43 (5 H, m, arom. H). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ = 26.99.

Diethyl isopropylaminophenylmethyl phosphonate 14'a



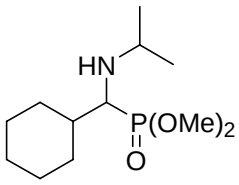
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.99 (3 H, d, J = 6.9 Hz, NCH(CH_3)$_2$), 1.01 (3 H, d, J = 6.9 Hz, NCH(CH_3)$_2$), 1.11 (3 H, t, J = 6.9 Hz, OCH_2CH_3), 1.30 (3 H, t, J = 6.9 Hz, OCH_2CH_3), 1.80 (1 H, br s, NH), 2.68 (1 H, septet, J = 5.8 Hz, NCH), 3.70-3.83 (1 H, m, OCH_2CH_3), 3.88-4.01 (1 H, m, OCH_2CH_3), 4.06-4.22 (3 H, m, OCH_2CH_3 and CHP), 7.24-7.42 (5 H, m, arom. H). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ = 24.74.

Dimethyl (2*E*)-1-isopropylamino-3-phenylprop-2-enyl phosphonate 14b



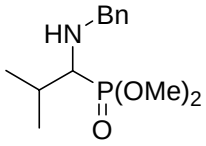
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.03 (3 H, d, J = 6.1 Hz, CH_3), 1.09 (3 H, d, J = 6.3, CH_3), 1.56 (1 H, br s, NH), 2.95 (1 H, septet, J = 6.3 Hz, NCH), 3.78 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 3.83 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 3.82 (1 H, ddd, J_{HP} = 20.0, J = 8.5, 0.8 Hz, CHP), 6.12 (1 H, ddd, J = 15.8, 8.5, J_{HP} = 5.8 Hz, PhCH=C*H*), 6.61 (1 H, dd, J = 16.0, J_{HP} = 4.7 Hz, PhC*H*=CH), 7.21-7.43 (5 H, m, arom. H). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ = 27.02.

Dimethyl cyclohexylisopropylaminomethyl phosphonate 14c



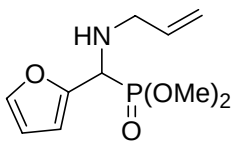
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.99 (3 H, dd, J = 6.1, 3.0 Hz, CH_3), 1.03 (3 H, dd, J = 6.2, 3.0 Hz, CH_3), 1.09-1.45 (6 H, m, cHexyl and NH), 1.58-1.83 (6 H, m, cHexyl), 2.77 (1 H, dt, J_{HP} = 16.8, J = 3.0 Hz, CHP), 2.92-3.02 (1 H, m, NCH), 3.75 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 3.78 (3 H, d, J_{HP} = 10.5 Hz, OCH_3). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ = 31.77.

Dimethyl 1-benzylamino-2-methylpropyl phosphonate 14d



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.01 (3 H, d, J = 6.9 Hz, CH_3), 1.02 (3 H, dd, J = 6.6, J_{HP} = 1.1 Hz, CH_3), 1.78 (1 H, br s, NH), 2.08-2.23 (1 H, m, NCH), 2.78 (1 H, dd, J_{HP} = 14.5, J = 3.5 Hz, CHP), 3.76 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 3.79 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 3.84 (1 H, dd, J_{AB} = 12.6, J_{HP} = 1.4 Hz, CH_aH$_b$Ph), 4.02 (1 H, d, J_{AB} = 12.9 Hz, CH$_a$$H_b$Ph), 7.21-7.39 (5 H, m, arom. H). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ = 31.72.

Dimethyl allylaminofuran-2-ylmethyl phosphonate 14e



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.83 (1 H, br s, NH), 2.96 (1 H, dd, J_{AB} = 13.8, J = 6.6 Hz, CH_2), 3.18 (1 H, dd, J_{AB} = 13.9, J = 5.5 Hz, CH_2), 3.53 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 3.69 (3 H, d, J_{HP} = 10.5 Hz, OCH_3), 4.06 (1 H, d, J_{HP} = 22.0 Hz, CHP), 4.96-5.08 (2 H, m, =CH_2), 5.61-5.77 (1 H, m, CH_2CH=), 6.22-6.28 (2 H, m, =CH), 7.30-7.32 (1 H, m, CHO). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ = 24.15.

4.6 ISOCHROMENONE SYNTHESIS

4.6.1 Batch procedure

The batch procedure was based on a literature procedure.[39] Generally, 3.00 g of 2-formyl benzoic acid (20 mmol, 1 equiv) and 2.40 g of acetic acid (40

mmol, 2 equiv) in 25 mL of methanol were added to a solution of 1,56 g of potassium cyanide (24 mmol, 1.2 equiv) and 40 mmol of the corresponding amine (2 equiv) in 25 mL of methanol. The outlet was connected to a sequence of 2 flasks of 3 M NaOH to trap the residual HCN released. The mixture was heated to reflux for an additional 3 h. After cooling, the crystalline product was collected *via* filtration, washed with methanol and water and dried with P_4O_{10}.

4.6.2 Optimised procedure under microreactor conditions (Table 3.17, entry 5)

In a measuring cylinder, 3.15 g of 2-formyl benzoic acid (21 mmol, 1 equiv) and 2.52 g of acetic acid (42 mmol, 2 equiv) were dissolved in 70 mL of methanol. The other measuring cylinder contained 3.91 g of aniline (42 mmol, 2 equiv) and 1.64 g of potassium cyanide (25.2 mmol, 1.2 equiv) dissolved in 70 mL of methanol. Both solutions were connected to the inlets of the device. The outlet was connected to a measuring cylinder, which was for his part connected to a sequence of 2 flasks of 3 M NaOH to trap the residual HCN released. The outlet of the RTU was constantly kept under a nitrogen atmosphere. The ***general microreactor setup*** was followed. About 30 mL was collected for work up. The work up consisted of the removal of the solvent *via* evaporation under a N_2 atmosphere. The residual mixture was filtered and the crystals were washed with methanol and water. The crystals were dried with P_4O_{10}.

4.6.3 General procedure for the plug flow reactions (Table 3.18)

A concentration of 0.4 M of 2-formyl benzoic acid was used instead of 0.3 M (*vide supra*, § 4.6.2). The other reagents were used in the same ratio. Both solutions were connected to the microreactor inlets. A HPLC pump was connected between the microreactor and the RTU *via* a T-connection (see Figure 3.20). A solution of Fluorinert® FC-70 was connected to the pump. The flow rates ($r_{piston\ pumps}$ and r_{HPLC}) were calculated by measuring the

outgoing volume of reaction mixture and Fluorinert® FC-70. The residence time τ was calculated as follows:

$$\tau\,(\text{min}) = \frac{V_{\text{microreactor}}}{r_{\text{total}}} + \frac{V_{\text{RTU}}}{r_{\text{total}} + r_{\text{HPLC}}} \quad \text{with } r_{\text{total}} = 2\, r_{\text{piston pump}} \tag{3.3}$$

with $V_{\text{microreactor}}$ = inner volume of the microreactor (mL)
V_{RTU} = inner volume of the RTU (mL)
r_{total} = total flow rate of the 2 piston pumps (mL/min)
$r_{\text{piston pump}}$ = flow rate of the piston pump (mL/min)
r_{HPLC} = flow rate of the HPLC pump (mL/min)

The reaction mixture fraction (*rmf*) at the output was calculated as follows:

$$rmf\,(\text{-}) = \frac{V_{\text{reaction mixture}}}{V_{\text{reaction mixture}} + V_{\text{Fluorinert}}} \tag{3.2}$$

with $V_{\text{reaction mixture}}$ = volume of the reaction mixture in the sample (mL)
$V_{\text{Fluorinert}}$ = volume of Fluorinert® FC-70 in the sample (mL)

Fluorinert® FC-70 was separated and the rest of the work up was identical to the procedure described in § 4.6.2. To recuperate the Fluorinert® FC-70, the fluorous solvent was extracted once with an equal amount of dichloromethane and once with an equal amount of water.

4.6.4 Qualitative HCN measurement

For the qualitative detection of HCN, a known HCN spot test was used.[353] The HCN detection solution was made as follows. Approximately 5 mg of copper ethyl acetoacetate and 4,4”-methylenebis(N,N-dimethylaniline) were dissolved in 1 to 2 mL of chloroform. To make a HCN detection paper, a filter paper of approximately 3 cm Ø was made and moisturised with a drop of the detection solution. The colourless detection paper was put at the outlet

of the reaction mixture. The appearance of a blue colour indicated a positive result. This was tested on a 25 mL batch scale and on the microreactor setup. For both evaluations, the procedures described above were used with one important modification. In order to test not the excess of KCN, an equimolar amount of KCN was used instead of the normal 1.2 equivalents.

4.6.5 Quantitative HCN measurement

4.6.5.1 Titration procedure

The titration procedure is based on a known procedure of the EPA.[358,359] For the indicator solution, 20 mg of 5-(4-dimethylaminobenzylidene)rhodanine ($C_{12}H_{12}N_2OS_2$) was dissolved in 100 mL of acetone. The standard silver nitrate solution was made as follows. Approximately 5 g of $AgNO_3$ was crushed and dried to constant weight at 50 °C. Exactly 1.6324 g of dried $AgNO_3$ was weighed and dissolved in 500 mL of distilled water. For the CN^- measurement in the batch procedures, this solution was used for titration. In the microreactor procedure, this solution was diluted 200 times before use as titration agent because of the low CN^- concentrations.

The 125 mL NaOH solution (which contains the CN^- ions) was diluted to 250 mL with distilled water. Exactly 50 mL was pipetted and titrated with the silver nitrate solution until the end point was reached. Because of the difficult visibility of the colour change, the solution was continuously compared with a solution at the end point. This procedure was repeated at least 3 times. Also a blank NaOH solution was titrated to correct for background CN^- ions. The molar amount of CN^- ions in the batch procedure was calculated as follows:

$$CN^-(\text{mmol}) = \frac{(V_{\text{titration}} - V_{\text{blanco}}) \cdot C_{AgNO_3}}{M_{AgNO_3}} \cdot 2 \cdot \frac{250}{50} \cdot 1000 \qquad (4.4)$$

with $V_{\text{titration}}$ = volume of silver nitrate solution necessary to reach the end point of titration of the sample (mL)

V_{blanco} = volume of silver nitrate solution necessary to reach the end point of titration of a blanco sample (mL)

C_{AgNO_3} = silver nitrate concentration (3.2692 x 10^{-3} g/mL)

M_{AgNO_3} = molecular weight of silver nitrate (169.87 g/mol)

For the microreactor procedure this was also divided with 200, to correct for the dilution of the silver nitrate solution.

4.6.5.2 Reliability tests

To optimise the CN^- capture and the titration procedure for this particular reaction setup, different tests were performed.

1. Reliability test

For every new solution of silver nitrate that was made, a known amount of KCN was dissolved in distilled water and titrated with the silver nitrate solution (3.2692 x 10^{-3} g/mL).

2. Recuperation test

A two neck flask was filled with 0.293 g of potassium cyanide (4.5 mmol) in 15 mL methanol. One outlet was connected to a gas scrubber which was filled with 50 mL of 0.25 N NaOH or with 125 mL of 1 N NaOH. *Via* the other outlet, a solution of 0.450 g of acetic acid (7.5 mmol) in 10 mL methanol was slowly added to the KCN solution. Meanwhile, the reaction mixture was heated at 50 °C for 3 h. Afterwards, the gas scrubber was disconnected and the NaOH solution was subjected to the titration procedure.

4.6.5.3 Batch procedure to measure the HCN release (250 mL)

A three neck flask was filled with a mixture of 5.63 g of 2-formyl benzoic acid (37.5 mmol, 1 equiv), 6.98 g of aniline (75 mmol, 2 equiv) and 2.93 g of

potassium cyanide (45 mmol, 1.2 equiv) in 250 mL of methanol. The flask was connected to a gas scrubber which was filled with 125 mL of 1 N NaOH. The whole system was flushed for 30 min with nitrogen. Meanwhile, a syringe was filled with 4.33 mL of acetic acid (4.50 g, d = 1.04 g/mL, 75 mmol, 2 equiv). After 30 min, the nitrogen was shut down. The acetic acid was added *via* a syringe pump (at a flow rate of 10 mL/h) while the mixture was heated. After adding the acetic acid, the mixture was heated at reflux for another 3 h. Finally, the mixture was cooled down, while the system was again flushed for 30 min with nitrogen. Afterwards, the gas scrubber was disconnected and the NaOH solution was subjected to the titration procedure. For the setup on a 25 mL scale, the above procedure was identical, with exception of the amounts of reagent that has to be divided by 10.

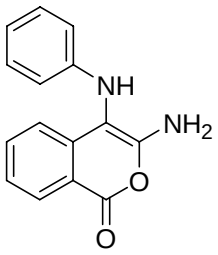
4.6.5.4 Microreactor procedure to measure the HCN release

For the microreactor procedure, the setup was identical to the optimised procedure described in § 4.6.2. The only exception was that a gas scrubber, which was filled with 125 mL of 1 N NaOH, was connected to the end of the RTU. The system was started up and the first fraction was collected. After collection of the first fraction (start up fraction), this fraction and the first gas scrubber were removed carefully. Meanwhile, a second collection flask (steady state fraction) and gas scrubber were connected. The same procedure was repeated for the third fraction (steady state fraction). For the fourth fraction (shutdown fraction), the same procedure was used but in the meanwhile the reaction flasks at the inlet were replaced by solvent in order to flush the system. Finally, the different NaOH solutions in the gas scrubbers were subjected to the titration procedure.

4.6.6 Spectral data of the 3,4-diamino-1H-isochromen-1-ones

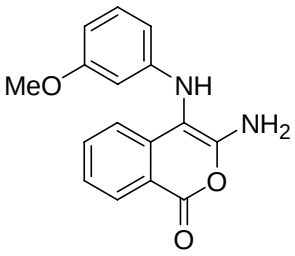
The spectral data of compounds **17a-e** and **17g** were in accordance with the literature.[39]

3-Amino-4-(phenylamino)-*1H*-isochromen-1-one 17a



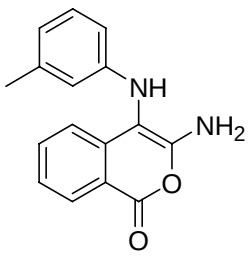
^{1}H NMR (300 MHz, DMSO, ppm): δ = 6.52-6.62 (5 H, m, H-2', H-4', H-6' and NH_2), 6.82 (1 H, s, NH), 7.03-7.12 (4 H, m, H-5, H-7, H-3' and H-5'), 7.52 (1 H, ddd, *J* = 8.1, 7.1, 1.4 Hz, H-6), 7.92 (1 H, dd, *J* = 8.0, 0.8 Hz, H-8).

3-Amino-4-(3-methoxyphenylamino)-*1H*-isochromen-1-one 17b



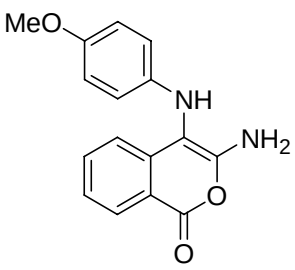
^{1}H NMR (300 MHz, DMSO, ppm): δ = 3.63 (3 H, s, OCH_3), 6.11-6.22 (3 H, m, H-2', H-4' and H-6'), 6.54 (2 H, s, NH_2), 6.83 (1 H, s, NH), 6.96 (1 H, t, *J* = 8.1 Hz, H-5'), 7.04-7.11 (2 H, m, H-5 and H-7), 7.53 (1 H, ddd, *J* = 8.1, 7.0, 1.4 Hz, H-6), 7.91 (1 H, dd, *J* = 8.0, 0.8 Hz, H-8).

3-Amino-4-(3-methylphenylamino)-*1H*-isochromen-1-one 17c



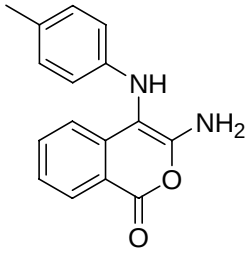
^{1}H NMR (300 MHz, DMSO, ppm): δ = 2.15 (3 H, s, CH_3), 6.36-6.43 (3 H, m, H-2', H-4' and H-6'), 6.53 (2 H, s, NH_2), 6.75 (1 H, s, NH), 6.94 (1 H, t, *J* = 8.0 Hz, H-5'), 7.03-7.12 (2 H, m, H-5 and H-7), 7.53 (1 H, ddd, *J* = 8.1, 7.0, 1.4 Hz, H-6), 7.92 (1 H, dd, *J* = 7.8, 0.8 Hz, H-8).

3-Amino-4-(4-methoxyphenylamino)-*1H*-isochromen-1-one 17d



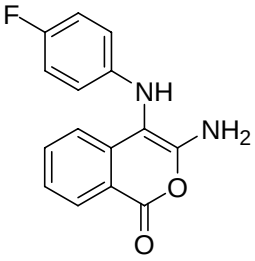
^{1}H NMR (300 MHz, DMSO, ppm): δ = 3.62 (3 H, s, OCH_3), 6.47 (1 H, s, NH), 6.50 (2 H, s, NH_2), 6.52 (2 H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.70 (2 H, d, *J* = 8.8 Hz, H-3' and H-5'), 7.04-7.11 (2 H, m, H-5 and H-7), 7.52 (1 H, ddd, *J* = 8.5, 7.1, 1.4 Hz, H-6), 7.91 (1 H, d, *J* = 7.4 Hz, H-8).

3-Amino-4-(4-methylphenylamino)-*1H*-isochromen-1-one 17e



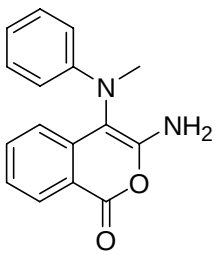
^{1}H NMR (300 MHz, DMSO, ppm): δ = 2.14 (3 H, s, CH_3), 6.45-6.51 (4 H, m, H-2', H-6' and NH_2), 6.62 (1 H, s, NH), 6.88 (2 H, d, *J* = 8.3 Hz, H-3' and H-5'), 7.01-7.11 (2 H, m, H-5 and H-7), 7.52 (1 H, ddd, *J* = 8.3, 7.0, 1.4 Hz, H-6), 7.91 (1 H, dd, *J* = 7.7, 0.8 Hz, H-8).

3-Amino-4-(4-fluorophenylamino)-*1H*-isochromen-1-one 17f



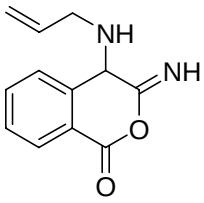
IR (KBr, cm^{-1}): ν_{max} = 3474, 3375, 3303, 3158, 1748 (C=O), 1631, 1602, 1547, 1508, 1482, 1351, 1302, 1266, 1220, 1151, 1098, 1026, 982, 822, 760, 678, 507. ^{1}H NMR (300 MHz, DMSO, ppm): δ = 6.53-6.59 (4 H, m, H-2', H-6' and NH_2), 6.79 (1 H, s, NH), 6.91 (2 H, pseudo-t, *J* = 8.8 Hz, H-3' and H-5'), 7.03-7.11 (2 H, m, H-5 and H-7), 7.53 (1 H, pseudo-t, *J* = 7.7 Hz, H-6), 7.92 (1 H, dd, *J* = 8.0, 0.8 Hz, H-8). ^{13}C NMR (75 MHz, DMSO, ppm): δ = 91.3 (C-4), 114.1 (C-2' and C-6', d, $J_{C\text{-}F}$ = 6.9 Hz), 114.6 (C-8a), 115.9 (C-3' and C-5', d, $J_{C\text{-}F}$ = 21.8 Hz), 120.1 (C-5), 122.7 (C-7), 129.9 (C-8), 135.5 (C-6), 142.2 (C-4a), 144.9 (C-1'), 155.4 (C-4', d, $J_{C\text{-}F}$ = 229.0 Hz), 156.8 (C-3), 160.9 (C=O). ^{19}F NMR (282 MHz, DMSO, ppm): δ = -128.6 (1 F, septet, *J* = 4.0 Hz). LRMS (70 eV, ES^+): m/z = 271 ($M + H^+$). Mp (°C): 191.0-191.3. Yellow powder. R_f (PE/EA 50:50) = 0.52.

3-Amino-4-(methylphenylamino)-*1H*-isochromen-1-one 17g



^{1}H NMR (300 MHz, DMSO, ppm): δ = 3.16 (3 H, s, CH_3), 6.60-6.66 (3 H, m, H-2', H-4' and H-6'), 6.70-6.74 (3 H, m, H-5 and NH_2), 7.04-7.17 (3 H, m, H-7, H-3' and H-5'), 7.48 (1 H, ddd, *J* = 8.1, 7.0, 1.4 Hz, H-6), 7.94 (1 H, dd, *J* = 8.0, 0.8 Hz, H-8).

