**Efficient and catalyst-free condensation of acyl chlorides and alcohols using continuous flow**

**Abstract**

An efficient and catalyst-free procedure for the condensation of acyl chlorides and alcohols using continuous flow was developed. Different esters could be obtained with excellent conversions starting from the corresponding acyl chlorides and alcohols in very short reaction times (5-6.7 min). The reaction was performed solventless for liquid reagents but requires a solvent for solid reagents in order to prevent clogging of the microreactor.

**Key-words**: Esterification, continuous flow, acid chloride, catalyst-free

**Introduction**

The reaction between an acyl chloride and an alcohol is a well-known reaction and is used a lot in organic chemistry as protection strategy for hydroxyl groups.1 Typically, this reaction is performed in the presence of a catalyst. Among the base catalysts used for the esterification of acyl chlorides are pyridine, Et3N and 4-dimethylaminopyridine (DMAP).1,2a Other bases, such as 1,4‑diazabicyclo[2.2.2]octane (DABCO)2a,2b, *N*,*N*,*N’*,*N’*-tetramethylethylenediamine (TMEDA)2c or NaOH2d, can also be used. Next to these bases, other catalysts are reported in literature: BiCl33a, ZnO3b,3c,3d, Al2O33e,3f,3g, ZrOCl2.8H2O3h, TiO23i, BiFeO33j,CeCl33k, LiClO43l and Tl3m. However, in the light of “green chemistry”, there is a continuous search for more sustainable processes. For the esterification of acyl chlorides, this means the search for processes which can be performed solventless and/or without the use of a catalyst or base. Most of the catalysts mentioned above can be used solventless but Ranu *et al*. reported a solvent-free and catalyst-free procedure for the condensation of acyl chlorides and alcohols.4 Different alcohols were reacted with acetyl or propanoyl chloride with an isolated yield between 88% and 93%. However, the scale of their reactions was limited to 5 mmol and the number of acid chlorides investigated was limited. This prompted us to evaluate the catalyst-free condensation of acyl chlorides and alcohols using continuous flow in order to obtain an industrial relevant, practical, efficient and green procedure (Scheme 1).



**Scheme 1:** Condensation of acid chlorides and alcohols using continuous flow

Performing the condensation of acyl chlorides and alcohols catalyst-free also results in an economical advantage because the costs for the catalyst are eliminated. This means a huge economic profit for industry. Besides, the use of microreactor technology is inherently safer than batch technology because of the small internal volume associated with the microreactor chip. Although there are a few examples of esterification reactions using microreactor technology, to the best of our knowledge, this is the first procedure reported starting from acid chlorides. Known esterification reactions in literature using continuous flow include Fischer-type esterifications5a,5b,5c, the use of lipases5d,5e,5fand other types of esterifications5g,5h,5i.

**Results and discussion**

To evaluate the condensation of acid chlorides and alcohols under continuous flow, the reaction between benzoyl chloride **1** and methanol was chosen as generic reaction (Scheme 1). All reactions were performed solventless unless the starting material was solid in a microreactor with an internal volume of 10 µl.



In a first series of experiments, the optimal conditions for a microreactor procedure were developed. The reaction temperature, the residence time and the stoichiometric ratio of both reagents were varied and the results were evaluated using IR (νC=O benzoyl chloride= 1770 cm-1; νC=O methyl benzoate = 1720 cm-1). From these experiments, it was clear that the reaction temperature has to be above the atmospheric boiling point of methanol (Tb = 65°C). Good conversions were obtained with a reaction temperature of 80°C whereas the conversion was limited at 50°C. In order to prevent the formation of gas bubbles in the microreactor chip when the reaction mixture is heated above the atmospheric boiling point of the alcohol, a back pressure regulator (BPR) of 10 bar was used. The most important experiments were repeated in order to determine the conversion by GC (Table 1).

**Table 1:** Condensation of benzoyl chloride and MeOH, EtOH or iPrOH: GC-conversion (%)

|  |  |  |
| --- | --- | --- |
|  |  | **Alcohol (eq.)** |
| **T****(°C)** | **RTa****(sec)** | **1** | **1.1** | **1.2** | **1.3** | **1.5** | **2** |
| **MeOH** |
| 80 | 100 | - | - | - | - | - | 97 |
| 80 | 200 | - | - | 96 | - | 98 | 97 |
| 80 | 300 | 95 | - | 99 | 100 | - | - |
| 90 | 300 | 95 | - | - | - | - | - |
| 100 | 300 | - | 99 | - | - | - | - |
| **EtOH** |
| 80 | 300 | - | - | - | 88 | 93 | 98 |
| 100 | 300 | - | - | - | 99 | - | - |
| 110 | 300 | - | 95 | - | 100 | - | - |
| 130 | 300 | - | 99 | - | - | - | - |
| 130 | 400 | - | 99 | - | - | - | - |
| 140 | 300 | - | 99 | - | - | - | - |
| 140 | 400 | - | 99 | - | - | - | - |
| **iPrOH** |
| 80 | 300 | - | - | - | - | - | 61 |
| 100 | 300 | - | - | - | 92 | 95 | - |
| 110 | 300 | - | - | - | 99 | 100 | - |
| 120 | 300 | - | - | - | 100 | - | - |

Full conversion of benzoyl chloride and methanol into methyl benzoate is possible using a residence time of 300 sec, a reaction temperature of 80°C and as little as 1.3 equivalents of MeOH. At lower residence times, traces of benzoyl chloride were detected in the reaction mixture, even if the stoichiometric ratio MeOH/BnCl is increased. In order to obtain full conversion with a stoichiometric ratio beneath 1.3, the reaction temperature was increased but without success. However, 99% conversion was obtained with a reaction temperature of 100°C and 1.1 equivalents MeOH.

In a next series of experiments, the optimised conditions for the condensation of benzoyl chloride and methanol, were used for the condensation of benzoyl chloride and ethanol. However at a temperature of 80°C, the stoichiometric ratio EtOH/BnCl has to be above 1.3 in order to obtain good conversions. Probably, this is due to the fact that a reaction temperature of 80°C is close to the atmospheric boiling point of EtOH (Tb = 78°C). Increasing the reaction temperature (110°C) makes it possible to obtain full conversion with 1.3 equivalents of EtOH. Excellent conversions (99%) were obtained for a stoichiometric ratio EtOH/BnCl of 1.1 when the reaction temperature was raised (130°C or 140°C) in combination with a residence time of 300 sec or 400 sec.

When benzoyl chloride was reacted with iPrOH instead of EtOH, the conversion was bad at a reaction temperature of 80°C, even with 2 equivalents iPrOH. Raising the reaction temperature makes it possible to obtain good conversions. For the condensation of benzoyl chloride and iPrOH, the optimised conditions are a reaction temperature of 120°C, a residence time of 300 sec and 1.3 equivalents of iPrOH.

With the optimised conditions for the different alcohols, other acid chlorides were converted into their corresponding esters (Table 2).

**Table 2**: Condensation of acid chlorides and alcohols under catalyst-free continuous flow conditions

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Entry** | **Acid chloride****(M)a** | **Alcohol****(M)a** | **RT****(sec)** | **T****(°C)** | **Alcohol****(eq.)** | **Conversion****(%)** |
| **1** | C6H5COCl | MeOH | 300 | 80 | 1.3 | 100b |
| **2** | C6H5COCl | EtOH | 300 | 110 | 1.3 | 100 |
| **3** | C6H5COCl | iPrOH | 300 | 120 | 1.3 | 100 |
| **4** | CH3(CH2)2COCl | MeOH | 300 | 80 | 1.3 | 100 |
| **5** | CH3(CH2)2COCl | EtOH | 300 | 110 | 1.3 | 100 |
| **6** | CH3(CH2)2COCl | iPrOH | 300 | 120 | 1.3 | 100 |
| **7** | CH3OCH2COCl | MeOH | 300 | 80 | 1.3 | 91 |
| **8** | CH3OCH2COCl | EtOH | 300 | 110 | 1.3 | 97 |
| **9** | CH3OCH2COCl | iPrOH | 300 | 120 | 1.3 | 100 |
| **10** | C6H5COCl | *p*-cresol(2 M) | 400 | 140 | 2 | 98 |
| **11** | CH3(CH2)2COCl | *p*-cresol(2 M) | 400 | 140 | 2 | 99 |
| **12** | 4-BrC6H4COCl(1.5 M) | *p*-cresol(1.5M) | 400 | 140 | 2 | 79 |
| a When the starting material was solid, the compound was dissolved in CH3CN.b Isolated yield after running the microreactor for 5.6h: 90%. |

All previous results were obtained in solvent-free and catalyst-free conditions. To extent the scope of the reaction, the continuous flow procedure was evaluated for solid acid chlorides and alcohols in solution.