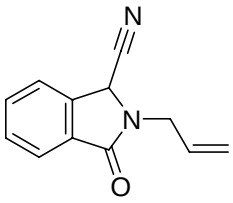
4-Allylamino-3-imino-isochroman-1-one 124h



IR (KBr, cm^{-1}): ν_{max} = 3349, 3178 (2 x NH), 1689, 1675 (C=O and C=N). ^{1}H NMR (300 MHz, DMSO, ppm): δ = 3.59 (1 H, dd, *J* = 15.7 Hz, 7.1 Hz, NHCH_aH$_b$), 4.51-4.58 (1 H, pseudo-dd, *J* = 15.7 Hz, 4.7 Hz, NHCH$_a$$H_b$), 5.11 (1 H, s, NCH), 5.16 (1 H, pseudo-d, *J* = 11.8 Hz, CH=CH_aH$_b$), 5.20 (1 H, pseudo-d, *J* = 5.2 Hz, CH=CH$_a$$H_b$), 5.80-5.93 (1 H, m, C*H*=CH$_a$H$_b$), 7.50-7.72 (5 H, m, arom. H + C=NH), 8.05 (1 H, s, NH).). ^{13}C NMR (75 MHz, DMSO, ppm): δ = 43.2 (NHCH$_2$), 62.4 (C-4), 117.7 (=CH$_2$), 122.4 (C-7), 122.8 (C-5), 128.6 (C-8), 131.4 (C-8a), 131.7 (C-6), 133.3 (=CH), 141.5 (C-4a), 167.6 (C=O), 168.5 (C=NH). LRMS (70 eV, ES$^+$): m/z = 217 (M + H$^+$). Mp (°C): 200.0-201.0. White powder. R_f (CH_2Cl_2/MeOH 95:5) = 0.21.

2-Allyl-3-oxo-2,3-dihydro-*1H*-isoindole-1-carbonitrile 128

Spectral data were according to literature.[387]



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.91 (1 H, ddt, *J* = 15.4, 8.0, 0.8 Hz, NCH_aH$_b$), 4.79 (1 H, ddt, *J* = 15.4, 4.7, 1.4 Hz, NCH$_a$$H_b$), 5.34-5.43 (3 H, m, CH=CH_2 and C*H*CN), 5.80-5.93 (1 H, m, C*H*=CH$_2$), 7.59-7.72 (3 H, m, arom. H), 7.90 (1 H, d, *J* = 7.3 Hz, arom. H).

4.7 SYNTHESIS OF 1*H*-ISOCHROMENO[3,4-*d*]IMIDAZOL-5-ONES

4.7.1 Batch reactions (Table 3.21)

Condition A:[367]

0.252 g (1 mmol, 1 equiv) of compound **17a** and 19 mg (0.1 mmol, 0.1 equiv) of p-tosyl sulfonic acid monohydrate were added to 10 mL of the orthoester **18a** or **18b**. The mixture was stirred at room temperature. After completion of the reaction, followed by TLC, the mixture was poured in 50 mL of ethyl

acetate and was washed twice with 50 mL of saturated $NaHCO_3$. The water phase was extracted 2 times with 50 mL of ethyl acetate and the combined organic layers were dried with $MgSO_4$. The $MgSO_4$ was filtered and the solvent was evaporated to obtain the end product.

Condition B:[367]
0.252 g (1 mmol, 1 equiv) of compound **17a** and 83 µL (1 mmol, 1 equiv) of 12.1 N HCl were added to 5 mL of the orthoester **18a** or **18b**. The mixture was stirred at room temperature. After completion of the reaction, followed by TLC, the mixture was poured in 50 mL of dichloromethane and was washed twice with 50 mL of saturated $NaHCO_3$. The water phase was extracted 2 times with 50 mL of dichloromethane and the combined organic layers were dried with $MgSO_4$. The $MgSO_4$ was filtered and the solvent was evaporated to obtain the end product.

Condition C:[368]
0.252 g (1 mmol, 1 equiv) of compound **17a**, 37 µL (0.5 mmol, 0.5 equiv) of trifluoro acetic acid and 5 mmol (5 equiv) of the orthoester **18a** or **18b** were added to 10 mL of dichloromethane. The mixture was stirred at room temperature. After completion of the reaction, followed by TLC, the mixture was poured in 50 mL of dichloromethane and was washed twice with 50 mL of saturated $NaHCO_3$. The water phase was extracted 2 times with 50 mL of dichloromethane and the combined organic layers were dried with $MgSO_4$. The $MgSO_4$ was filtered and the solvent was evaporated to obtain the end product.

4.7.2 Optimised procedure in the microreactor (Table 3.22, entry 12)

3-amino-4-(phenylamino)-1*H*-isochromen-1-one **17a** (3.53 g, 14 mmol) was dissolved in 70 mL of N,N-dimethyl formamide in a measuring cylinder. The other measuring cylinder contained p-toluene sulfonic acid monohydrate (0.266 g, 1.4 mmol) and triethyl orthoformate **18a** (10.36 g, 70 mmol) dissolved in 70 mL of N,N-dimethyl formamide. Both solutions were connected to the inlets of the device and the ***general microreactor setup***

was followed. About 10 mL of the reaction mixture was quenched with 20 mL of water. Another 80 mL of water was added to the mixture after collection and this was extracted with 50 mL of dichloromethane. The organic phase was subsequently washed with 100 mL of water, 2 times 100 mL of 0.5 N HCl and 100 mL of brine. The organic phase was dried with $MgSO_4$. After filtration of the drying agent, the solvent was evaporated to obtain the end product **19a**.

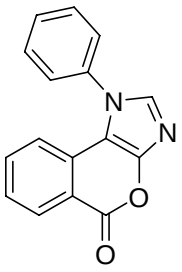
This procedure has been used to obtain the results of Table 3.22, entry 12. The other results were obtained in the same way, except for minor changes such as concentration, temperature, flow rate (~ τ), equivalents of reagents and starting 3-amino-4-(arylamino)-1*H*-isochromen-1-one **17** as stated with the experiments. In the case of incomplete conversions, such as the samples at the microreactor outlet, a ^{1}H NMR spectrum of the crude mixture was recorded. In both starting products **17** and end products **19**, the anisotropic effect of the carbonyl moiety causes a significant downfield shift of the aromatic *ortho*-protons (respectively H-8 and H-6). This results in a shift of both signals from the rest of the aromatic signals and makes a clear integration possible. The degree of conversion was calculated using the integration of these signals in the ^{1}H NMR spectrum. The yield of the reaction was calculated from the total mass of end product collected and the degree of conversion.

In the experiments with the stopped-flow technique (Table 3.23), the same conditions were used as in the general microreactor procedure. Samples were taken only at the microreactor outlet. A flow time of 1 min was chosen, and a stop time of 3 or 5 min. With a total volume of 2 mL and a flow rate of 0.2 mL/min.pump, the total residence time increased from 3 min to 12 or 18 min respectively.

In Table 3.24, entries 6, 11, 12 and 13, 0.5 equivalents of trifluoro acetic acid were used instead of 0.1 equivalents of p-toluene sulfonic acid monohydrate and also fresh DMF was used.

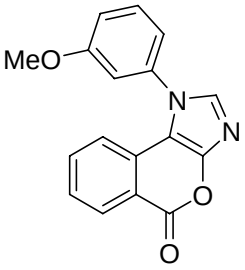
4.7.3 Spectral data of the 1H-isochromeno[3,4-d]imidazol-5-ones

1-Phenyl-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19a



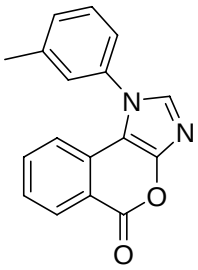
IR (KBr, cm^{-1}): ν_{max} = 3436, 3136, 1729 (C=O), 1718, 1616, 1498, 1470, 1418, 1380, 1316, 1218, 1070, 1037, 1017, 824, 777, 760, 706, 683, 644, 554. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 6.94 (1 H, d, *J* = 8.0 Hz, H-9), 7.36 (1 H, td, *J* = 7.6, 1.0 Hz, H-7), 7.46-7.56 (4 H, m, H-2, H-8, H-2' and H-6'), 7.63-7.68 (3 H, m, H-3', H-4' and H-5'), 8.35 (1 H, d, *J* = 8.0 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 109.0 (C-9b), 119.0 (C-9), 119.2 (C-5a), 126.7 (3 C, C-7, C-2' and C-6'), 129.7 (C-9a), 130.2 (3 C, C-3', C-4' and C-5'), 132.3 (C-6), 134.9 (C-8), 136.3 (C-1'), 136.5 (C-2), 151.4 (C-3a), 161.7 (C=O). LRMS (70 eV, ES^+): m/z = 263 ($M + H^+$). Mp (°C): 221.7-222.4. Yellow crystals. R_f (PE/EA 50:50) = 0.32.

1-(3-Methoxyphenyl)-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19b



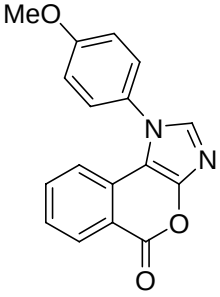
IR (KBr, cm^{-1}): ν_{max} = 3089, 1735 (C=O), 1619, 1605, 1494, 1477, 1417, 1377, 1334, 1271, 1222, 1064, 1029, 845, 798, 757, 684. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.89 (3 H, s, OCH_3), 7.00-7.03 (2 H, m, H-9 and H-2'), 7.09 (1 H, ddd, *J* = 7.7, 1.5, 0.8 Hz, H-4' or H-6'), 7.16 (1 H, ddd, *J* = 8.3, 2.5, 0.8 Hz, H-4' or H-6'), 7.37 (1 H, pseudo-td, *J* = 7.6, 1.2 Hz, H-7), 7.48-7.54 (2 H, m, H-8 and H-5'), 7.55 (1 H, s, H-2), 8.37 (1 H, pseudo-d, *J* = 7.4 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 55.8 (OCH_3), 109.0 (C-9b), 112.3 (C-2'), 115.9 (C-4' or C-6'), 118.7 (C-4' or C-6'), 119.2 (C-9 and C-5a), 126.6 (C-7), 129.7 (C-9a), 130.9 (C-5'), 132.3 (C-6), 134.8 (C-8), 136.4 (C-2), 137.3 (C-1'), 151.3 (C3-a), 160.8 (C-3'), 161.7 (C=O). LRMS (70 eV, ES^+): m/z = 293 ($M + H^+$). Mp (°C): 166.6-167.2. Orange yellow powder. R_f (PE/EA 50:50) = 0.32.

1-m-Tolyl-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19c



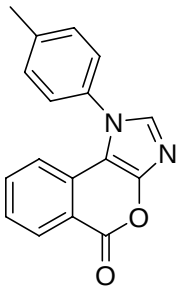
IR (KBr, cm^{-1}): ν_{max} = 3126, 1732 (C=O), 1615, 1550, 1494, 1472, 1414, 1378, 1333, 1216, 1068, 1043, 1019, 809, 762, 708, 684, 636. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.50 (3 H, s, CH_3), 6.96 (1 H, d, *J* = 8.0 Hz, H-9), 7.27-7.53 (6 H, m, H-7, H-8, H-2', H-4', H-5' and H-6'), 7.54 (1 H, s, H-2), 8.37 (1 H, dd, *J* = 8.0, 0.8 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 21.5 (CH_3), 109.0 (C-9b), 119.1 (C-9 and C-5a), 123.7 (C-6'), 126.6 (C-7), 127.1 (C-2'), 129.8 (C-9a), 129.9 (C-5'), 130.9 (C-4'), 132.3 (C-6), 134.9 (C-8), 136.2 (C-1'), 136.5 (C-2), 140.6 (C-3'), 151.3 (C-3a), 161.8 (C=O). LRMS (70 eV, ES^+): m/z = 277 ($M + H^+$). Mp (°C): 166.4-168.6. Brown orange powder. R_f (PE/EA 70:30) = 0.17.

1-(4-Methoxyphenyl)-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19d



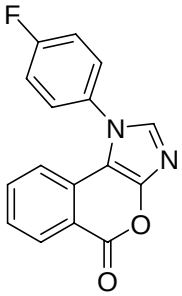
IR (KBr, cm^{-1}): ν_{max} = 3100, 1741 (C=O), 1618, 1550, 1509, 1476, 1413, 1380, 1303, 1261, 1027, 835, 757. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.95 (3 H, s, OCH_3), 6.93 (1 H, d, *J* = 8.0 Hz, H-9), 7.08-7.16 (2 H, m, H-3' and H-5'), 7.34-7.40 (1 H, m, H-7), 7.40-7.44 (2 H, m, H-2' and H-6'), 7.46-7.50 (1 H, m, H-8), 7.52 (1 H, s, H-2), 8.39 (1 H, pseudo-d, *J* = 8.0 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 55.8 (OCH_3), 109.3 (C-9b), 115.2 (C-3' and C-5'), 118.9 (C-9), 119.2 (C-5a), 126.6 (C-7), 128.0 (C-2' and C-6'), 128.9 (C-1'), 129.9 (C-9a), 132.3 (C-6), 134.8 (C-8), 136.7 (C-2), 151.1 (C-3a), 160.8 (C-4'), 161.8 (C=O). LRMS (70 eV, ES^+): m/z = 293 ($M + H^+$). Mp (°C): 169.2-169.4. Pale yellow powder. R_f (PE/EA 70:30) = 0.22.

1-p-Tolyl-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19e



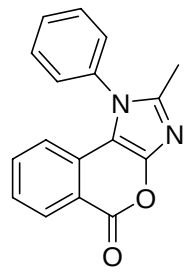
IR (KBr, cm^{-1}): ν_{max} = 3117, 1736 (C=O), 1619, 1509, 1476, 1421, 1380, 1334, 1215, 1138, 1067, 1033, 822, 757, 685, 525. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.53 (3 H, s, CH_3), 6.96 (1 H, d, *J* = 8.0 Hz, H-9), 7.34-7.52 (6 H, m, H-7, H-8, H-2', H-3', H-5' and H-6'), 7.53 (1 H, s, H-2), 8.38 (1 H, pseudo-d, *J* = 8.0 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 21.5 (CH_3), 109.1 (C-9b), 119.0 (C-9), 119.2 (C-5a), 126.4 (2 C, C-2' and C-6'), 126.6 (C-7), 129.8 (C-9a), 130.7 (2 C, C-3' and C-5'), 132.3 (C-6), 133.7 (C-1'), 134.8 (C-8), 136.5 (C-2), 140.5 (C-4'), 151.3 (C-3a), 161.8 (C=O). LRMS (70 eV, ES^+): m/z = 277 ($M + H^+$). Mp (°C): 170.3-171.4. Pale yellow powder. R_f (PE/EA 70:30) = 0.34.

1-(4-Fluorophenyl)-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19f



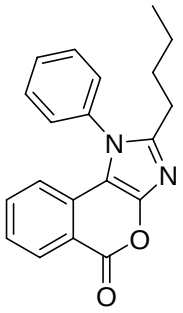
IR (KBr, cm^{-1}): ν_{max} = 3139, 1717 (C=O), 1618, 1553, 1508, 1418, 1382, 1333, 1300, 1253, 1209, 1159, 1142, 1087, 1065, 1033, 1019, 846, 765, 735, 687, 659, 612, 551. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 6.89 (1 H, d, *J* = 7.7 Hz, H-9), 7.31-7.42 (3 H, m, H-7, H-3' and H-5'), 7.49-7.55 (4 H, m, H-2, H-8, H-2' and H-6'), 8.38 (1 H, dd, *J* = 8.0, 1.1 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 109.2 (C-9b), 117.3 (C-3' and C-5', d, J_{C-F} = 22.9 Hz), 118.8 (C-9), 119.2 (C-5a), 126.8 (C-7), 128.7 (C-2' and C-6', d, J_{C-F} = 8.0 Hz), 129.5 (C-9a), 132.3 (C-1', d, J_{C-F} = 3.4 Hz), 132.4 (C-6), 134.9 (C-8), 136.6 (C-2), 151.3 (C-3a), 161.7 (C=O), 163.3 (C-4', d, J_{C-F} = 254.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ = -109.3 (1 F, septet, *J* = 4.0 Hz). LRMS (70 eV, ES^+): m/z = 281 ($M + H^+$). Mp (°C): 223.4-224.8. Orange yellow powder. R_f (PE/EA 50:50) = 0.38.

2-Methyl-1-phenyl-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19i



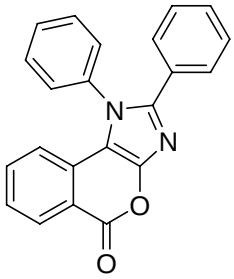
IR (KBr, cm^{-1}): ν_{max} = 3573, 3436, 3058, 1734 (C=O), 1622, 1599, 1556, 1499, 1396, 1363, 1317, 1301, 1266, 1213, 1069, 1018, 998, 787, 752, 700, 682, 544, 514. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.32 (3 H, s, CH_3), 6.57 (1 H, d, *J* = 8.2 Hz, H-9), 7.27 (1 H, td, *J* = 7.7, 1.1 Hz, H-7), 7.39 (1 H, td, *J* = 7.7, 1.4 Hz, H-8), 7.44-7.47 (2 H, m, H-2' and H-6'), 7.62-7.69 (3 H, m, H-3', H-4' and H-5'), 8.30 (1 H, d, *J* = 8.0 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 13.7 (CH_3), 109.1 (C-9b), 118.0 (C-9), 118.6 (C-5a), 125.8 (C-7), 127.8 (C-2' and C-6'), 130.1 (C-9a), 130.4 (C-3', C-4' and C-5'), 132.2 (C-6), 134.8 (C-8), 136.3 (C-1'), 145.5 (C-2), 150.4 (C-3a), 161.9 (C=O). LRMS (70 eV, ES^+): m/z = 277 ($M + H^+$). Mp (°C): 243.4-244.0. Yellow crystals. R_f (PE/EA 50:50) = 0.26.

2-Butyl-1-phenyl-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19j



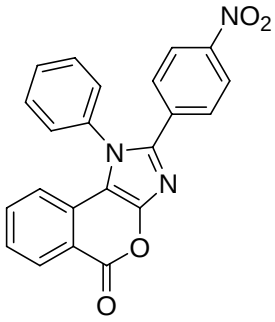
IR (KBr, cm^{-1}): ν_{max} = 2957, 2935, 2862, 1721 (C=O), 1620, 1592, 1548, 1486, 1393, 1357, 1263, 1064, 1017, 768, 707, 685. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.85 (3 H, t, *J* = 7.4 Hz, CH_3), 1.30 (2 H, sextet, *J* = 7.4 Hz, CH_2CH_3), 1.68 (2 H, quintet, *J* = 7.7 Hz, $CH_2CH_2CH_3$), 2.57 (2 H, t, *J* = 7.7 Hz, CCH_2), 6.50 (1 H, d, *J* = 8.0 Hz, H-9), 7.27 (1 H, t, *J* = 7.6 Hz, H-7), 7.37 (1 H, t, *J* = 7.6 Hz, H-8), 7.42-7.46 (2 H, m, H-2' and H-6'), 7.62-7.71 (3 H, m, H-3', H-4' and H-5'), 8.34 (1 H, d, *J* = 8.2 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 13.8 (CH_3), 22.4 (CH_2CH_3), 26.8 (CCH_2), 30.2 ($CH_2CH_2CH_3$), 108.9 (C-9b), 118.0 (C-9), 118.7 (C-5a), 125.7 (C-7), 128.1 (C-2' and C-6'), 130.2 (C-9a), 130.4 (C-3', C-4' and C-5'), 132.2 (C-6), 134.7 (C-8), 136.2 (C-1'), 149.4 (C-2), 150.6 (C-3a), 162.0 (C=O). LRMS (70 eV, ES^+): m/z = 319 ($M + H^+$). Mp (°C): 140.6-141.7. Pale yellow crystals. R_f (PE/EA 70:30) = 0.24.

1,2-Diphenyl-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19k



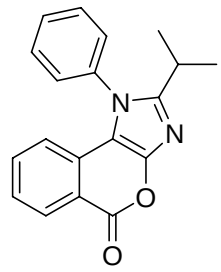
IR (KBr, cm^{-1}): ν_{max} = 3841, 3737, 3673, 3650, 3568, 1732 (C=O), 1618, 1509, 1494, 1382, 1068, 1024, 755, 694. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 6.59 (1 H, d, *J* = 8.2 Hz, H-9), 7.21-7.70 (12 H, m, H-7, H-8 and arom. H), 8.38 (1 H, d, *J* = 7.7 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 110.7 (C-9b), 118.5 (C-9), 119.1 (C-5a), 126.2 (C-7), 128.4 (2 C, arom. CH), 128.6 (2 C, arom. CH), 128.7 (2 C, arom. CH), 129.1 (C-1''), 129.3 (arom. CH), 130.0 (C-9a), 130.5 (C-3', C-4' and C-5'), 132.4 (C-6), 134.8 (C-8), 137.2 (C-1'), 145.8 (C-2), 151.1 (C-3a), 161.7 (C=O). LRMS (70 eV, ES^+): m/z = 339 ($M + H^+$). Mp (°C): 256.7-257.3. Pale pink crystals. R_f (PE/EA 70:30) = 0.39.

2-(4-Nitrophenyl)-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19l



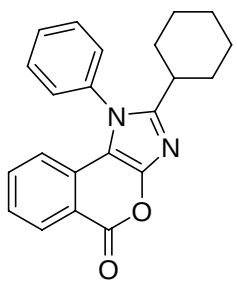
IR (KBr, cm^{-1}): ν_{max} = 3568, 1732 (C=O), 1615, 1509, 1330, 1016, 853, 766, 704. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 6.60 (1 H, dd, *J* = 7.4, 1.4 Hz, H-9), 7.38 (1 H, td, *J* = 7.4, 1.4 Hz, H-7), 7.44 (1 H, td, *J* = 7.4, 1.7 Hz, H-8), 7.51-7.56 (2 H, m, H-2' and H-6'), 7.62 (2 H, dm, *J* = 9.1 Hz, H-2'' and H-6''), 7.66-7.78 (3 H, m, H-3', H-4' and H-5'), 8.09 (2 H, dm, *J* = 9.1 Hz, H-3'' and H-5''), 8.41 (1 H, dd, *J* = 7.7, 1.7 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 112.1 (C-9b), 118.8 (C-9), 119.6 (C-5a), 123.7 (C-3'' and C-5''), 127.0 (C-7), 128.3 (C-2' and C-6'), 129.0 (C-2'' and C-6''), 129.4 (C-9a), 131.0 (C-3' and C-5'), 131.2 (C-4'), 132.6 (C-6), 135.0 (C-8 and C-1''), 136.7 (C-1'), 142.9 (C-2), 147.6 (C-4''), 151.1 (C-3a), 161.3 (C=O). LRMS (70 eV, ES^+): m/z = 384 ($M + H^+$). Mp (°C): 254.3-254.7. Yellow crystals. R_f (PE/EA 70:30) = 0.30.

2-Isopropyl-1-phenyl-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19m



IR (KBr, cm^{-1}): ν_{max} = 3573, 3435, 2973, 2920, 1726 (C=O), 1618, 1497, 1406, 1369, 1271, 1215, 1167, 1087, 1065, 1030, 1016, 785, 764, 710, 683, 572. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.29 (6 H, d, *J* = 6.9 Hz, CH(C*H*$_3$)$_2$), 2.85 (1 H, septet, *J* = 6.9 Hz, C*H*(CH$_3$)$_2$), 6.45 (1 H, d, *J* = 8.0 Hz, H-9), 7.26 (1 H, td, *J* = 7.7, 1.1 Hz, H-7), 7.36 (1 H, td, *J* = 7.7, 1.4 Hz, H-8), 7.43-7.46 (2 H, m, H-2' and H-6'), 7.62-7.68 (3 H, m, H-3', H-4' and H-5'), 8.34 (1 H, dd, *J* = 8.0, 0.8 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 21.9 (2 C, CH(*C*H$_3$)$_2$), 26.3 (*C*H(CH$_3$)$_2$), 108.7 (C-9b), 118.0 (C-9), 118.7 (C-5a), 125.7 (C-7), 128.2 (C-2' and C-6'), 130.3 (C-9a), 130.4 (C-3', C-4' and C-5'), 132.2 (C-6), 134.7 (C-8), 136.2 (C-1'), 150.7 (C-3a), 153.9 (C-2), 161.9 (C=O). LRMS (70 eV, ES$^+$): m/z = 305 (M + H$^+$). Mp (°C): 225.7-225.9. White crystals. R_f (PE/EA 70:30) = 0.37.

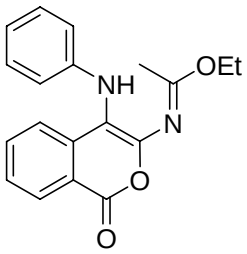
2-Cyclohexyl-1-phenyl-*1H*-isochromeno[3,4-*d*]imidazol-5-one 19n



IR (KBr, cm^{-1}): ν_{max} = 3573, 3414, 2931, 2851, 1714 (C=O), 1619, 1551, 1497, 1477, 1449, 1403, 1369, 1319, 1294, 1271, 1211, 1066, 1019, 761, 703, 682, 653, 574. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.05-1.34 (2 H, m, cHexyl), 1.62-1.79 (8 H, m, cHexyl), 2.40-2.50 (1 H, m, cHexyl), 6.43 (1 H, d, *J* = 8.0 Hz, H-9), 7.26 (1 H, t, *J* = 7.7 Hz, H-7), 7.35 (1 H, td, *J* = 7.6, 0.8 Hz, H-8), 7.41-7.45 (2 H, m, H-2' and H-6'), 7.62-7.71 (3 H, m, H-3', H-4' and H-5'), 8.33 (1 H, d, *J* = 8.0 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 25.6 (C-4''), 26.0 (C-3'' and C-5''), 32.0 (C-2'' and C-6''), 35.8 (C-1''), 108.6 (C-9b), 118.0 (C-9), 118.6 (C-5a), 125.6 (C-7), 128.1 (C-2' and C-6'), 130.3 (C-9a), 130.4 (C-3', C-4' and C-5'), 132.2 (C-6), 134.7 (C-8), 136.1 (C-1'), 150.7 (C-3a), 153.2 (C-2), 161.9 (C=O). LRMS (70 eV, ES$^+$): m/z = 345 (M + H$^+$). Mp (°C): 217.4-217.8. Pale yellow crystals. R_f (PE/EA 70:30) = 0.42.

Ethyl N-(1-oxo-4-phenylamino-1*H*-isochromen-3-yl)acetimidate 136i

Purification of the intermediate **136i** occurred by crystallisation in diethyl ether without heating the solvent, because heating resulted in formation of the end product **19i**.



IR (KBr, cm^{-1}): ν_{max} = 3324 (NH), 1721, 1706 (C=O and C=N), 1639, 1599, 1559, 1495, 1478, 1368, 1283, 1255, 1226, 1161, 1052, 1025, 905, 839, 753, 693. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.24 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3), 2.07 (3 H, s, CH_3), 4.14 (2 H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.98 (1 H, br s, NH), 6.62 (2 H, dd, *J* = 8.4, 1.0 Hz, H-2" and H-6"), 6.79 (1 H, t, *J* = 7.4 Hz, H-4"), 7.15 (2 H, dd, *J* = 8.5, 7.4 Hz, H-3" and H-5"), 7.40 (1 H, td, *J* = 7.4, 1.1 Hz, H-7'), 7.51-7.54 (1 H, m, H-5'), 7.63 (1 H, td, *J* = 7.6, 1.1 Hz, H-6'), 8.27 (1 H, dd, *J* = 8.0, 0.8 Hz, H-8'). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 14.0 (OCH_2CH_3), 19.2 (CH_3), 63.3 (OCH_2CH_3), 106.8 (C-4'), 114.4 (C-2" and C-6"), 118.8 (C-8'a), 119.1 (C-4"), 122.7 (C-5'), 126.5 (C-7'), 129.3 (C-3" and C-5"), 130.1 (C-8'), 135.0 (C-6'), 139.2 (C-4'a), 146.9 (C-1"), 150.7 (C-3'), 161.8 (C=O), 167.5 (C=N). LRMS (70 eV, ES^+): m/z = 323 ($M + H^+$), 277 ($M + H^+ - EtOH$). Mp (°C): 110.9-111.5. Yellow crystals. R_f (PE/EA 70:30) = 0.48.

Chapter 5 - Summary and Perspectives

Microreactor technology is a rather new type of technology which has gained a high interest during the last 2 decennia. A closer look into the literature reports learns that especially since 1997 a lot of literature has appeared on microreactors. Organic synthesis in microreactors is only a very small part of it, which means the technology is used in a much broader concept than organic synthesis alone.

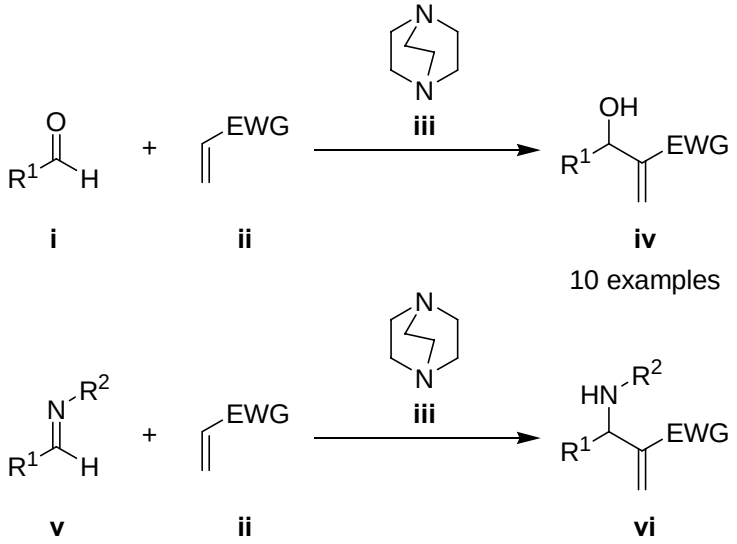
Microreactors, as part of the wide group of microsystems, were generally defined as 'miniaturised reaction systems fabricated by using, at least partially, methods of microtechnology and precision engineering'. Nowadays the broader definition also contains down-scaled designs of existing reactors and modern reactor concepts such as falling-film reactors, packed-bed reactors and structured catalysts e.g. foams.

From an economical point of view, studies are made which state that more or less 50 % of today's chemical reactions could benefit from continuous processes which are mainly based on microreaction technology. Generally, a lot of advantages for organic synthesis are suggested by developers and manufacturers of microreactor systems of which a better mass and heat transfer, a safer handling of reactions, a higher selectivity and an easier scale up are the most important. Several experiments were performed as a proof-of-concept for this technology. Most of these studies however were performed on easy, well known reactions.

The goal of this thesis was to evaluate the use of a microreactor system for some selected multicomponent reactions. In this study, a commercial available microreactor system was used: the CYTOS® College System

containing generally two piston pumps, a microreactor unit and a residence time unit for handling longer reactions (Figure 3.1).

As a first example, the Baylis-Hillman reaction (Scheme 5.1), a carbon-carbon bond forming reaction between e.g. an aldehyde **i** and an activated alkene **ii** with the aid of tertiary amines, such as DABCO **iii**, or phosphines was evaluated. The reaction appears to be very slow in batch conditions. Out of the wide variety of possible reagents in the Baylis-Hillman reaction, the reaction between 4-nitrobenzaldehyde and methyl acrylate with DABCO as a catalyst was chosen to be optimised.



Scheme 5.1: Baylis-Hillman and aza-Baylis-Hillman reaction.

The optimisation consisted of several steps including the selection of the appropriate mixing of the reagents, the solvent and the temperature. The mixing of the reagents had to be chosen carefully, to avoid side reactions such as the formation of a stable betaine. Therefore, preliminary mixing of methyl acrylate and DABCO was avoided. As a solvent system, a 1:1 (v/v) mixture of water and 1,4-dioxane proved to be the best choice. Other solvents, such as dichloromethane or sulfolane, did not result in better conversions. Moreover, in the case of sulfolane, clogging problems occurred. To obtain the highest possible concentration in the microreactor, the aldehyde and the catalyst were dissolved in a 3:7 (v/v) water/1,4-dioxane mixture, while the activated alkene was dissolved in a 7:3 (v/v) water/1,4-dioxane mixture. This gave the desired

1:1 (v/v) mixture in the microreactor. Concerning the reaction temperature, room temperature proved to be the best option. Higher temperatures resulted in lower conversions, while lower temperatures were not possible using the above solvent system. In summary, a mixture of 0.4 M of 4-nitrobenzaldehyde and 1 equivalent of DABCO in a 3:7 (v/v) water/1,4-dioxane mixture was reacted with 3 equivalents of methyl acrylate in a 7:3 (v/v) water/1,4-dioxane mixture at room temperature. After 2 h of reaction, a conversion of 93 % was achieved. A comparison with the batch reaction showed that there was approximately 30 % decrease in reaction time for this specific example. However, due to this rather small acceleration of the Baylis-Hillman reaction, it was not possible to investigate very slow Baylis-Hillman reactions.

Several aldehydes and alkenes were tested using these optimised conditions. This resulted in a conversion between 52 and 100 %. To obtain complete conversion in the uncompleted reactions, the stopped-flow technique was used: by alternative pumping and pausing the flow, the residence time in the system was increased. This gave somewhat higher conversions, and some reactions were driven to completion. However, applying these conditions in an industrial scale will not be economical feasible due to the long start up procedure and the lower yield of the experiments.

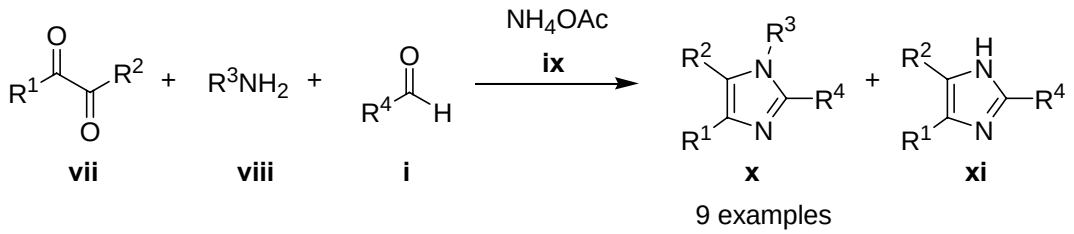
In a next part of the Baylis-Hillman research, the influence of the residence time unit was investigated. It was observed that including the residence time unit gave better results at the same residence time. A clear explanation of this phenomenon was not found, but probably the difference in flow rates between the experiments plays an important role. After introducing some modifications in the procedure, a comparison of the Baylis-Hillman reaction was made in 2 different microreactors and the conventional batch procedure. This showed a better performance in the batch procedure, but no explanation was found.

In a final part of this study, the aza-Baylis-Hillman was investigated (Scheme 5.1), whereby the aldehyde **i** is replaced by an imine **v**. To avoid competition

with the Baylis-Hillman reaction, it was necessary to form the imine in advance. Unfortunately, in that case only a maximal conversion of 49 % was obtained.

A second evaluated reaction was the production of imidazoles *via* a four-component reaction (Scheme 5.2), based on a microwave-assisted optimised literature procedure. However, because of the problems of the scalability of microwave technology, a study of this reaction using microreactor technology seemed interesting. Imidazoles are considered as important heterocyclic structures from biological and synthetical point of view.

The reaction itself was a modified Radziszewski reaction, in which an α-diketone **vii**, a primary amine **viii**, an aldehyde **i** and ammonium acetate **ix** reacted towards tetrasubstituted imidazoles **x** (in the case the primary amine was absent, trisubstituted imidazoles **xi** were formed).

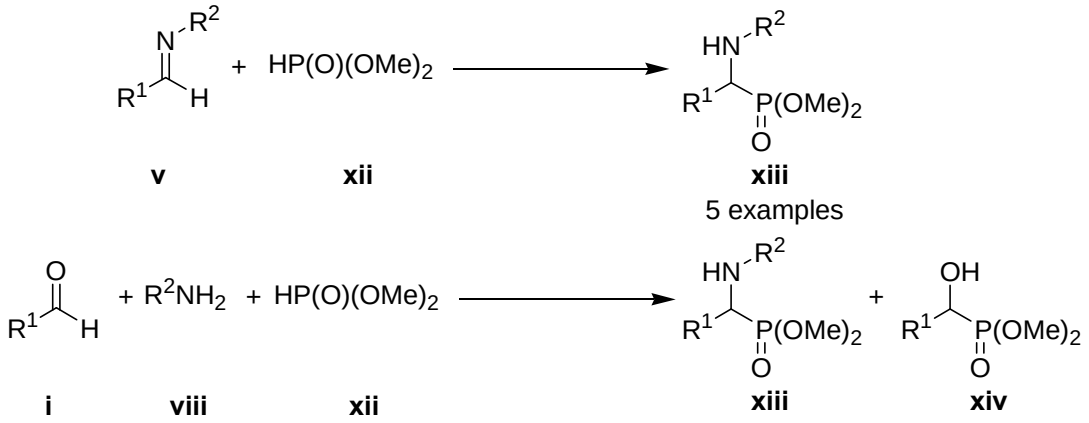


Scheme 5.2: Imidazole 4-CR.

The reaction of benzil, benzylamine, isobutyraldehyde and ammonium acetate under acidic conditions was used to optimise this four-component condensation in the microreactor environment. Two main problems occurred during the optimisation. One was the search for an appropriate solvent, since no solvent was found that dissolves all reagents. Finally, an appropriate solvent mixture was developed. The α-diketone and the aldehyde were dissolved in DMF or NMP (depending on the selected reaction temperature) and the amine and ammonium acetate were dissolved in a primary (high boiling) alcohol. The second problem was the low selectivity towards the tetrasubstituted imidazole, because part of the starting material reacted towards the trisubstituted imidazole. When performing the reaction in pure acetic acid at 50 °C, a selective formation of the tetrasubstituted compound

was noticed. Therefore, the amount of acetic acid was increased from 2 equivalents to 10 equivalents. Finally, in the optimised procedure a mixture of 0.5 M α-diketone, 1 equivalent of aldehyde and 5 equivalents of acetic acid in NMP was reacted in the microreactor with a mixture of 1 equivalent of ammonium acetate, 1.2 equivalents of amine and 5 equivalents of acetic acid in *n*-pentanol. The temperature was adjusted to 120 °C and the residence time was 118 min. A study towards the general applicability of this reaction under microreactor conditions using different α-diketones, amines and aldehydes yielded between 18 and 78 % of the imidazoles.

Since the type of microreactor used in this doctoral study is specially designed for the production of larger quantities of products, it was also interesting to test the production of chemical compounds on a larger scale. Therefore, as a third investigated reaction, the multicomponent reaction producing α-aminophosphonates was thoroughly studied. α-Aminophosphonates **xiii** are considered as important compounds, with several biological activities due to their structural analogy with the corresponding α-amino acids. Starting from a preformed aldimine **v** and dialkyl phosphite **xii**, a batch procedure was modified to be suitable for the microreactor setup (Scheme 5.3).



Scheme 5.3: α-Aminophosphonate formation.

A first modification consisted of the temperature adjustment. While the batch procedure proceeded at the reflux temperature of methanol, working at that temperature was not possible in the microreactor due to vapour formation and a corresponding broad residence time distribution. Secondly, it was

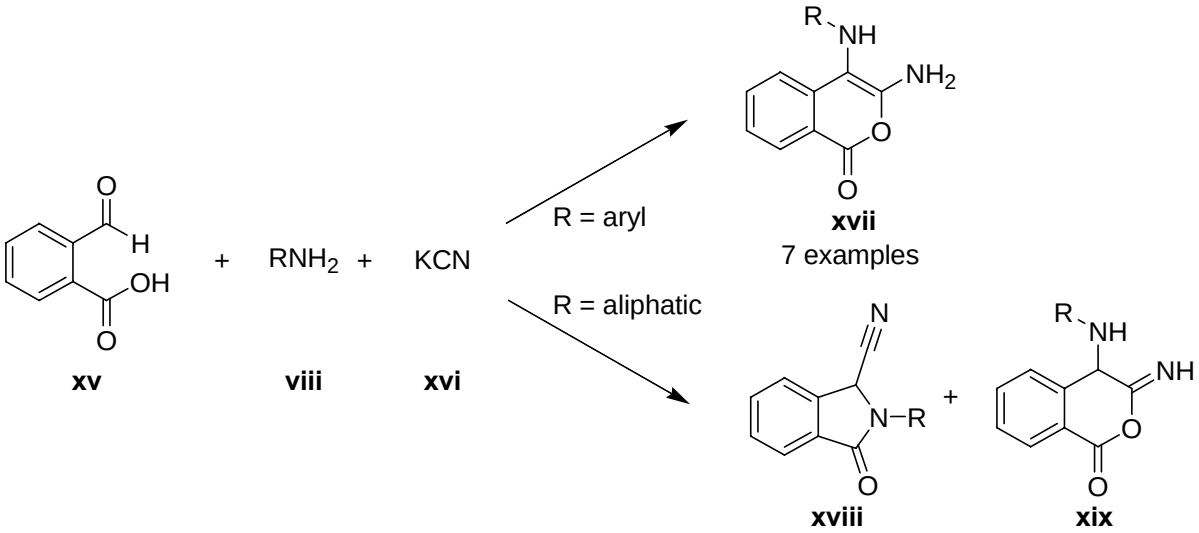
investigated to be able to work with less than 2 equivalents of dialkyl phosphite. However, no complete conversion was observed anymore. To further increase the output, the input concentrations of the reagents was increased to an optimal concentration in the microreactor of 40 mass% for the imine. Higher concentrations resulted again in a decrease of the conversion. A final optimisation consisted of a residence time decrease. To preserve a complete conversion, a shift towards higher boiling solvents was necessary. Although the conversion was still complete, this route was abandoned since the use of other alcohols resulted in side-product formation due to interesterification. Thus, in the optimised procedure, 20 mass% of the aldimine in methanol was mixed in the microreactor with 2 equivalents of the dialkyl phosphite in methanol, at 50 °C and a residence time of 78 min. Using this procedure, it was possible to obtain a variety of α-aminophosphonates with a throughput of 195 to 250 g/day.

Switching to the three-component reaction between the aldehyde **i**, the amine **viii** and the dialkyl phosphite **xii** resulted in a competition between the formation of the α-aminophosphonates **xiii** and the α-hydroxy-methylphosphonates **xiv**. Using orthoesters to promote the imine formation partially avoided this competition, which resulted in somewhat higher conversions. Unfortunately, complete conversion to the α-aminophosphonate using the 3-CR was never obtained and formation of the side-product would result in an extra purification step. Therefore, this route was abandoned.

A final interest in this doctoral thesis was the ability to work with toxic reagents in a safe way. For this study, the multicomponent reaction to produce 3-amino-4-(arylamino)-1*H*-isochromen-1-ones **xvii** was chosen as an interesting example. To produce this compound, *in situ* generation of hydrogen cyanide is necessary. In this reaction, 2-formyl benzoic acid **xv** reacts with an amine **viii** in the presence of potassium cyanide **xvi** and acetic acid (Scheme 5.4).

The optimisation study was started from a literature procedure with some minor modifications. The reaction temperature was changed from the

methanol reflux temperature to 50 °C in order to obtain well defined residence times. Importantly, to obtain safe conditions, the acetic acid and potassium cyanide, necessary to generate hydrogen cyanide, were added separately to the microreactor. During the optimisation study, problems with crystallisation of the end product occurred. It was possible to solve this in two different ways.



Scheme 5.4: Formation of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones.

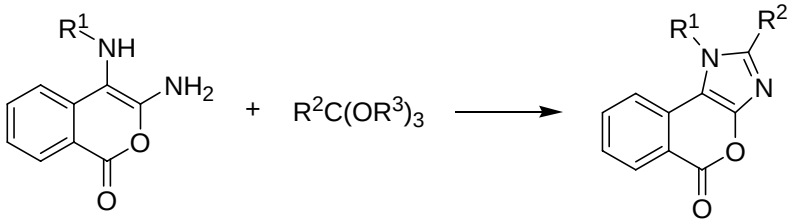
The first way consisted of a decrease in residence time, a decrease in concentration or a combination. Optimisation of both residence time and concentration of the starting products resulted in the following optimised procedure: 0.30 M of 2-formyl benzoic acid and 2 equivalents of acetic acid in methanol were added separately from a mixture of 1.2 equivalents of potassium cyanide and 2 equivalents amine in methanol to the microreactor system. The reaction was run at a temperature of 50 °C with a residence time of 39 min. A generalisation of this first procedure using different aromatic amines made it possible to produce between 33 and 63 g/day of the end product. In the case of an aliphatic amine, the Strecker product **xviii** was the main product formed, together with a small amount of the non-tautomerised end product **xix**.

The other way required a change in the setup. Between the microreactor and the residence time unit, an extra input was connected. *Via* that input, the inert

solvent Fluorinert® FC-70 was added to the system. Using this setup, reaction bubbles were formed separated from each other by the inert solvent. As a result, no crystallisation occurred in the system and it was possible to work at the highest possible concentrations of the starting product, i.e. 0.4 M 2-formyl benzoic acid. Moreover, due to the insolubility of the added solvent, it was possible to easily recuperate the solvent.

It was further explored if the microreactor setup was safer in handling toxic reaction conditions, compared to batch reactions. Therefore, the release of HCN to the environment was studied qualitatively and quantitatively. Using a colour formation procedure, it was already qualitatively visible that the HCN formation was slower in the microreactor procedure. By modifying an existing, U.S. Environmental Protection Agency approved, measurement method of hydrogen cyanide in water, it was possible to measure the amount of hydrogen cyanide released. Using the microreactor, the toxic reagent release was decreased approximately by two orders of magnitude.

This 3-amino-4-(arylamino)-1*H*-isochromen-1-one compound was then further ring closed using the vicinal amino groups in order to attach an imidazole core to the molecule. As an end product, 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **xxi** were obtained (Scheme 5.5). After selection of an appropriate ring closing method, based on some batch experiments, optimisation studies in the microreactor were performed.



Scheme 5.5: Formation of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones.

Optimisation included the search for the appropriate temperature, the number of equivalents of the orthoester **xx** and the catalytic amount of acid.

It was possible to obtain complete conversion at the end of the system, i.e. the microreactor and the residence time unit. However, the reaction was too slow to obtain complete conversion at the end of the microreactor. Even using the stopped-flow technique did not result in complete conversion at the end of the microreactor. The optimised conditions consisted in the reaction of 0.2 M of the 3-amino-4-(arylamino)-1*H*-isochromen-1-one in dimethyl formamide and a mixture of 5 equivalents of the orthoester with 0.1 equivalents of p-toluenesulfonic acid in dimethyl formamide at room temperature and a residence time of 30 min. During the generality study, complete conversion was not always observed when using these conditions. By switching to the maximal residence time of 118 min or by changing the acid catalyst to trifluoro acetic acid instead of p-toluenesulfonic acid, mostly complete conversion was obtained. In the cases of complete conversion, it was possible to produce between 9 and 53 g/day of the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones.

In summary, different types of multicomponent reactions were successfully optimised towards a continuous microreactor system. The optimised reaction conditions of the studied reactions are summarised in Table 5.1. From the results achieved in this doctoral thesis, some remarks and further perspectives towards the use of microreactor technology as an industrial tool have to be made.

The type of microreactor setup used in this research suits very well for large scale production of chemicals. Once the appropriate reaction conditions are developed, large amount of a compound are produced in a short time. However, in my opinion some modifications are necessary when using this setup for the initial screening of these suitable reaction conditions. A switch to pumps which are accurate at lower flow rates (e.g. syringe pumps) is necessary, together with a low volume residence time unit. In this way, a large waste of starting material and solvents is avoided during the screening period.

Specifically towards the application for MCRs, it is observed that using microreactor technology is only possible under certain conditions. In contrast

to a batch procedure, a prerequisite to perform MCRs in the microreactor is a suitable solvent or solvent system wherein all reagents dissolve. Otherwise, fouling of the microchannels occurs and a periodical flushing of the system is necessary which eliminates the advantage of continuous processing. Especially in the case of long reaction times this would be a major drawback due to the long start up period to reach steady state conditions.

Furthermore, it is demonstrated that it is not possible to just apply known batch conditions in a microreactor procedure. Depending on the studied reaction, small or large modifications are necessary. Therefore, different types of solutions are possible such as the stopped-flow technique or the use of an inert solvent to avoid crystallisation. However, the use of the stopped-flow technique is limited because of the decreased throughputs per time unit.

Finally, it is proven that the use of microreactor technology is suitable to considerably diminish the hazards using toxic reagents in a procedure. The performance of hazardous reactions in microreactor systems is definitely advantageous.

Generally, it is believed that developing one microreactor which can handle all reaction types is not possible. Depending on the type of chemical reaction, specific adjustments of the microreactor are necessary. Therefore, I am convinced that one should strive towards the development of a modular microreactor system. In the future, the use of microreactor technology in industry will certainly increase, however not fully replace the existing methods in industrial applications. In my view, the main field wherein microreactor technology will play an important role is the medium to large scale production of easy accessible organic compounds using dangerous (exothermic, toxic) reaction procedures. Especially if there is an issue of selectivity, microreactor technology is a solution.

Table 5.1: Optimised reaction procedures.[a]

Inlet	*Mixtures*	*Solvent*	*τ (min)*	*Temperature (°C)*	*Throughput (g/day)*
	Baylis-Hillman reaction				
A	0.4 M of aldehyde, 1 equiv of DABCO	3:7 (v/v) water/1,4-dioxane	118	22	1.7-22.4
B	3 equiv of alkene	7:3 (v/v) water/1,4-dioxane			
	Imidazole formation				
A	0.5 M of α-diketone, 1 equiv of aldehyde, 5 equiv of acetic acid	NMP	118	120	5.5-39.5
B	1 equiv of NH_4OAc, 1.2 equiv of amine, 5 equiv of acetic acid	*n*-pentanol			
	α-Aminophosphonates				
A	40 mass% of aldimine	MeOH	78	50	196.8-256.8
B	2 equiv dialkyl phosphite	MeOH			
	Formation of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones				
A	0.30 M of 2-formyl benzoic acid, 2 equiv of acetic acid	MeOH	39	50	33.8-62.6
B	1.2 equiv of KCN, 2 equiv of amine	MeOH			
	Formation of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones				
A	0.2 M of 3-amino-4-(arylamino)-1*H*-isochromen-1-one	DMF	30	22	9.4-53.0
B	5 equiv of orthoester, 0.1 equiv of p-TsOH	DMF			

[a] Concentrations before mixing in the microreactor.

Chapter 6 - Samenvatting en Perspectieven

Microreactor technologie is een recent ontwikkelde technologie, die vooral de laatste 2 decennia aan interesse heeft gewonnen. Vooral sinds 1997 is er hieromtrent veel literatuur verschenen. De organische synthese is hierin slechts een beperkt onderdeel, waaruit blijkt dat deze technologie in een veel bredere context bestudeerd wordt.

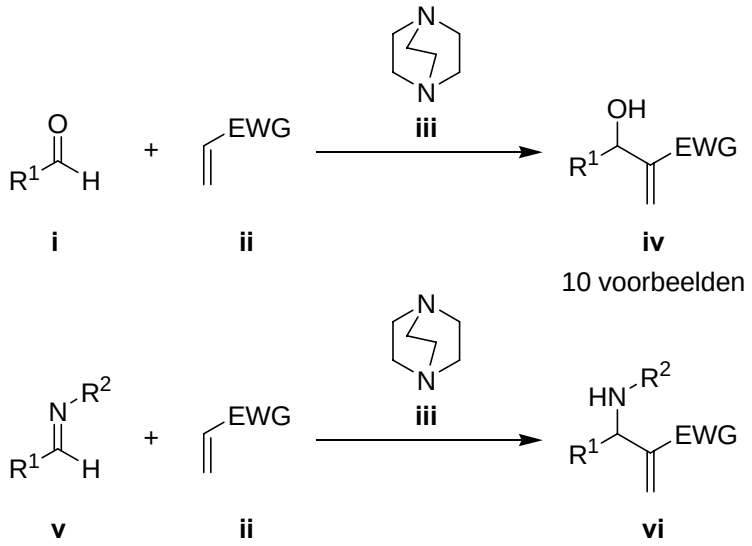
Een algemene definitie van microreactoren, als onderdeel van het brede gamma aan microsystemen, bestaat uit 'geminiaturiseerde systemen die, op zijn minst gedeeltelijk, geproduceerd worden met behulp van microtechnologie en precisie engineering'. Vandaag de dag worden kleinschalige ontwerpen van bestaande reactoren en moderne reactorconcepten zoals vallende film reactoren, gepakte bed reactoren en gestructureerde katalysatoren (vb. met schuimstructuur) ook tot de verzameling van microreactoren gerekend.

Uit onderzoek vanuit economisch invalshoek werd besloten dat ongeveer 50 % van de huidige chemische reacties voordeel zou kunnen hebben bij het gebruik van continue processen die grotendeels gebaseerd zijn op microreactor technologie. Algemeen wordt door de ontwikkelaars en producenten van microreactor systemen een verscheidenheid aan voordelen voor de organische synthese toegeschreven waarvan de belangrijkste een betere massa- en warmtetransfer, veiligere reactieomstandigheden, een hogere selectiviteit en een eenvoudigere opschaling zijn. Verschillende reacties werden al bestudeerd om de werkzaamheid van dit concept te bewijzen. De meeste studies gebruikten echter eenvoudige, goed gekende reacties.

Het doel van dit proefschrift was het evalueren van een microreactor systeem voor multicomponent reacties. In dit onderzoek werd gebruik gemaakt van

een commercieel microreactor systeem: het CYTOS® College System dat algemeen bestaat uit 2 pistonpompen, een microreactor eenheid en een verblijftijdseenheid om langere reacties te bestuderen (Figuur 3.1).

In de eerste plaats werd de Baylis-Hillman reactie bestudeerd (Schema 6.1). Dit is een koolstof-koolstof binding vormende reactie tussen vb. een aldehyde **i** en een geactiveerd alkeen **ii** met behulp van tertiaire amines, zoals DABCO **iii**, of fosfines. De reactie verloopt algemeen vrij traag onder batch omstandigheden. Voor de optimalisatie van de Baylis-Hillman reactie werd gekozen voor de reactie tussen 4-nitrobenzaldehyde, methylacrylaat en DABCO als katalysator.



Schema 6.1: Baylis-Hillman en aza-Baylis-Hillman reactie.

De optimalisatie bestond uit verschillende stappen waaronder de juiste keuze van mengen van de reagentia, de solventkeuze en de temperatuur. De keuze van mengen van de reagentia bleek belangrijk om nevenproducten, zoals de vorming van een stabiel betaine, te voorkomen. Daarom werd methylacrylaat en DABCO niet op voorhand gemengd. Een mengsel van water en 1,4-dioxaan in een 1:1 (v/v) verhouding was de beste keuze voor het solvent-systeem. Andere solventen, zoals dichloromethaan en sulfolaan, gaven lagere omzettingen. Bovendien trad er verstopping op in het geval van sulfolaan als solvent. Om de concentratie van eindproducten te maximaliseren in de microreactor, werden het aldehyde en de katalysator opgelost in een 3:7 (v/v)

mengsel van water en 1,4-dioxaan. Het geactiveerde alkeen daarentegen werd opgelost in een 7:3 (v/v) mengsel van water en 1,4-dioxaan. Zo werd de gewenste 1:1 (v/v) solventverhouding in de microreactor verkregen. De optimale reactietemperatuur bleek kamertemperatuur te zijn. Bij hogere temperaturen werden lagere omzettingen verkregen, terwijl het niet mogelijk was om bij lagere temperaturen te werken met het gebruikte solventsysteem. Samenvattend werd een mengsel van 0.4 M 4-nitrobenzaldehyde en 1 equivalent DABCO in 3:7 (v/v) water/1,4-dioxaan bij kamertemperatuur gereageerd met 3 equivalenten methylacrylaat in 7:3 (v/v) water/1,4-dioxaan. Na 2 uur reactie werd 93 % omzetting bereikt. Uit een vergelijking met de conventionele batch reactie bleek dat er een daling van 30 % in reactietijd verkregen werd voor dit specifieke voorbeeld. Ondanks deze beperkte toename in reactiesnelheid, werden geen tragere Baylis-Hillman reacties bestudeerd.

Vervolgens werden verschillende aldehyden en alkenen getest, gebruik makende van deze geoptimaliseerde omstandigheden. Er werden omzettingen tussen 52 en 100 % verkregen. Om volledige omzetting te krijgen in alle reacties, werd de 'stopped-flow' techniek geïntroduceerd. Daarbij werd de verblijftijd in het systeem verhoogd door de pompen alternerend te laten pompen en te pauzeren. Dit leverde hogere conversies op met soms complete omzetting. Het gebruik van deze techniek is echter economisch niet haalbaar wegens de verlengde opstartprocedure en de lagere productiehoeveelheid per tijdseenheid in vergelijking met de normale procedure.

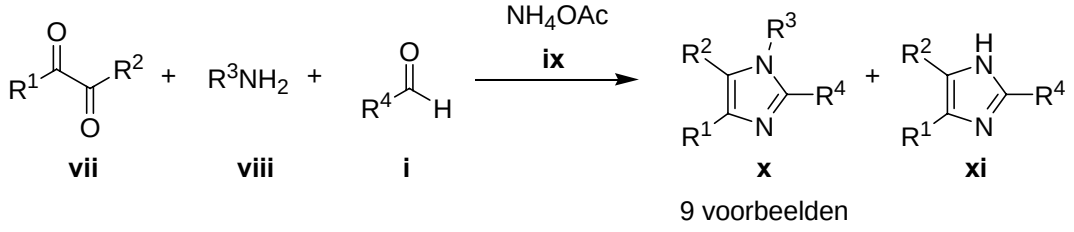
In een volgende deel van het onderzoek naar de Baylis-Hillman reactie, werd de invloed van de verblijftijdseenheid bestudeerd. Er werd waargenomen dat, bij een zelfde verblijftijd, betere resultaten verkregen werden als de verblijftijdseenheid werd gebruikt. Een duidelijke verklaring voor dit fenomeen werd echter niet gevonden. Waarschijnlijk speelt het verschil in vloeisnelheid tussen de experimenten hierbij een belangrijke rol. Nadat een aantal modificaties in de procedure werden doorgevoerd, werd de Baylis-Hillman reactie vergeleken in 2 verschillende microreactoren en de

conventionele batch procedure. De batch procedure gaf de beste resultaten, maar een passende verklaring werd niet gevonden.

In een laatste deel van deze studie, werd de aza-Baylis-Hillman reactie onderzocht (Schema 6.1). Hierbij wordt het aldehyde **i** in de reactie vervangen door een imine **v**. Om competitie met de Baylis-Hillman reactie te vermijden, was het noodzakelijk om het imine vooraf te vormen. Er werd slechts een maximale omzetting van 49 % naar het aza-Baylis-Hillman adduct verkregen.

Een tweede reactie die geëvalueerd werd was de productie van imidazolen *via* een viercomponentsreactie (Schema 6.2). Hiervoor werd gestart van een in de literatuur geoptimaliseerde procedure die gebruik maakt van microgolven. Door het gebrek aan opschaling van microgolfreactoren leek onderzoek van deze reactie in microreactoren interessant. Imidazolen zijn bovendien belangrijke heterocyclische structuren vanuit biologisch en synthetisch standpunt.

De bestudeerde reactie bestond uit een gemodificeerde Radziszewski reactie, waarbij een α-diketon **vii**, een primair amine **viii**, een aldehyde **i** en ammoniumacetaat **ix** reageren met vorming van tetragesubstitueerde imidazolen **x** (als het primair amine afwezig is, worden trigesubstitueerde imidazolen **xi** gevormd).



Schema 6.2: Imidazool 4-CR.

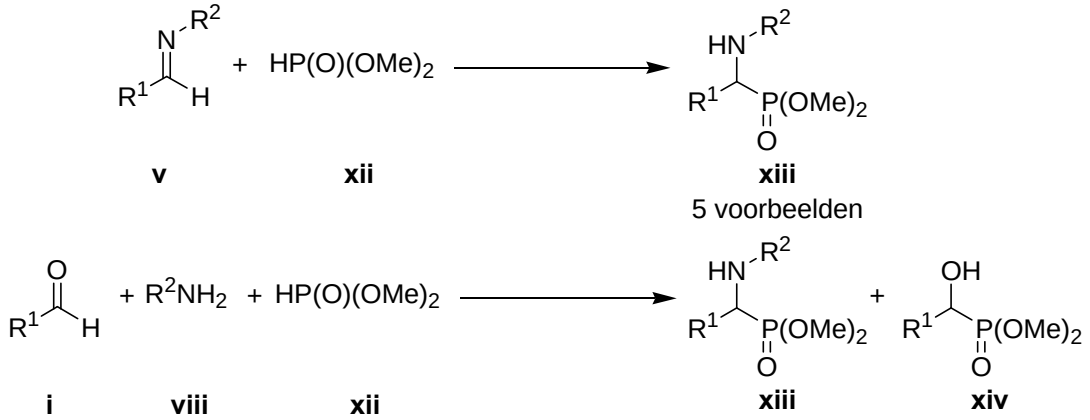
De reactie tussen benzil, benzylamine, isobutyraldehyde en ammoniumacetaat onder zure omstandigheden werd gebruikt om deze viercomponents-condensatie te optimaliseren onder microreactor omstandigheden. Gedurende de optimalisatie traden 2 belangrijke problemen op. Enerzijds was er de zoektocht naar een geschikt solvent, aangezien er geen enkel solvent

gevonden werd waarin alle reagentia oplosten. Uiteindelijk werd geopteerd voor een solventmengsel. Het α-diketon en het aldehyde werden opgelost in DMF of NMP (afhankelijk van de geselecteerde reactietemperatuur) en het amine en ammoniumacetaat werden opgelost in een primair (hoogkokend) alcohol. Anderzijds werd een lage selectiviteit vastgesteld naar het tetra-gesubstitueerde imidazool, omdat een deel van de startproducten werd omgezet naar het trigesubstitueerde imidazool. Wanneer de reactie echter werd uitgevoerd in azijnzuur bij 50 °C, werd een selectieve omzetting naar de tetragesubstitueerde component vastgesteld. Daarom werd de hoeveelheid azijnzuur verhoogd van 2 naar 10 equivalenten. Uiteindelijk bestond de geoptimaliseerde procedure uit de reactie in de microreactor van een mengsel van 0.5 M α-diketon, 1 equivalent aldehyde en 5 equivalenten azijnzuur in NMP met een mengsel van 1 equivalent ammoniumacetaat, 1.2 equivalenten amine en 5 equivalenten azijnzuur in *n*-pentanol. De temperatuur werd ingesteld op 120 °C en de verblijftijd bedroeg 118 min. Algemene toepassing van deze procedure, waarbij verschillende α-diketonen, amines en aldehydes gebruikt werden, leverde een opbrengst tussen 18 en 78 % op.

Omdat het type microreactor in deze studie speciaal ontworpen werd om grotere hoeveelheden van componenten te produceren, leek het ook interessant om de productie van chemische componenten op een grotere schaal te onderzoeken. Daarom werd de productie van α-aminofosfonaten **xiii** *via* een derde multicomponentsreactie intensief onderzocht. α-Aminofosfonaten worden bovendien als belangrijke componenten beschouwd, met verscheidene biologische activiteiten door hun structurele analogie met de overeenkomstige α-aminozuren. Vertrekkende vanuit een op voorhand geproduceerd aldimine **v** en dialkylfosfiet **xii**, werd een bestaande batch procedure gemodificeerd naar de microreactor setup (Schema 6.3).

Een eerste modificatie bestond uit de temperatuursaanpassing. Terwijl de batch procedure bij de refluxtemperatuur van methanol verliep, was dit niet mogelijk in de microreactor omdat er vorming van gasbellen optrad met een brede verblijftijdverdeling tot gevolg. Vervolgens werd de mogelijkheid onderzocht om te werken zonder overmaat aan dialkylfosfiet. Daarbij werd

echter een onvolledige omzetting vastgesteld. Daarna werden de concentraties van de reagentia geoptimaliseerd naar 20 massa% imine om de productie te verhogen. Bij hogere concentraties werd een daling van de omzetting waargenomen. Een laatste optimalisatiestap bestond uit de vermindering van de verblijftijd. Om de volledige omzetting te bewaren, werd hiervoor overgeschakeld op het gebruik van hoogkokende solventen. Hoewel nog steeds een volledige omzetting optrad, werd deze route niet verder uitgediept daar er nevenproducten gevormd werden *via* interveresteringsreacties. Dus, in de geoptimaliseerde procedure werd 40 massa% aldimine in methanol gemengd in de microreactor met 2 equivalenten dialkylfosfiet, bij 50 °C en een reactietijd van 78 min. Gebruik makende van deze procedure, was het mogelijk om verschillende α-aminofosfonaten te produceren aan een snelheid van 195 tot 250 g/dag.

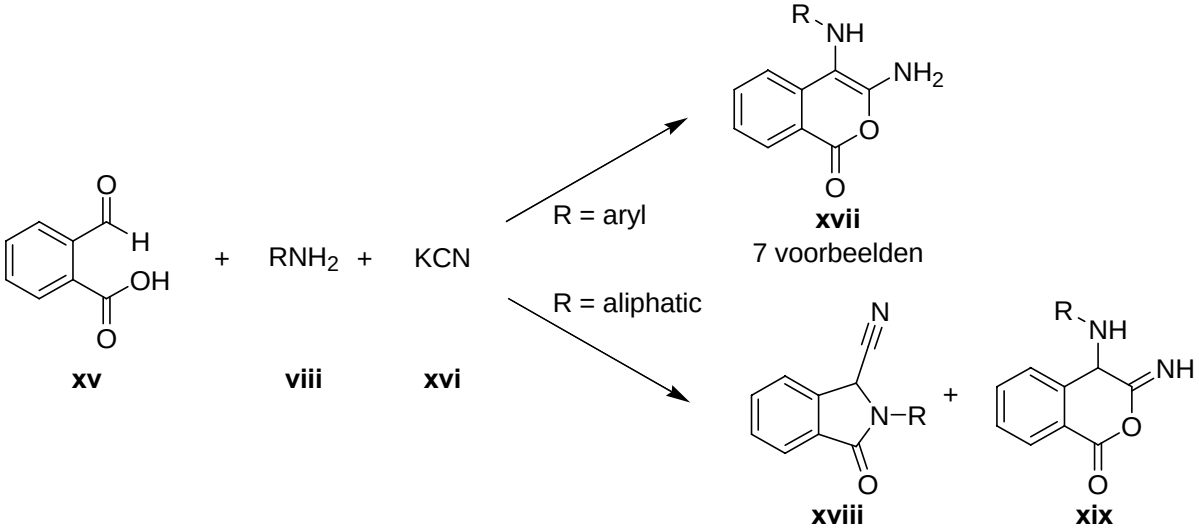


Schema 6.3: Vorming van α-aminofosfonaten.

Wanneer omgeschakeld werd naar de driecomponentsreactie tussen het aldehyde **i**, het amine **viii** en het dialkylfosfiet **xii**, trad er een competitie op tussen de vorming van de α-aminofosfonaten **xiii** en de α-hydroxy-methylfosfonaten **xiv**. Door gebruik te maken van orthoesters om de iminering te bevorderen werd deze competitie gedeeltelijk vermeden. Een complete omzetting naar de α-aminofosfonaten werd echter nooit verkregen. Omdat de vorming van een nevenproduct een extra opzuiveringsstap vereist, werd deze route verlaten.

Een laatste interessegebied in dit onderzoek was de mogelijkheid nagaan om op een veilige manier te werken met toxische producten. Als voorbeeldreactie bij deze studie werd gekozen voor de multicomponentsreactie voor productie van 3-amino-4-(arylamino)-1*H*-isochromen-1-onen **xvii**. Om deze component te vormen, is *in situ* productie van waterstofcyanide noodzakelijk. Tijdens de reactie reageert 2-formyl benzoëzuur **xv** met een amine **viii** in de aanwezigheid van kaliumcyanide **xvi** en azijnzuur (Schema 6.4).

Voor de optimalisatie werd er gestart vanuit een gemodificeerde literatuur procedure. Hierbij werd de reactietemperatuur verlaagd van de reflux-temperatuur van methanol tot 50 °C om een wel gedefinieerde verblijftijd te garanderen. Om veilig te werken, werd het azijnzuur en kaliumcyanide *via* afzonderlijke kanalen toegevoegd aan de microreactor. Gedurende de optimalisatie traden problemen op van vroegtijdige kristallisatie van het eindproduct in de microreactor. Dit kon op 2 manieren opgelost worden.



Schema 6.4: Vorming van 3-amino-4-(arylamino)-1*H*-isochromen-1-onen.

Een eerste oplossing bestond erin om de verblijftijd te verminderen, de concentratie te verlagen of deze 2 te combineren. Optimalisatie van zowel de verblijftijd als de concentratie van de startproducten resulteerde in volgende geoptimaliseerde procedure: 0.30 M 2-formylbenzoëzuur en 2 equivalenten azijnzuur in methanol werd afzonderlijk aan een mengsel van 1.2 equivalenten kaliumcyanide en 2 equivalenten amine in methanol aan de microreactor

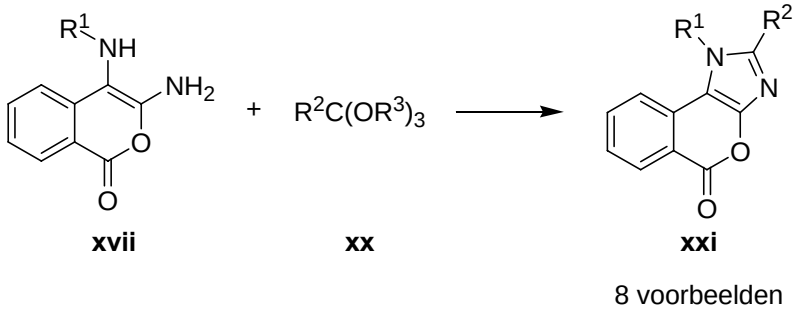
toegevoegd. De reactie verliep gedurende 39 min bij een temperatuur van 50 °C. Deze procedure was algemeen toepasbaar op een verscheidenheid aan aromatische amines met een productie van 33 tot 63 g/dag van het eindproduct. Als een alifatisch amine gebruikt werd, werd het Strecker product **xviii** verkregen, samen met een kleine hoeveelheid van het niet-getautomeriseerde eindproduct **xix**.

Voor de andere oplossing was een verandering van de opstelling vereist. Hierbij werd er tussen de microreactor en de verblijftijdseenheid een extra ingang toegevoegd. *Via* deze invoer werd het inerte solvent Fluorinert® FC-70 toegevoegd aan het systeem. Deze opstelling maakte het mogelijk om afzonderlijke reactiebellen te produceren die van elkaar gescheiden werden door het inerte solvent. Daardoor werd kristallisatie in het systeem vermeden en was het eveneens mogelijk om bij hogere concentraties van het startproduct (0.4 M 2-formylbenzoëzuur) te werken. Bovendien kon het inerte solvent, door zijn onoplosbaarheid, gemakkelijk gerecycleerd worden.

Vervolgens werd een vergelijkende studie tussen de batch procedure en de microreactor opstelling naar de veiligheid van deze toxische reactie uitgevoerd. Dit gebeurde door de vrijstelling van HCN in de omgeving kwalitatief en kwantitatief te meten. Gebruik makende van een kleurreactie werd er kwalitatief vastgesteld dat de HCN vorming trager was in de batch procedure. Door modificatie van een bestaande, door de U.S. Environmental Protection Agency goedgekeurde kwantificatiemethode van HCN in water, was het mogelijk om de hoeveelheid vrijgesteld HCN te meten. Deze vrijstelling was ongeveer 2 grootteordes lager in het geval van de microreactor procedure.

Dit 3-amino-4-(arylamino)-1*H*-isochromen-1-on werd vervolgens verder ringgesloten ter hoogte van de vicinale aminogroepen om een imidazoolkern te incorporeren in de molecule. Als eindproduct werd dan het 1*H*-isochromeno[3,4-*d*]imidazol-5-on **xxi** verkregen (Schema 6.5). Na de selectie van een geschikte ringsluitingsreactie op basis van een aantal batch experimenten, werd een optimalisatiestudie in de microreactor uitgevoerd.

De optimalisatie bestond uit de zoektocht naar een geschikte reactietemperatuur, het aantal equivalenten orthoester **xx** en de katalytische hoeveelheid zuur. Een complete omzetting op het einde van het systeem (na de verblijftijdseenheid) was mogelijk. De reactie was echter te traag om een volledige omzetting na de microreactor te verkrijgen, zelfs na het gebruik van de 'stopped-flow' techniek. De geoptimaliseerde procedure bestond erin om 0.2 M 3-amino-4-(arylamino)-1*H*-isochromen-1-on in DMF bij kamertemperatuur te laten reageren in de microreactor met een mengsel van 5 equivalenten orthoester en 0.1 equivalenten p-tolueensulfonzuur in DMF gedurende 30 min. Wanneer deze geoptimaliseerde procedure werd getest voor andere startproducten, werd niet altijd een volledige omzetting verkregen. Een aanpassing naar de maximale verblijftijd van 118 min of het gebruik van trifluorazijnzuur als zure katalysator gaf meestal een volledige omzetting. Verschillende 1*H*-isochromeno[3,4-*d*]imidazol-5-onen, aan een productiesnelheid van 9 tot 53 g/dag, werden verkregen.



Schema 6.5: Vorming van 1*H*-isochromeno[3,4-*d*]imidazol-5-onen.

Samenvattend werden verschillende types van multicomponent reacties succesvol geoptimaliseerd naar een continu systeem, gebruik makend van een microreactor. De geoptimaliseerde reactieomstandigheden van de bestudeerde reacties worden samengevat in Tabel 6.1. Vanuit de resultaten behaald in dit werk, kunnen een aantal opmerkingen en perspectieven geformuleerd worden over het gebruik van microreactor technologie in industriële toepassingen.

Het type microreactor set-up in dit onderzoek is zeer geschikt voor de productie van chemische componenten op grote schaal. Een grote hoeveelheid van een product kan op korte tijd geproduceerd worden eenmaal

de geschikte reactieomstandigheden zijn ontwikkeld. Volgens mij zijn er echter een aantal aanpassingen nodig wanneer deze set-up gebruikt wordt voor het screenen naar de geschikte omstandigheden. Een omschakeling naar pompen die accuraat zijn bij lagere vloeisnelheden (vb. plunjerpompen) en een verblijftijdseenheid met een klein volume zijn hierbij nodig. Zo wordt een groot verlies aan startmateriaal en solvent vermeden gedurende de screening fase.

Uit dit onderzoek blijkt verder dat het gebruik van microreactor technologie voor MCRs enkel onder bepaalde voorwaarden mogelijk is. In tegenstelling tot een batchprocedure is het vinden van een solvent of solventsysteem waarin alle reagentia oplosbaar zijn vereist. Anders treedt er verstopping van de microkanalen op waardoor periodiek spoelen noodzakelijk wordt. Daardoor wordt echter het voordeel van continue processing tenietgedaan. Dit zou vooral bij lange reactietijden een enorm nadeel zijn door de lange opstartprocedure die dan nodig is om de evenwichtstoestand te bereiken.

Daarnaast werd er aangetoond dat het niet mogelijk is om zomaar de batch procedure te implementeren naar een microreactor procedure. Afhankelijk van de bestudeerde reactie is het daarom noodzakelijk om kleine of grote wijzigingen door te voeren en mogelijke oplossingen zijn vb. het gebruik van de 'stopped-flow' techniek of het gebruik van een inert solvent om kristallisatie te vermijden. Het gebruik van de 'stopped-flow' techniek is gelimiteerd door de verlaagde productiehoeveelheid per tijdseenheid.

Ten slotte werd ook bewezen dat het gebruik van een microreactor systeem de mogelijkheid biedt om toxische gevaren te verminderen. De toepassing van gevaarlijke reacties in microreactoren is zeer zeker voordelig.

Algemeen kan gesteld worden dat het niet mogelijk is om een microreactor te ontwikkelen dat alle types reacties kan uitvoeren. Afhankelijk van het type chemische reactie, moeten er specifieke aanpassingen gebeuren aan de microreactor. Daarom denk ik dat er moet gezocht worden naar een modulair microreactor systeem. In de toekomst zal het gebruik van de microreactor

technologie in de industrie zeker toenemen, maar ze zal de bestaande methoden in de industriële toepassingen niet volledig gaan vervangen. Naar mijn mening wordt het belangrijkste toepassingsgebied voor de microreactor technologie de productie van gemakkelijk toegankelijke organische componenten op medium tot grote schaal, waarbij gebruik wordt gemaakt van gevaarlijke (exotherme, toxische) reacties. Vooral als de selectiviteit een belangrijke rol speelt, is het gebruik van microreactor technologie een oplossing.

Tabel 6.1: Geoptimaliseerde reactieprocedures.[a]

Invoer	*Mengsels*	*Solvent*	*τ (min)*	*Temperatuur (°C)*	*Productie (g/dag)*
	Baylis-Hillman reactie				
A	0.4 M aldehyde, 1 equiv DABCO	3:7 (v/v) water/1,4-dioxaan	118	22	1.7-22.4
B	3 equiv alkeen	7:3 (v/v) water/1,4-dioxaan			
	Imidazoolvorming				
A	0.5 M α-diketon, 1 equiv aldehyde, 5 equiv azijnzuur	NMP	118	120	5.5-39.5
B	1 equiv NH_4OAc, 1.2 equiv amine, 5 equiv azijnzuur	*n*-pentanol			
	α-Aminophosphonaten				
A	40 massa% aldimine	MeOH	78	50	196.8-256.8
B	2 equiv dialkylfosfiet	MeOH			
	Vorming van 3-amino-4-(arylamino)-1*H*-isochromen-1-onen				
A	0.30 M 2-formylbenzoëzuur, 2 equiv azijnzuur	MeOH	39	50	33.8-62.6
B	1.2 equiv KCN, 2 equiv amine	MeOH			
	Vorming van 1*H*-isochromeno[3,4-*d*]imidazol-5-onen				
A	0.2 M 3-amino-4-(arylamino)-1*H*-isochromen-1-on	DMF	30	22	9.4-53.0
B	5 equiv orthoester, 0.1 equiv p-TsOH	DMF			

[a] Concentraties vóór menging in de microreactor.

Chapter 7 - References

[1] D.M. Roberge, L. Ducry, N. Bieler, P. Cretton and B. Zimmermann, *Chem. Eng. Technol.* **2005**, *28*, 318-323.

[2] E.E. Baird and P.B. Dervan, *J. Am. Chem. Soc.* **1996**, *118*, 6141-6146.

[3] K. Gordon and S. Balasubramanian, *J. Chem. Technol. Biotechnol.* **1999**, *74*, 835-851.

[4] B. Henkel, M. Sax and A. Dömling, *Tetrahedron Lett.* **2003**, *44*, 3679-3682.

[5] J.S. Lazo and P. Wipf, *J. Pharmacol. Exp. Ther.* **2000**, *293*, 705-709.

[6] F. Darvas, G. Dorman, L. Urge, I. Szabo, Z. Ronai and M. Sasvari-Szekely, *Pure. Appl. Chem.* **2001**, *73*, 1487-1498.

[7] C. Pinilla, J.R. Appel, E. Borràs and R.A Houghten, *Nat. Med.* **2003**, *9*, 118-122.

[8] B. Cornils and W.A. Herrmann, *Applied homogeneous catalysis with organometallic compounds - A comprehensive handbook*, **2000**, Wiley-VCH, Weinheim, Germany.

[9] G. Ertl, H. Knözinger and J. Weitkamp, *Handbook of heterogeneous catalysis*, **1997**, Wiley-VCH, Weinheim, Germany.

[10] K.E. Price, S.J. Broadwater, A.R. Bogdan, I. Keresztes, J.L. Steinbacher and D.T. McQuade, *Macromolecules* **2006**, *39*, 7681-7685.

[11] A. Dömling, *Chem. Rev.* **2006**, *106*, 17-89.

[12] J. Zhu and H. Bienaymé, *Multicomponent reactions*, **2005**, Wiley-VCH, Weinheim, Germany.

[13] Tufts Center for the Study of Drug Development (Tufts CSDD), Tufts University, Boston, USA, website: "http://csdd.tufts.edu/".

[14] Pharmaceutical Research and Manufacturers of America, *Drug discovery and development - Understanding the R&D process*, **2007**, Washington DC, USA, website: "http://www.phrma.org/".

[15] J.A. DiMasi, R.W. Hansen and H.G. Grabowski, *J. Health Econ.* **2003**, *22*, 151-185.

[16] M. Li, G. White, D. Wilkinson and K.J. Roberts, *Chem. Eng. J.* **2005**, *108*, 81-90.

[17] D. Janasek, J. Franzke and A. Manz, *Nature* **2006**, *442*, 374-380.

[18] Royal Society of Chemistry, *EHSC Note - Safety issue in the scale up of chemical reactions*, **19/07/2007**, website: "http://www.rsc.org/".

[19] W. Löhder and L. Bergann, *Ger. (East)* **1986**, DD 246257. *Chem. Abstr.* **1986**, *108*, 23827.

[20] K. Schubert, W. Bier, G. Linder and D. Seidel, *Chem. Ing. Tech.* **1989**, *61*, 172-173.

[21] E.R. Delsman, M.H.J.M. de Croon, G.D. Elzinga, P.D. Cobden, G.J. Kramer and J.C. Schouten, *Chem. Eng. Technol.* **2005**, *28*, 367-375.

[22] B. Beck, A. Picard, E. Herdtweck and A. Dömling, *Org. Lett.* **2004**, *6*, 39-42.

[23] C. Simon, F. Lieby-Muller, J. Peyronel, T. Constantieux and J. Rodriguez, *Synlett* **2003**, 2301-2304.

[24] J. Azizian, A.R. Karimi, A.A. Mohammadi, M.R. Mohammadizadeh, *Synthesis* **2004**, 2263-2265.

[25] R.S. Bon, B. van Vliet, N.E. Sprenkels, R.F. Schmitz, F.J.J. de Kanter, C.V. Stevens, M. Swart, F.M. Bickelhaupt, M.B. Groen and R.V.A. Orru, *J. Org. Chem.* **2005**, *70*, 3542-3553.

[26] G. Guillena, D.J. Ramón and M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693-700.

[27] D. Basavaiah, P.D. Rao and R.S. Hyma, *Tetrahedron* **1996**, *52*, 8001-8062.

[28] D. Basavaiah, A.J. Rao and T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811-891.

[29] E. Gelens, F.J.J. De Kanter, R.F. Schmitz, L.A.J.M. Sliedregt, B.J. Van Steen, C.G. Kruse, R. Leurs, M.B. Groen and R.V.A. Orru, *Mol. Div.* **2006**, *10*, 17-22.

[30] S.E. Wolkenberg, D.D. Wisnoski, W.H. Leister, Y. Wang, Z. Zhao and C.W. Lindsley, *Org. Lett.* **2004**, *6*, 1453-1456.

[31] F. Bellina, S. Cauteruccio and R. Rossi, *Tetrahedron* **2007**, *63*, 4571-4624.

[32] B. Radziszewski, *Chem. Ber.* **1882**, *15*, 1493.

[33] E. Grossbard and D. Atkinson, *The herbicide glyphosate*, **1985**, Butterworth, London, United Kingdom.

[34] A.D. Baylis, *Pest Manag. Sci.* **2000**, *56*, 299-308.

[35] P. Kafarski and B. Lejczak, *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193-215.

[36] M.C. Allen, W. Fuhrer, B. Tuck, R. Wade and J.M. Wood, *J. Med. Chem.* **1989**, *32*, 1652-1661.

[37] F.R. Atherton, C.H. Hassall and R.W. Lambert, *J. Med. Chem.* **1986**, *29*, 29-40.

[38] E. Van Meenen, K. Moonen, D. Acke and C.V. Stevens, *Arkivoc* **2006**, *(i)*, 31-45.

[39] T. Opatz and D. Ferenc, *Eur. J. Org. Chem.* **2005**, 817-821.

[40] W. Ehrfeld, V. Hessel and H. Löwe, *Microreactors - New Technology for Modern Chemistry*, **2000**, Wiley-VCH, Weinheim, Germany.

[41] V. Hessel, *Inaugural lecture*, **10/02/2006**, TU Eindhoven, The Netherlands.

[42] P. Löb, H. Löwe and V. Hessel, *J. Fluorine Chem.* **2004**, *125*, 1677-1694.

[43] A.R. Bogdan, B.P. Mason, K.T. Sylvester and D.T. McQuade, *Angew. Chem. Int. Ed.* **2007**, *46*, 1698-1701.

[44] L. Kiwi-Minsker and A. Renken, *Catal. Today* **2005**, *110*, 2-14.

[45] M.W. Losey, M.A. Schmidt and K.F. Jensen, *Ind. Eng. Chem. Res.* **2001**, *40*, 2555-2562.

[46] K.F. Jensen, *Chem. Eng. Sci.* **2001**, *56*, 293-303.

[47] G.N. Doku, W. Verboom, D.N. Reinhoudt and A. van den Berg, A. *Tetrahedron* **2005**, *61*, 2733-2742.

[48] B.P. Mason, K.E. Price, J.L. Steinbacher, A.R. Bogdan and D.T. McQuade, *Chem. Rev.* **2007**, *107*, 2300-2318.

[49] M. Brivio, W. Verboom and D.N. Reinhoudt, *Lab Chip* **2006**, *6*, 329-344.

[50] P.D.I. Fletcher, S.J. Haswell, E. Pombo-Villar, B.H. Warrington, P. Watts, S.Y.F. Wong and X. Zhang, *Tetrahedron* **2002**, *58*, 4735-4757.
[51] P. Watts and C. Wiles, *Chem. Commun.* **2007**, 443-467.
[52] K. Geyer, J.D.C. Codée and P.H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434-8442.
[53] P. Watts and S.J. Haswell, *Curr. Opin. Chem. Biol.* **2003**, *7*, 380-387.
[54] K. Jähnisch, V. Hessel, H. Löwe and M. Baerns, *Angew. Chem. Int. Ed.* **2004**, *43*, 406-446.
[55] C. Wiles, P. Watts, S.J. Haswell and E. Pombo-Villar, *Tetrahedron* **2005**, *61*, 10757-10773.
[56] A. Manz and J.C.T. Eijkel, *Pure Appl. Chem.* **2001**, *73*, 1555-1561.
[57] J. El-Ali, P.K. Sorger and K.F. Jensen, *Nature* **2006**, *442*, 403-411.
[58] Y. Li, B. Yuan, H. Ji, D. Han, S. Chen, F. Tian and X. Jiang, *Angew. Chem. Int. Ed.* **2007**, *46*, 1094-1096.
[59] S.J. Lee and S.Y. Lee, *Appl. Microbiol. Biotechnol.* **2004**, *64*, 289-299.
[60] A.K. Gnanappa, C. Ke, O. Slattery and M. Sheehan, in B.G. Sammakia, T.T. Lee, Y.K. Yoshi, D.W. Copeland, J.H. Pang, K. Jonnalagadda, G. Lu, S. Tonapi, S. Park, M. Asheghi, V.A. Chiriac, M.K. Ellsworth and G.R. Ahmed (eds.), *Proceedings of the 10th Intersociety Conference on Thermal and Thermomechanical Phenomena in Electronics Systems*, **2006**, 1330-1335.
[61] M. Carles, T. Lee, S. Moganti, R. Lenigk, K.W.K. Tsim, N.Y. Ip, I.M. Hsing and N.J. Sucher, *Fresenius' J. Anal. Chem.* **2001**, *371*, 190-194.
[62] J. Cheng, C. Hsieh, Y. Chuang and J. Hsieh, *Analyst* **2005**, *130*, 931-940.
[63] K. Yamashita, D. Ogura, Y. Yamaguchi, M. Miyazaki, M. Briones, H. Nakamura and H. Maeda, *Anal. Bioanal. Chem.* **2005**, *382*, 1477-1483.
[64] U. Lehmann, C. Vandevyver, V.K. Parashar and M.A.M. Gijs, *Angew. Chem. Int. Ed.* **2006**, *45*, 3062-3067.
[65] R.K.P. Benninger, O. Hofmann, B. Önfelt, I. Munro, C. Dunsby, D.M. Davis, M.A.A. Neil, P.M.W. French and A.J. deMello, *Angew. Chem. Int. Ed.* **2007**, *46*, 2228-2231.
[66] M.B. Kerby, R.S. Legge and A. Tripathi, *Anal. Chem.* **2006**, *78*, 4810-4814.
[67] H.F. Arata, Y. Rondelez, H. Noji and H. Fujita, *Anal. Chem.* **2005**, *77*, 8273-8280.
[68] C. Berne, L. Betancor, H.R. Luckarift and J.C. Spain, *Biomacromolecules* **2006**, *7*, 2631-2636.
[69] A. Collins, E. Mikeladze, M. Bengtsson, M. Kokaia, T. Laurell and E. Csoregi, *Electroanalysis* **2001**, *13*, 425-431.
[70] T.S. Sim, E.M. Kim, H.S. Joo, B.G. Kim, Y.K. Kim, *Lab Chip* **2006**, *6*, 1056-1061.
[71] T. Yamamoto, T. Nojima and T. Fujii, *Lab Chip* **2002**, *2*, 197-202.
[72] D. Belder, M. Ludwig, L. Wang and M.T. Reetz, *Angew. Chem. Int. Ed.* **2006**, *45*, 2463-2466.

[73] P. Hoffmann, U. Häusig, P. Schulze and D. Belder, *Angew. Chem. Int. Ed.* **2007**, *46*, 4913-4916.

[74] M.C. Mitchell, V. Spikmans, A. Manz and A.J. deMello, *J. Chem. Soc., Perkin Trans. 1* **2001**, 514-518.

[75] H. Wensink, F. Benito-Lopez, D.C. Hermes, W. Verboom, H.J.G.E. Gardeniers, D.N. Reinhoudt and A. van den Berg, *Lab Chip* **2005**, *5*, 280-284.

[76] L. Mu, Y. Liu, S. Cai and J. Kong, *Chem. Eur. J.* **2007**, *13*, 5113-5120.

[77] A. Ymeti, J. Greve, P.V. Lambeck, T. Wink, S.W.F.M. van Hövell, T.A.M. Beumer, R.R. Wijn, R.G. Heideman, V. Subramaniam and J.S. Kanger, *Nano Lett.* **2007**, *7*, 394-397.

[78] A. Huebner, M. Srisa-Art, D. Holt, C. Abell, F. Hollfelder, A.J. deMello and J.B. Edel, *Chem. Commun.* **2007**, 1218-1220.

[79] H. Wang and C. Lu, *Chem. Commun.* **2006**, 3528-3530.

[80] Y. Tan, K. Hettiarachchi, M. Siu, Y. Pan and A.P. Lee, *J. Am. Chem. Soc.* **2006**, *128*, 5656-5658.

[81] V.I. Vullev, J. Wan, V. Heinrich, P. Landsman, P.E. Bower, B. Xia, B. Millare and G. Jones, *J. Am. Chem. Soc.* **2006**, *128*, 16062-16072.

[82] J. Wang, M.P. Chartathi, B. Tian and R. Polsky, *Anal. Chem.* **2000**, *72*, 2514-2518.

[83] J.P. Ferrance, Q. Wu, B. Giordano, C. Hernandez, Y. Kwok, K. Snow, S. Thibodeau and J.P. Landers, *Anal. Chim. Acta* **2003**, *500*, 223-236.

[84] S. Taghavi-Moghadam, A. Kleemann and K.G. Golbig, *Org. Process Res. Dev.* **2001**, *5*, 652-658.

[85] H. Löwe, V. Hessel and A. Mueller, *Pure Appl. Chem.* **2002**, *74*, 2271-2276.

[86] A. deMello and R. Wootton, *Lab Chip* **2002**, *2*, 7N-13N.

[87] S.J. Haswell and P. Watts, *Green Chem.* **2003**, *5*, 240-249.

[88] P. Watts and S.J. Haswell, *Drug Discovery Today* **2003**, *8*, 586-593.

[89] D.A. Snyder, C. Noti, P.H. Seeberger, F. Schael, T. Bieber, G. Rimmel and W. Ehrfeld, *Helv. Chim. Acta* **2005**, *88*, 1-9.

[90] D. Kralisch and G. Kreisel, *Chem. Eng. Sci.* **2007**, *62*, 1094-1100.

[91] G.M. Whitesides, *Nature* **2006**, *442*, 368-373.

[92] T. Schwalbe, V. Autze and G. Wille, *Chimia* **2002**, *56*, 636-646.

[93] W. Ehrfeld, K. Golbig, V. Hessel, H. Löwe and T. Richter, *Ind. Eng. Chem. Res.* **1999**, *38*, 1075-1082.

[94] N. Aoki, S. Hasebe and K. Mae, *Chem. Eng. J.* **2004**, *101*, 323-331.

[95] C.N. Baroud, F. Okkels, L. Ménétrier and P. Tabeling, *Phys. Rev. E* **2003**, *67*, 060104(R).

[96] D. Bothe, C. Stemich and H. Warnecke, *Chem. Eng. Sci.* **2006**, *61*, 2950-2958.

[97] V. Hessel, H. Löwe and F. Schönfeld, *Chem. Eng. Sci.* **2005**, *60*, 2479-2501.

[98] C. Hong, J. Choi and C.H. Ahn, *Lab Chip*, **2004**, *4*, 109-113.

[99] K. Sritharan, C.J. Strobl, M.F. Schneider, A. Wixforth and Z. Guttenberg, *Appl. Phys. Lett.* **2006**, *88*, 054102.

[100] P. Löb, V. Hessel, H. Klefenz, H. Löwe and K. Mazanek, *Lett. Org. Chem.*, **2005**, *2*, 767-779.

[101] T. Kawaguchi, H. Miyata, K. Ataka, K. Mae and J. Yoshida, *Angew. Chem. Int. Ed.* **2005**, *44*, 2413-2416.

[102] X. Zhang, S. Stefanick and F. Villani, *Org. Process Res. Dev.* **2004**, *8*, 455-460.

[103] G. Panke, T. Schwalbe, W. Stirner, S. Taghavi-Moghadam and G. Wille, *Synthesis* **2003**, 2827-2830.

[104] L. Ducry and D.M. Roberge, *Angew. Chem. Int. Ed.* **2005**, *44*, 7972-7975.

[105] W.F. Ferstl, M.S. Schwarzer and S.L. Loebbecke, *Chem. Ing. Tech.* **2004**, *76*, 1326-1327.

[106] G. Wille, G. Jas and V. Autze, *ChemFiles* **2005**, *5*, 10-11.

[107] G. Dummann, U. Quittmann, L. Gröschel, L. D.W. Agar, O. Wörz and K. Morgenschweis, *Catal. Today* **2003**, *79*, 433-439.

[108] K. Midorikawa, S. Suga and J. Yoshida, *Chem. Commun.* **2006**, 3794-3796.

[109] A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae and J. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11666-11675.

[110] J. Mu, X. Yin and Y. Wang, *Synlett* **2005**, 3163-3165.

[111] M.T. Rahman, T. Fukuyama, N. Kamata, M. Sato and I. Ryu, *Chem. Commun.* **2006**, 2236-2238.

[112] E.R. Murphy, J.R. Martinelli, N. Zaborenko, S.L. Buchwald and K.F. Jensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 1734-1737.

[113] P.W. Miller, N.J. Long, A.J. deMello, R. Vilar, J. Passchier and A. Gee, *Chem. Commun.* **2006**, 546-548.

[114] P.W. Miller, N.J. Long, A.J. deMello, R. Vilar, H. Audrain, D. Bender, J. Passchier and A. Gee, *Angew. Chem. Int. Ed.* **2007**, *46*, 2875-2878.

[115] H. Audrain, *Angew. Chem. Int. Ed.* **2007**, *46*, 1772-1775.

[116] R.D. Chambers, M.A. Fox, G. Sandford, J. Trmcic and A. Goeta, *J. Fluorine Chem.* **2007**, *128*, 29-33.

[117] O. Wörz, K.P. Jäckel, T. Richter and A. Wolf, *Chem. Eng. Sci.* **2001**, *56*, 1029-1033.

[118] R. Schenk, V. Hessel, C. Hofmann, J. Kiss, H. Löwe and A. Ziogas, *Chem. Eng. J.* **2004**, *101*, 421-429.

[119] V. Hessel, P. Löb and H. Löwe, Microreactor organic processing for fine chemicals, *Young Chemist Workshop - Micro Reactor Technology*, **16-18/03/2006**, Enschede, The Netherlands, 3-4.

[120] K. Tanaka, S. Motomatsu, K. Koyama, S. Tanaka and K. Fukase, *Org. Lett.* **2007**, *9*, 299-302.

[121] P. He, P. Watts, F. Marken and S.J. Haswell, *Angew. Chem. Int. Ed.* **2006**, *45*, 4146-4149.

[122] H. Song, J.D. Tice and R.F. Ismagilov, *Angew. Chem. Int. Ed.* **2003**, *42*, 768-772.
[123] I. Shestopalov, J.D. Tice and R.F. Ismagilov, *Lab Chip* **2004**, *4*, 316-321.
[124] B. Zheng, L.S. Roach and R.F. Ismagilov, *J. Am. Chem. Soc.* **2003**, *125*, 11170-11171.
[125] B. Zheng, J.D. Tice, L.S. Roach and R.F. Ismagilov, *Angew. Chem. Int. Ed.* **2004**, *43*, 2508-2511.
[126] C.J. Gerdts, V. Tereshko, M.K. Yadav, I. Dementieva, F. Collart, A. Joachimiak, R.C. Stevens, P. Kuhn, A. Kossiakoff and R.F. Ismagilov, *Angew. Chem. Int. Ed.* **2006**, *45*, 8156-8160.
[127] S.L. Poe, M.A. Cummings, M.P. Haaf and D.T. McQuade, *Angew. Chem. Int. Ed.* **2006**, *45*, 1544-1548.
[128] H. Song, D.L. Chen and R.F. Ismagilov, *Angew. Chem. Int. Ed.* **2006**, *45*, 7336-7356.
[129] E. Comer and M.G. Organ, *Chem. Eur. J.* **2005**, *11*, 7223-7227.
[130] E. Comer and M.G. Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8160-8167.
[131] N.S. Wilson, C.R. Sarko and G.P. Roth, *Org. Process Res. Dev.* **2004**, *8*, 535-538.
[132] W.S. Bremner and M.G. Organ, *J. Comb. Chem.* **2007**, *9*, 14-16.
[133] V. Hessel, C. Hofmann, H. Löwe, A. Meudt, S. Scherer, F. Schönfeld and B. Werner, *Org. Process Res. Dev.* **2004**, *8*, 511-523.
[134] C. Wille, H. Gabski, T. Haller, H. Kim, L. Unverdorben and R. Winter, *Chem. Eng. J.* **2004**, *101*, 179-185.
[135] V. Hoellein, H. Kim, L. Schneider and C. Wille, *PCT Int. Appl.* **2005**, 105927. *Chem. Abstr.* **2005**, *143*, 441979.
[136] C. Wille, V. Autze, H. Kim, U. Nickel, S. Oberbeck, T. Schwalbe and L. Unverdorben, Session Tba06 "Application of Microdevices for Production, Energy and Transportation Systems" *IMRET 6 - 6th International Conference on Microreaction Technology*, **2002**, New Orleans, Louisiana, USA.
[137] D.L. Chen, C.J. Gerdts and R.F. Ismagilov, *J. Am. Chem. Soc.* **2005**, *127*, 9672-9673.
[138] J.L. Steinbacher and D.T. McQuade, *J. Polym. Sci. Pol. Chem.* **2006**, *44*, 6505-6533.
[139] E. Quevedo, J. Steinbacher and D.T. McQuade, *J. Am. Chem. Soc.* **2005**, *127*, 10498-10499.
[140] S.L. Anna, N. Bontoux and H.A. Stone, *Appl. Phys. Lett.* **2003**, *82*, 364-366.
[141] J. Kim, A.S. Utada, A. Fernández-Nieves, Z. Hu and D.A. Weitz, *Angew. Chem. Int. Ed.* **2007**, *46*, 1819-1822.
[142] Z. Nie, W. Li, M. Seo, S. Xu and E. Kumacheva, *J. Am. Chem. Soc.* **2006**, *128*, 9408-9412.
[143] P. Laval, J. Salmon, G. Cristobal and M. Joanicot, Investigating kinetics of nucleation using microfluidics, *Young Chemist Workshop - Micro Reactor Technology*, **16-18/03/2006**, Enschede, The Netherlands, 37-38.
[144] Z. Nie, S. Xu, M. Seo, P.C. Lewis and E. Kumacheva, *J. Am. Chem. Soc.* **2005**, *127*, 8058-8063.

[145] T. Iwasaki, A. Nagaki and J. Yoshida, *Chem. Commun.* **2007**, 1263-1265.

[146] A. Nagaki, K. Kawamura, S. Suga, T. Ando, M. Sawamoto and J.Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 14702-14703.

[147] C. Serra, C. Rosenfeld, C. Brochon and G. Hadziiannou, Homogeneous polymerizations in microfluidic devices, *Young Chemist Workshop - Micro Reactor Technology*, **16-18/03/2006**, Enschede, The Netherlands, 39-40.

[148] T. Iwasaki and J. Yoshida, *Macromolecules* **2005**, *38*, 1159-1163.

[149] C. Basheer, F.S.J. Hussain, H.K. Lee and S. Valiyaveettil, *Tetrahedron Lett.* **2004**, *45*, 7297-7300.

[150] G.M. Greenway, S.J. Haswell, D.O. Morgan, V. Skelton and P. Styring, *Sens. Actuators, B: Chem.* **2000**, *63*, 153-158.

[151] N.T.S. Phan, J. Khan and P. Styring, *Tetrahedron* **2005**, *61*, 12065-12073.

[152] Y. Uozumi, Y.M.A. Yamada, T. Beppu, N. Fukuyama, M. Ueno and T. Kitamori, *J. Am. Chem. Soc.* **2006**, *128*, 15994-15995.

[153] J. Hogan, *Nature* **2006**, *442*, 351-352.

[154] Institut für Mikrotechnik Mainz (Germany), *Microstructured reactor nitroglycerine plant - Test runs successfully finished*, press release **09-11-2005**, Mainz, Germany, website: "http://www.imm-mainz.de/".

[155] D. Kirschneck and G. Tekautz, *Chem. Eng. Technol.* **2007**, *30*, 305-308.

[156] J.N. Lee, C. Park and G.M. Whitesides, *Anal. Chem.* **2003**, *75*, 6544-6554.

[157] I.R. Baxendale, J. Deeley, C.M. Griffiths-Jones, S.V. Ley, S. Saaby and G.K. Tranmer, *Chem. Commun.* **2006**, 2566-2568.

[158] C. Wiles, P. Watts, S.J. Haswell and E. Pombo-Villar, *Lab Chip* **2002**, *2*, 62-64.

[159] S. Liu, T. Fukuyama, M. Sato and I. Ryu, *Org. Process Res. Dev.* **2004**, *8*, 477-481.

[160] M. Baumann, I.R. Baxendale, S.V. Ley, C.D. Smith and G.K. Tranmer, *Org. Lett.* **2006**, *8*, 5231-5234.

[161] A. Aota, M. Nonaka, A. Hibara and T. Kitamori, *Angew. Chem. Int. Ed.* **2007**, *46*, 878-880.

[162] R.V.A. Orru and M. de Greef, *Synthesis* **2003**, 1471-1499.

[163] J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133-1144.

[164] J. Sapi and J. Laronze, *Arkivoc* **2004**, *(vii)*, 208-222.

[165] C.O. Kappe, *Tetrahedron* **1993**, *49*, 6937-6963.

[166] C.O. Kappe, **in** J. Zhu and H. Bienaymé (eds.), *Multicomponent reactions*, **2005**, Wiley-VCH, Weinheim, 95-120.

[167] M. Tramontini and L. Angiolini, *Tetrahedron* **1990**, *46*, 1791-1837.

[168] M. Arend, B. Westermann and N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1045-1070.

[169] M.M.B. Marques, *Angew. Chem. Int. Ed.* **2006**, *45*, 348-352.

[170] L. Banfi, A. Basso, G. Guanti and R. Riva, **in** J. Zhu and H. Bienaymé (eds.), *Multicomponent reactions*, **2005**, Wiley-VCH, Weinheim, 1-32.

[171] G.A. Groβ, G. Mayer, J. Albert, D. Riester, J. Osterodt, H. Wurziger and A. Schober, *Angew. Chem. Int. Ed.* **2006**, *45*, 3102-3106.

[172] P. Dubois, G. Marchand, Y. Fouillet, J. Berthier, T. Douki, F. Hassine, S. Gmouh and M. Vaultier, *Anal. Chem.* **2006**, *78*, 4909-4917.

[173] P. Dubois, G. Marchand, S. Gmouh and M. Vaultier, *Chem. Eur. J.* **2007**, *13*, 5642-5648.

[174] Syrris Ltd, Royston, UK, website: "http://www.syrris.com/".

[175] R.C. Wheeler, O. Benali, M. Deal, E. Farrant, S.J.F. MacDonald and B.H. Warrington, *Org. Process Res. Dev.* **2007**, *11*, 704-710.

[176] CPC - Cellular Process Chemistry Systems GmbH: Heiligkreuzweg 90, D-55130 Mainz,Germany, www.cpc-net.com. T. Schwalbe, K. Golbig, M. Hohmann, P. Georg, A. Oberbeck, B. Dittmann, J. Stasna and S. Oberbeck (Cellular Process Chemistry Inc., USA), *Eur. Pat. Appl.* **2001**, EP 1123734. *Chem. Abstr.* **2001**, *135*, 154468b.

[177] K. Morita, *Japan Patent* **1968**, 6803364. *Chem. Abstr.* **1968**, *69*, 58828s.

[178] K. Morita, Z. Suzuki and H. Hirose, *Bull. Chem. Soc. Jpn.* **1968,** *41,* 2815. *Chem. Abstr.,* **1968,** *70,* 57078.

[179] A.B. Baylis and M.E.D. Hillman, *German Offen.* **1972**, 2155113. *Chem. Abstr.,* **1972,** *77,* 34174q.

[180] F. Coelho, W.P. Almeida, D. Veronese, C.R. Mateus, E.C. Silva Lopes, R.C. Rossi, G.P. Silveira and C.H. Pavam, *Tetrahedron* **2002**, *58*, 7437-7447.

[181] V.K. Aggarwal, I. Emme and S.Y. Fulford, *J. Org. Chem.* **2003**, *68*, 692-700.

[182] W. Pei, H. Wei and G. Li, *Chem. Commun.* **2002**, 2412-2413.

[183] P. Caumul and H.C. Hailes, *Tetrahedron Lett.* **2005**, *46*, 8125-8127.

[184] V.K. Aggarwal, D.K. Dean, A. Mereu and R. Williams, *J. Org. Chem.* **2002**, *67*, 510-514.

[185] J. Cai, Z. Zhou, G. Zhao and C. Tang, *Org. Lett.* **2002**, *4*, 4723-4725.

[186] P.R. Krishna, A. Manjuvani and E.R. Sekhar, *Arkivoc* **2005**, *(iii)*, 99-109.

[187] P.R. Krishna, A. Manjuvani, V. Kannan and G.V.M. Sharma, *Tetrahedron Lett.* **2004**, *45*, 1183-1185.

[188] S. Chandrasekhar, C. Narsihmulu, B. Saritha and S.S. Sultana *Tetrahedron Lett.* **2004**, *45*, 5865-5867.

[189] G.H.P. Roos and P. Rampersadh, *Synth. Commun.* **1993**, *23*, 1261-1266.

[190] P.M. Rose, A.A. Clifford and C.M. Rayner, *Chem. Commun.* **2002**, 968-969.

[191] Y. Hayashi, K. Okado, I. Ashimine and M. Shoji, *Tetrahedron Lett.* **2002**, *43*, 8683-8686.

[192] M. Kawamura and S. Kobayashi, *Tetrahedron Lett.* **1999**, *40*, 1539-1542.

[193] M. Shi, J.K. Jiang and Y.S. Feng, *Org. Lett.* **2000**, *2*, 2397-2400.

[194] C.L. Johnson, R.E. Donkor, W. Nawaz and N. Karodia, *Tetrahedron Lett.* **2004**, *45*, 7359-7361.

[195] L.R. Reddy and K.R. Rao, *Org. Prep. Proced. Int.* **2000**, *32*, 185-203.
[196] M.L. Bode and P.T. Kaye, *Tetrahedron Lett.* **1991**, *32*, 5611-5614.
[197] Y. Fort, M.C. Berthe and P. Caubere, *Tetrahedron* **1992**, *48*, 6371-6384.
[198] M. Shi, C. Li and J. Jiang, *Tetrahedron* **2003**, *59*, 1181-1189.
[199] L.S. Santos, C.H. Pavam, W.P. Almeida, F. Coelho and M.N. Eberlin, *Angew. Chem. Int. Ed.* **2004**, *43*, 4330-4333.
[200] K.E. Price, S.J. Broadwater, H.M. Jung and D.T. McQuade, *Org. Lett.* **2005**, *7*, 147-150.
[201] K.E. Price, S.J. Broadwater, B.J. Walker and D.T. McQuade, *J. Org. Chem.* **2005**, *70*, 3980-3987.
[202] V.K. Aggarwal, S.Y. Fulford and G.C. Lloyd-Jones, *Angew. Chem. Int. Ed.* **2005**, *44*, 1706-1708.
[203] J. Xu, *J. Mol. Struct.: THEOCHEM* **2006**, *767*, 61-66.
[204] M.E. Krafft, T.F.N. Haxell, K.A. Seibert and K.A. Abboud, *J. Am. Chem. Soc.* **2006**, *128*, 4174-4175.
[205] A. Gilbert, T.W. Heritage and N.S. Isaacs, *Tetrahedron: Asymmetry* **1991**, *2*, 969-972.
[206] F. Coelho, G. Diaz, C.A.M. Abella and W.P. Almeida, *Synlett* **2006**, 435-439.
[207] G. Masson, C. Housseman and J. Zhu, *Angew. Chem. Int. Ed.* **2007**, *46*, 4614-4628.
[208] Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219-10220.
[209] S. Kawahara, A. Nakano, T. Esumi, Y. Iwabuchi and S. Hatakeyama, *Org. Lett.* **2003**, 3103-3105.
[210] I.E. Markó, P.R. Giles and N.J. Hindley, *Tetrahedron* **1997**, *53*, 1015-1024.
[211] C.M. Mocquet and S.L. Warriner, *Synlett* **2004**, 356-358.
[212] K. Matsui, S. Takizawa and S. Hiroaki, *Tetrahedron Lett.* **2005**, *46*, 1943-1946.
[213] N.T. McDougal and S.E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094-12095.
[214] K. Yang, W. Lee, J. Pan and K. Chen, *J. Org. Chem.* **2003**, *68*, 915-919.
[215] D. Basavaiah and J.S. Rao, *Tetrahedron Lett.* **2004**, *45*, 1621-1625.
[216] B. Alcaide, P. Almendros, C. Aragoncillo and R. Rodríguez-Acebes, *J. Org. Chem.* **2004**, *69*, 826-831.
[217] B.M. Trost, O.R. Thiel and H. Tsui, *J. Am. Chem. Soc.* **2002**, *124*, 11616-11617.
[218] C.R. Mateus and F. Coelho, *J. Braz. Chem. Soc.* **2005**, *16*, 386-396.
[219] S. Batra, A.K. Roy, A. Patra, A.P. Bhaduri, W.R. Surin, S.A.V. Raghavan, P. Sharma, K. Kapoor and M. Dikshit, *Bioorg. Med. Chem.* **2004**, *12*, 2059-2077.
[220] S. Batra and A.K. Roy, *Synthesis* **2004**, 2550-2554.
[221] D. Basavaiah, R.J. Reddy and J.S. Rao *Tetrahedron Lett.* **2006**, *47*, 73-77.
[222] V. Singh and S. Batra, *Synthesis* **2006**, 63-72.
[223] P. Narender, U. Srinivas, B. Gangadasu, B. Biswas and V.J. Rao, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5378-5381.
[224] G.P. de Carvalho e Silveira and F. Coelho, *Tetrahedron Lett.* **2005**, *46*, 6477-6481.

[225] V. Singh, R. Pathak, S. Kanojiya and S. Batra, *Synlett* **2005**, 2465-2468.
[226] P. Shanmugam and P. Rajasingh, *Synlett* **2005**, 939-942.
[227] L. Fernandes, A.J. Bortoluzzi and M.M. Sá, *Tetrahedron* **2004**, *60*, 9983-9989.
[228] R.O.M.A. de Souza, B.A. Meireles, L.C.S. Aguiar and M.L.A.A. Vasconcellos, *Synthesis* **2004**, 1595-1600.
[229] J.N. Kim, J.M. Kim and K.Y. Lee, *Synthesis* **2003**, 821-824.
[230] M. Bailey, I.E. Markó, W.D. Ollis and P.R. Rasmussen, *Tetrahedron Lett.* **1990**, *31*, 4509-4512.
[231] R. Buchholz and H.M.R. Hoffmann, *Helv. Chim. Acta* **1991**, *74*, 1213-1220.
[232] V. Nair and K.G. Abhilash, *Synthesis* **2005**, 1967-1970.
[233] R. Räcker, K. Döring and O. Reiser, *J. Org. Chem.* **2000**, *65*, 6932-6939.
[234] P.T. Kaye, M.A. Musa, X.W. Nocanda and R.S. Robinson, *Org. Biomol. Chem.* **2003**, *1*, 1133-1138.
[235] S.E. Drewes, O.L. Njamela, N.D. Emslie, N. Ramesar and J.S. Field, *Synth. Commun.* **1993**, *23*, 2807-2815.
[236] C. Yu, B. Liu and L. Hu, *J. Org. Chem.* **2001**, *66*, 5413-5418.
[237] L.K. Kohn, C.H. Pavam, D. Veronese, F. Coelho, J.E. de Carvalho and W.P. Ameida, *Eur. J. Med. Chem.* **2006**, *41*, 738-744.
[238] Y. Lin, C. Lin, C. Liu and T.Y.R. Tsai, *Tetrahedron* **2006**, *62*, 872-877.
[239] Y. Lin, C. Liu and T.Y.R. Tsai, *Tetrahedron Lett.* **2005**, *46*, 1859-1861.
[240] S.I. Pereira, J. Adrio, A.M.S. Silva and J.C. Carretero, *J. Org. Chem.* **2005**, *70*, 10175-10177.
[241] X. Mi, S. Luo and J. Cheng, *J. Org. Chem.* **2005**, *70*, 2338-2341.
[242] S. Luo, P.G. Wang and J. Cheng, *J. Org. Chem.* **2004**, *69*, 555-558.
[243] J. You, J. Xu and J.G. Verkade, *Angew. Chem. Int. Ed.* **2003**, *42*, 5054-5056.
[244] L.M. Walsh, C.L. Winn and J.M. Goodman, *Tetrahedron Lett.* **2002**, *43*, 8219-8222.
[245] P. Styring, N.T.S. Phan, D.H. Brown, T. Hanasaki, B. O'Sullivan, R.W.K. Allen, A.I. Parracho and P.L. Lau, Rate enhancement in micro flow reactors, *Switching from Batch to Continuous Processing Conference*, **22-23/11/2004**, London, UK.
[246] C. Wiles, P. Watts, S.J. Haswell and E. Pombo-Villar, *Lab Chip* **2001**, *1*, 100-101.
[247] C. Wiles, P. Watts and S.J. Haswell, *Org. Process Res. Dev.* **2004**, *8*, 28-32.
[248] R.O.M.A. de Souza and M.L.A.A. Vasconcellos, *Catal. Commun.* **2004**, *5*, 21-24.
[249] S. Rafel and J.W. Leahy, *J. Org. Chem.* **1997**, *62*, 1521-1522.
[250] R. Octavio, M.A. de Souza and M.L.A.A. Vasconcellos, *Synth. Commun.* **2003**, *33*, 1383-1389.
[251] D. Basavaiah, D.S. Sharada, N. Kumaragurubaran and R.M. Reddy, *J. Org. Chem.* **2002**, *67*, 7135-7137.
[252] G. Li, H. Wei, J.J. Gao and T.D. Caputo, *Tetrahedron Lett.* **2000**, *41*, 1-5.
[253] M. Shi, C. Li and J. Jiang, *Chem. Commun.* **2001**, 833-834.
[254] N.E. Leadbeater and C. van der Pol, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2831-2835.

[255] Y.J. Im, J.H. Gong, H.J. Kim and J.N. Kim, *Bull. Korean Chem. Soc.* **2001**, *22*, 1053-1055.

[256] B. Das, J. Banerjee, A. Majhi and G. Mahender, *Tetrahedron Lett.* **2004**, *45*, 9225-9227.

[257] J.S. Yadav, M.K. Gupta, S.K. Pandey, B.V.S. Reddy and A.V.S. Sarma, *Tetrahedron Lett.* **2005**, *46*, 2761-2763.

[258] I.R. Baxendale, C.M. Griffiths-Jones, S.V. Ley and G.K. Tranmer, *Synlett* **2006**, 427-430.

[259] M. Haro, V. Rodríguez, P. Cea, M.C. López and C. Lafuente, *Int. J. Thermophys.* **2004**, *25*, 669-678.

[260] E.R. Delsman, M.H.J.M. de Croon, G.D. Elzinga, P.D. Cobden, G.J. Kramer and J.C. Schouten, *Chem. Eng. Technol.* **2005**, *28*, 367-375.

[261] M. Brivio, R.E. Oosterbroek, W. Verboom, M.H. Goedbloed, A. van de Berg and D.N. Reinhoudt, *Chem. Commun.* **2003**, 1924-1925.

[262] S. Paníc, S. Loebbecke, T. Tuercke, J. Antes and D. Bošković, *Chem. Eng. J.* **2004**, *101*, 409-419.

[263] Z. Ni, E.G. Seebauer and R.I. Masel, *Ind. Eng. Chem. Res.* **2005**, *44*, 4267-4271.

[264] Y. Shi and M. Shi, *Eur. J. Org. Chem.* **2007**, 2905-2916.

[265] Y. Xu and M. Shi, *J. Org. Chem.* **2004**, *69*, 417-425.

[266] I.T. Raheem and E.N. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701-1708.

[267] D. Balan and H. Adolfsson, *Tetrahedron Lett.* **2003**, *44*, 2521-2524.

[268] D. Balan and H. Adolfsson, *J. Org. Chem.* **2002**, *67*, 2329-2334.

[269] G. Lelais and D. Seebach, *Biopolymers* **2004**, *76*, 206-243.

[270] W.R. McKay and G.R. Proctor, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2435-2442.

[271] P.P. Graczyk, A. Khan, G.S. Bhatia, V. Palmer, D. Medland, H. Numata, H. Oinuma, J. Catchick, A. Dunne, M. Ellis, C. Smales, J. Whitfield, S.J. Neame, B. Shah, D. Wilton, L. Morgan, T. Patel, R. Chung, D. Desmond, J.M. Staddon, N. Sato and A. Inoue, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4666-4670.

[272] S.A. Laufer, W. Zimmermann and K.J. Ruff, *J. Med. Chem.* **2004**, *47*, 6311-6325.

[273] G.M. Sperandio da Silva, C.M.R. Sant'Anna and E.J. Barreiro, *Bioorg. Med. Chem.* **2004**, *12*, 3159-3166.

[274] J.A. Murry, *Curr. Opin. Drug Discov. Dev.* **2003**, *6*, 945-965.

[275] J.C. Lee, J.T. Laydon, P.C. McDonnell, T.F. Gallagher, S. Kumar, D. Green, D. McNulty, M.J. Blumenthal, J.R. Keys, S.W.L. Vatter, J.E. Strickler, M.M. McLaughlin, I.R. Siemens, S.M. Fisher, G.P. Livi, J.R. White, J.L. Adams and P.R. Young, *Nature* **2002**, *372*, 739-742.

[276] K.M. Marcantonio, L.F. Frey, D. Frantz, J. Murry, A. Soheili, R. Tillyer, E.J.J. Grabowski and P. Reider, *Abstracts of papers - 224th ACS National Meeting*, **18-22/08/2002**, Boston, MA, USA.

[277] S. Laufer, G. Wagner and D. Kotschenreuther, *Angew. Chem. Int. Ed.* **2002**, *41*, 2290-2293.

[278] N.J. Liverton, J.W. Butcher, C.F. Clairborne, D.A. Claremon, B.E. Libby, K.T. Nguyen, S.M. Pitzenberger, H.G. Selnick, G.R. Smith, A. Tebben, J.P. Vacca, S.L. Varga, L. Agarwal, K. Dancheck, A.J. Forsyth, D.S. Fletcher, B. Frantz, W.A. Hanlon, C.F. Harper, S.J. Hofsess, M. Kostura, J. Lin, S. Luell, E.A. O'Neill, C.J. Orevillo, M. Pang, J. Parsons, A. Rolando, Y. Sahly, D.M. Visco, and S.J. O'Keefe, *J. Med. Chem.* **1999**, *42*, 2180-2190.

[279] J.W. Black, G.J. Durant, J.C. Emmett and C.R. Ganellin, *Nature* **1974**, *248*, 65-67.

[280] Ü. Uçucu, N.G. Karaburun and İ. Işikdağ, *Il Farmaco* **2001**, *56*, 285-290.

[281] A. Mjalli and S. Sarshar, *U.S. Patent* **1997**, 5700826. *Chem. Abstr.* **1997**, *128*, 88918.

[282] Y. Niwano, H. Koga, H. Kodama, K. Kanai, T. Miyazaki and H. Yamaguchi, *Med. Mycol.* **1999**, *37*, 351-355.

[283] B. Baasner, G. Beck, H. Hagemann, M. Heil, F. Lieb, M. Dollinger, H. Santel, C. Erdelen and U. Wachendorff-Neumann, *German Offen.* **1996**, 4433857. *Chem. Abstr.,* **1996,** *124,* 343308.

[284] N.N., *Japan Kokai Tokkyo Koho* **1985**, 60051194. *Chem. Abstr.* **1985**, *103*, 104967.

[285] M. Antolini, A. Bozzoli, C. Ghiron, G. Kennedy, T. Rossi and A. Ursini, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1023-1028.

[286] A. Liberatore, J. Schulz, J. Pommier, M. Barthelemy, M. Huchet, P. Chabrier and D. Bigg, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3521-3523.

[287] D.W. Cheung and E.E. Daniel, *Nature* **1980**, *283*, 485-486.

[288] D.R. Williams, M. Lee, Y. Song, S. Ko, G. Kim and I. Shin, *J. Am. Chem. Soc.* **2007**, *129*, 9258-9259.

[289] P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, **2003**, Wiley-VCH, Weinheim, Germany.

[290] T. Welton, *Chem. Rev.* **1999**, *99*, 2071-2084.

[291] H.L. Lee, M. Bang and C.S. Pak, *Tetrahedron Lett.* **2005**, *46*, 7139-7142.

[292] J.M.D. Storey and C. Williamson, *Tetrahedron Lett.* **2005**, *46*, 7337-7339.

[293] W.A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 1290-1309.

[294] D. Bourissou, O. Guerret, F.P. Gabbaï and G. Bertrand, *Chem. Rev.* **2000**, *100*, 39-92.

[295] W.A. Herrmann and C. Köcher, *Angew. Chem. Int. Ed.* **1997**, *36*, 2162-2187.

[296] R.M. Acheson, *An Introduction to the Chemistry of Heterocyclic Compounds*, **1967**, John Wiley and Sons, New York, US.

[297] K. Wegner and W. Schunack, *Arch. Pharm.* **1974**, *307*, 492-495.

[298] G.W. Gribble and T.L. Gilchrist, *Progress in Heterocyclic Chemistry - Volume 13*, **2001**, Elsevier, Oxford, England.

[299] G.W. Gribble and T.L. Gilchrist, *Progress in Heterocyclic Chemistry - Volume 14*, **2002**, Elsevier, Oxford, England.

[300] G.W. Gribble and J.A. Joule, *Progress in Heterocyclic Chemistry - Volume 15*, **2003**, Elsevier, Oxford, England.

[301] G.W. Gribble and J.A. Joule, *Progress in Heterocyclic Chemistry - Volume 16*, **2004**, Elsevier, Oxford, England.

[302] G.W. Gribble and J.A. Joule, *Progress in Heterocyclic Chemistry - Volume 17*, **2005**, Elsevier, Oxford, England.

[303] W. Li and Y.J. Lam, *Comb. Chem.* **2005**, *7*, 644-647.

[304] Y.M. Losksha, A.A. El-Barbary, M.A. El-Badawi, C. Nielsen and E.B. Pedersen, *Bioorg. Med. Chem.* **2005**, *13*, 4209-4220.

[305] J.A. Murry, D. Frantz, L. Frey, A. Soheili, K. Marcantonio, R. Tillyer, E.J.J. Grabowski and P.J. Reider, *ACS Sym. Ser.* **2004**, *870*, 161-180. *Chem. Abstr.* **2004**, *141*, 225392.

[306] O.A. Attanasi, L. De Crescentini, G. Favi, P. Filippone, F. Mantellini and S. Santeusanio, *Synlett* **2004**, 549-551.

[307] H. Zhong, S. Dubberke, S. Muller, A. Rossler, T.W. Schulz, D.J. Korey, T. Otten, D.G. Walker and A. Abdel-Magid, *PCT Int. Appl.* **2002**, 076974. *Chem. Abstr.* **2002**, *137*, 263034.

[308] H.B. Lee and S. Balasubramanian, *Org. Lett.* **2000**, *2*, 323-326.

[309] P. Deprez, E. Mandine, A. Vermond and D. Lesuisse, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1287-1289.

[310] S. Balalaie, M.M. Hashemi and M. Akhbari, *Tetrahedron Lett.* **2003**, *44*, 1709-1711.

[311] S. Balalaie and A. Arabanian, *Green Chem.* **2000**, *2*, 274-276.

[312] C. Zhang, E.J. Moran, T.F. Woiwode, K.M. Short and A.M.M. Mjalli, *Tetrahedron Lett.* **1996**, *37*, 751-754.

[313] B. Krieg and G. Manecke, *Z. Naturforsch. (B)* **1967**, *22*, 132-141.

[314] F. Lions and E.J. Ritchie, *Proc. Royal Soc. New South Wales* **1941**, *74*, 365-372.

[315] M. Shih, C. Tsai, Y. Wang, M. Shieh, G. Lin and C. Wei, *Tetrahedron* **2007**, *63*, 2990-2999.

[316] M. Kidwai and P. Mothsra, *Tetrahedron Lett.* **2006**, *47*, 5029-5031.

[317] A. Puratchikody and M. Doble, *Bioorg. Med. Chem.* **2007**, *15*, 1083-1090.

[318] R.B. Sparks and A.P. Combs, *Org. Lett.* **2004**, *6*, 2473-2475.

[319] J. Liu, J. Chen, J. Zhao, Y. Zhao, L. Li and H. Zhang, *Synthesis* **2003**, 2661-2666.

[320] C. van Wolven, D. Dietrich and G. Henkel, *Z. Naturforsch. (B)* **2006**, *61*, 301-310.

[321] M. Okimoto, Y. Nagata, S. Sueda and Y. Takahashi, *Synth. Commun.* **2003**, *33*, 3771-3776.

[322] C.M. Comisar and P.E. Savage, *Green Chem.* **2005**, *7*, 800-806.

[323] C.M. Comisar and P.E. Savage, *Ind. Eng. Chem. Res.* **2007**, *46*, 1690-1695.

[324] E. Gelens, L. Smeets, L.A.J.M. Sliedregt, B.J. van Steen, C.G. Kruse, R. Leurs and R.V.A. Orru, *Tetrahedron Lett.* **2005**, *46*, 3751-3754.

[325] M.C. Bagley, R.L. Jenkins, M.C. Lubinu, C. Mason and R. Wood, *J. Org. Chem.* **2005**, *70*, 7003-7006.
[326] R.A. Cherkasov and V.I. Galkin, *Russ. Chem. Rev.* **1998**, *67*, 857-882.
[327] R. Gancarz, *Tetrahedron* **1995**, *51*, 10627-10632.
[328] W.M. Henderson and W.H. Shelver, *J. Pharm. Sci.* **1969**, *58*, 106-109.
[329] L.V. Hopkins, J.P. Vacik and W.H. Shelver, *J. Pharm. Sci.* **1972**, *61*, 114-116.
[330] A. Oussaid, F. Benyaqad, B. Oussaid, C. Pradel and B. Garrigues, *Phosphorus Sulfur Silicon Relat. Elem.* **2003**, *178*, 1183-1197.
[331] R. Gancarz and I. Gancarz, *Tetrahedron Lett.* **1993**, *34*, 145-148.
[332] S. Bhagat and A.K. Chakraborti, *J. Org. Chem.* **2007**, *72*, 1263-1270.
[333] K. Afarinkia, C.W. Rees and J.I.G. Cadogan, *Tetrahedron* **1990**, *46*, 7175-7196.
[334] E.D. Matveeva, T.A. Podrugina, E.V. Tishkovskaya, L.G. Tomilova and N.S. Zefirov, *Synlett* **2003**, 2321-2324.
[335] C. Qian and T. Huang, *J. Org. Chem.* **1998**, *63*, 4125-4128.
[336] A. Heydari, A. Karimian and J. Ipaktschi, *Tetrahedron Lett.* **1998**, *39*, 6729-6732.
[337] K. Manabe and S. Kobayashi, *Chem. Commun.* **2000**, 669-670.
[338] D. Lee, J. Lee, C. Song and D. Kim, *Bull. Korean Chem. Soc.* **2002**, *23*, 667-668.
[339] B.C. Ranu, A. Hajra and U. Jana, *Org. Lett.* **1999**, *1*, 1141-1143.
[340] E.K. Fields, *J. Am. Chem. Soc.* **1952**, *74*, 1528-1531.
[341] R. Tyka, *Tetrahedron Lett.* **1970**, *11*, 677-680.
[342] H. Cristau, A. Coulombeau, A. Genevois-Borella and J. Pirat, *Tetrahedron Lett.* **2001**, *42*, 4491-4494.
[343] J. Lewkowski, M. Rzezniczak and R. Skowronski, *Org. Prep. Proced. Int.* **2000**, *32*, 453-459.
[344] A.A. Sobanov, A.V. Zolotukhin, V.I. Galkin, R.A. Cherkasov and A.N. Pudovik, *Russ. J. Gen. Chem.* **2002**, *72*, 1067-1070.
[345] M. Sindt, B. Stephan, M. Schneider, and J.L. Mieloszynski, *Phosphorus Sulfur Silicon Relat. Elem.* **2001**, *174*, 163-175.
[346] J. Xu and N. Fu, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1223-1226.
[347] B.J. Rowe and C.D. Spilling, *Tetrahedron: Asymmetry* **2001**, *12*, 1701-1708.
[348] N. Azizi and M.R. Saidi, *Phosphorus Sulfur Silicon Relat. Elem.* **2003**, *178*, 1255-1259.
[349] V. Hessel, W. Ehrfeld, K. Golbig, C. Hofmann, S. Jungwirth, H. Löwe, T. Richter, M. Storz, A. Wolf, O. Wörz and J. Breysse, **in** W. Ehrfeld (ed.), *Microreaction Technology: Industrial Prospects, Proceedings of IMRET 3*, **1999**, Springer-Verlag, Berlin, Germany, 151-164.
[350] L.J. McCausland and P.W. Cains, *Drug Delivery Systems and Sciences* **2002**, *2(2)*, 47-51.
[351] J.R. Burns and C. Ramshaw, *Lab Chip* **2001**, *1*, 10-15.
[352] D.L. Chen, Using plugs in microfuidics as micro reactors for chemical assays and studying the effect of mixing on nucleation of protein crystals, *Young Chemist Workshop - Micro Reactor Technology*, **16-18/03/2006**, Enschede, The Netherlands, 11-12.
[353] F. Feigl and V. Anger, *Analyst* **1966**, *91*, 282-284.
[354] K.F. Castric and P.A. Castric, *Appl. Environ. Microbiol.* **1983**, *45*, 701-702.
[355] Y. Yang and J. Tae, *Org. Lett.* **2006**, *8*, 5721-5723.

[356] B. Markley, C.E. Meloan, J.L. Lambert and Y.C. Chiang, *Anal. Lett.* **1987**, *20*, 1225-1236.

[357] J. Andexer, J. Guterl, M. Pohl and T. Eggert, *Chem. Commun.* **2006**, 4201-4203.

[358] EPA Report #: SW-846 Ch 5 Method 9014: *Titrimetric and manual spectrophotometric determinative methods for cyanide*, **01/12/1996**, website: "http://www.epa.gov/".

[359] EPA Report #: SW-846 Ch 5 Update IIIB Method 9010C: *Total and amenable cyanide: distillation*, **30/10/2002**, website: "http://www.epa.gov/".

[360] T. Opatz and D. Ferenc, *Eur. J. Org. Chem.* **2006**, 121-126.

[361] G. Ma and A. Jha, *Org. Process Res. Dev.* **2005**, *9*, 847-852.

[362] H. Hemmerling, A. Merschenz-Quack and H. Wunderlich, *Z. Naturforsch. (B)* **2004**, *59*, 1143-1152.

[363] M. Finizio, *Eur. Pat. Appl.* **1982**, EP 61712. *Chem. Abstr.* **1982**, *98*, 72098.

[364] N. Chatterjie, B. Sinha and G.J. Alexander, *Res. Commun. Chem. Pathol. Pharmacol.* **1983**, *39*, 333-336. *Chem. Abstr.* **1983**, *98*, 179288.

[365] M. Eggenweiler, J. Rochus, M. Wolf, M. Gassen and O. Poeschke, *PCT Int. Apl.* **2001**, 029049. *Chem. Abstr.* **2001**, *134*, 331619.

[366] V.L. Savel'ev, N.T. Pryanishnikova, V.A. Zagorevskii, I.V. Chernyakova, O.S. Artamonova, V.V. Shavyrina and L.I. Malysheva, *Khimiko-Farmatsevticheskii Zhurnal* **1983**, *17*, 697-700. *Chem. Abstr.* **1983**, *99*, 158325.

[367] F.M. Rivas, A.J. Giessert and S.T. Diver, *J. Org. Chem.* **2002**, *67*, 1708-1711.

[368] Y. Chi and C. Sun, *Synlett* **2000**, 591-594.

[369] M. Fujita, H. Egawa, T. Miyamoto, J. Nakano and J. Matsumoto, *Chem. Pharm. Bull.* **1996**, *44*, 987-990.

[370] A.B. Alloum, K. Bougrin and M. Soufiaoui, *Tetrahedron Lett.* **2003**, *44*, 5935-5937.

[371] C.D. Wilfred and R.J.K. Taylor, *Synlett* **2004**, 1628-1630.

[372] R. Varala, A. Nasreen, R. Enugala and S.R. Adapa, *Tetrahedron Lett.* **2007**, *48*, 69-72.

[373] N.V. Ivanova, S.I. Sviridov and A.E. Stepanov, *Tetrahedron Lett.* **2006**, *47*, 8025-8027.

[374] R. Chesworth, M.D. Wessel, L. Heyden, F.M. Mangano, M. Zawistoski, L. Gegnas, D. Galluzzo, B. Lefker, K.O. Cameron, J. Tickner, B. Lu, T.A. Castleberry, D.N. Petersen, A. Brault, P. Perry, O. Ng, T.A. Owen, L. Pan, H. Ke, T.A. Brown, D.D. Thompson and P. DaSilva-Jardine, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5562-5566.

[375] B. Das, H. Holla and Y. Srinivas, *Tetrahedron Lett.* **2007**, *48*, 61-64.

[376] K. Bahrami, M.M. Khodaei and I. Kavianinia, *Synthesis* **2007**, 547-550.

[377] S.V. Ryabukhin, A.S. Plaskon, D.M. Volochnyuk and A.A. Tolmachev, *Synthesis* **2006**, 3715-3726.

[378] E. Farrant and S.S. Rahman, *Tetrahedron Lett.* **2000**, *41*, 5383-5386.

[379] M.A. Ismail, A. Batista-Parra, Y. Miao, W.D. Wilson, T. Wenzler, R. Brun and D.W. Boykin, *Bioorg. Med. Chem.* **2005**, *13*, 6718-6726.

[380] K. Starčević, M. Kralj, K. Ester, I. Sabol, M. Grce, K. Pavelić and G. Karminski-Zamola, *Bioorg. Med. Chem.* **2007**, *15*, 4419-4426.
[381] P.L. Beaulieu, B. Haché and E. von Moos, *Synthesis* **2003**, 1683-1692.
[382] T. Kataoka, T. Iwama, S. Tsujiyama, T. Iwamura and S. Watanabe, *Tetrahedron* **1998**, *54*, 11813-11824.
[383] A. Foucaud and E. le Rouillé, *Synthesis* **1990**, 787-789.
[384] J.H. Wynne, S.E. Price, J.R. Rorer and W.M. Stalick, *Synth. Commun.* **2003**, *33*, 341-352.
[385] S.L. Jain, V.B. Sharma and B. Sain, *J. Mol. Catal. A-Chem.* **2005**, *239*, 92-95.
[386] D. Balan and H. Adolfsson, *J. Org. Chem.* **2001**, *66*, 6498-6501.
[387] R.B. Othman, T. Bousquet, A. Fousse, M. Othman and V. Dalla, *Org. Lett.* **2005**, *7*, 2825-2828.

Curriculum Vitae

Personalia

Acke Davy
Vrouwestraat 25
9900 Eeklo

° 12/06/1980, Eeklo

Mobile: 0497/54.30.95
Email: acke_davy@yahoo.com

Education

October 1998-June 2003:

Bio-engineer (graduated with great distinction)
Ghent University
Thesis: « Optimisation of an ELISA for peanut protein detection in foodstuffs »
Promoters: Prof. dr. ir. A. Huyghebaert *and* dr. ir. B. De Meulenaer

February 2003:

Socrates Intensive Programme: « Agriculture: source of raw material for industry »
BOKU University Vienna, Austria

September 1992-June 1998:

Latin-mathematics and Sciences-mathematics
Sint-Vincentiuscollege, Eeklo

Career

October 2007-…:

Technical Management Trainee (TMT)
Cargill NV, Izegem (Belgium)

October 2003-September 2007:

PhD student (BOF scholarship)

Research Group SynBioC, Department Organic Chemistry, Faculty Bioscience Engineering, Ghent University
Title: « Evaluation of microreactor technology for multicomponent reactions »
Promoter: Prof. dr. ir. C.V. Stevens

Scientific career

Peer-reviewed publications in international SCI-journals (A1):

Davy R.J. Acke & Christian V. Stevens, **Microreactor technology: Continuous synthesis of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones**, European Journal of Organic Chemistry (2007), submitted.

Davy R.J. Acke & Christian V. Stevens, **A HCN-based reaction under microreactor conditions: continuous production of 3,4-diamino-1*H*-isochromen-1-ones**, Green Chemistry (2007), 9, 386-390.

Davy R.J. Acke & Christian V. Stevens, **Study of the Baylis-Hillman reaction in a microreactor environment: first continuous production of Baylis-Hillman adducts**, Organic Process Research & Development (2006), 10, 417-422.

Davy R.J. Acke, Romano V.A. Orru & Christian V. Stevens, **Continuous synthesis of tri- and tetrasubstituted imidazoles *via* a multicomponent reaction under microreactor conditions**, QSAR & Combinatorial Science (2006), 25, 474-483.

Ellen Van Meenen, Kristof Moonen, Davy Acke & Christian V. Stevens, **Straightforward continuous synthesis of α-aminophosphonates under microreactor conditions**, Arkivoc (2006), (i), 31-45.

Bruno De Meulenaer, Marjan De La Court, Davy Acke, Tineke De Meyere & Annic Van De Keere, **Development of an enzyme-linked immunosorbent assay for peanut proteins using chicken immunoglobulins**, Food and Agricultural Immunology (2005), 16, 129-148.

Other publication:

Davy Acke & Christian V. Stevens, **Van klein- naar grootschalig dankzij microreactoren**, Ingenieursblad (2005), 10, 50-55.

Oral presentation:

Lecture: Davy R.J. Acke, **Multicomponent reactions in microreactor technology**. Young Chemist Workshop on Microreactor Technology, Enschede (The Netherlands), March 16-18, 2006.

Posters and proceedings:

Poster: Davy R.J. Acke & Christian Stevens, **A HCN-based multicomponent reaction under microreactor conditions**. 10th Sigma-Aldrich Organic Synthesis Meeting, Spa (Belgium), December 7-8, 2006.

Poster: Davy R.J. Acke, Romano V.A. Orru & Christian V. Stevens, **Multicomponent reactions in microreactor technology: imidazole synthesis *via* a four-component reaction**. Mid Term Evaluation Meeting COST D32, Hamburg (Germany), June 7-9, 2006.

Poster: Davy R.J. Acke, Kristof Moonen, Ellen Van Meenen & Christian V. Stevens, **Straightforward continuous synthesis of α-aminophosphonates under microreactor conditions**. 8th Sigma-Aldrich Organic Synthesis Meeting, Spa (Belgium), December 2-3, 2004.

Proceeding: Davy R.J. Acke & Christian V. Stevens, **Avoiding the need to scale up. Continuous Baylis-Hillman reactions using microreactor technology**. Switching from Batch to Continuous Processing, London (United Kingdom), November 22-23, 2004.

Poster: Davy R.J. Acke & Christian V. Stevens, **Baylis-Hillman reaction under microreactor conditions**. 10th Belgian Organic Synthesis Symposium (BOSS 10), Louvain-la-Neuve (Belgium), July 12-16, 2004 *and* Start-up meeting COST D32 project, Alicante (Spain), July 8-9, 2004.

Conferences:

Third International Conference on Renewable Resources & Biorefineries (RRB3), Ghent (Belgium), June 4-6, 2007.

10th Sigma-Aldrich Organic Synthesis Meeting, Spa (Belgium), December 7-8, 2006.

Mid Term Evaluation Meeting COST D32, Hamburg (Germany), June 7-9, 2006.

Young Chemist Workshop on Microreactor Technology, Enschede (The Netherlands), March 16-18, 2006.

8th Sigma-Aldrich Organic Synthesis Meeting, Spa (Belgium), December 2-3, 2004.

Prof. Jack E. Baldwin (Oxford University, England):, 2nd Lilly European Distinguished Lectureship, Namur (Belgium), 17 November 2004.

Seminar: « Detection of antimutagenic and anticarcinogenic properties of Southern African plant species and their isolated components », Ghent (Belgium), October 22, 2004.

10th Belgian Organic Synthesis Symposium (BOSS 10), Louvain-la-Neuve (Belgium), July 12-16, 2004.

Start-up meeting COST D32 project, Alicante (Spain), July 8-9, 2004.

7th Sigma-Aldrich Organic Synthesis Meeting, Spa (Belgium), December 4-5, 2003.

Workshop Bilateral Scientific and Technological Co-operation Poland-Flanders: « Synthesis of phosphonylated amino acids and their oligopeptides for the design of new medicines and agrochemicals », Antwerp (Belgium), September 24, 2003.