In a first attempt, a solid acid chloride (4-BrC6H4COCl) in solution was reacted with neat MeOH. The acid chloride was dissolved in different solvents (dioxane, CH2Cl2 and CH3CN) and different concentrations were evaluated. These experiments were conducted with a reaction temperature of 80°C and a residence time of 300 sec. In the first trials, high concentrations of 4-bromobenzoyl chloride were used in order to get a good ratio between the flows of both reagents. However using CH2Cl2 (5 M) or dioxane (4 M) resulted in clogging of the microreactor channels. Lowering the concentration to 3.25 M in dioxane or CH3CN resulted in less than 5% conversion even if up to 3 equivalents of MeOH were used. Subsequently, the concentration of the CH3CN-solution was lowered up to 0.5 M in order to overcome possible mixing problems due to the viscosity of the 4-bromobenzoyl chloride solution. However, the conversion of the acid chloride was limited up to 10%.

Subsequently, a solid alcohol (*p*-cresol) in solution was reacted with neat benzoyl chloride (Table 2, entry 10). The alcohol was dissolved in dioxane or CH3CN with a concentration of 2 M. Initial experiments were conducted with a reaction temperature of 80°C, a residence time of 300 sec and 1.3 equivalents of *p*-cresol in CH3CN. However, using these conditions resulted in a limited conversion of 25% (GC). When the temperature was raised (120°C), the conversion increased (78% (GC)). A further increase of the reaction temperature (140°C) in combination with a residence time of 400 sec and 2 equivalents of *p*-cresol led to a conversion of 98% (GC). When the reactions were performed in dioxane, lower conversions were obtained. These optimised conditions were also applied on the condensation of butyryl chloride and *p*-cresol (Table 2, entry 11).

At last, the condensation between an acid chloride (4-BrC6H4COCl) and an alcohol (*p*-cresol) was evaluated when both reagents were dissolved in CH3CN. The reactions were performed at a temperature of 140°C and a residence time of 400 sec. Initial experiments revealed that 2 equivalents of *p*-cresol are needed in order to obtain reasonable conversions. Varying the concentration of both solutions finally led to the optimal conditions in which both reagents were dissolved in CH3CN with a concentration of 1.5 M. A conversion of 79% could be obtained (Table 2, entry 12).

In order to be able to perform this reaction on an industrial scale, the developed procedure was scaled‑up. The optimised conditions for the condensation of benzoyl chloride and MeOH were transferred to a microreactor with an internal volume of 13.4 ml. Using this system led to a capacity of 2.2 g/min methyl benzoate with an isolated yield of 98%.

**Conclusion**

The developed catalyst-free continuous flow procedure provides a green alternative for the existing methods of esterification of acid chlorides. Both aliphatic and phenolic hydroxyl groups reacted with different acid chlorides with formation of the corresponding esters in excellent conversions and very short reaction times (5 - 6.7 min). The reaction was performed solventless for liquid reagents but requires a solvent for solid reagents in order to prevent clogging of the microreactor channels. Upscaling the reaction resulted in a productivity of 2.2 g/min of ester with a yield of 98% which makes this reaction industrially relevant.

**Experimental**

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**References**

1 Greene, W.T.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, Wiley, New York, 4th ed.,
**2007**

2 (a) K. Ishihara, H. Kurihara, H. Yamamoto, *J. Org. Chem.,* 1993, **58**, 3791; (b) A.R. Hajipour, G. Mazloumi, *Synthetic Commun.,* 2002, **32**, 23; (c) T. Sano, K. Ohashi, T. Oriyama, *Synthesis,* 1999, **7**, 1141; (d) O.I. Volker, *Tetrahedron Lett.,* 1979, **26**, 2431

3 (a) R. Ghosh, S. Maiti, A. Chakraborty, *Tetrahedron Lett.,* 2004, **45**, 6775; (b) F. Tamaddon, M.A. Amrollahi, L. Sharafat, *Tetrahedron Lett.,* 2005, **46**, 7841; (c) M.H. Sarvari, H. Sharghi, *Tetrahedron,* 2005, **61**, 10903; (d) R. Tayebee, F. Cheravi, M. Mirzaee, M.M. Amini, *Chin. J. Chem.,* 2010, **28**, 1247; (e) V.K. Yadav, K.G. Babu, M. Mittal, *Tetrahedron,* 2001, **57**, 7047; (f) S. Paul, P. Nanda, R. Gupta, *Molecules,* 2003, **8**, 374; (g) V.K. Yadav, K.G. Babu, *J. Org. Chem.,* 2004, **69**, 577; (h) R. Ghosh, S. Maiti, A. Chakraborty, *Tetrahedron Lett.,* 2005, **46**, 147; (i) M.A. Pasha, K. Manjula, *Indian J. Chem.,* 2008, **47b**, 597; (j) S. Farhadi, M. Zaidi, *J. Mol. Catal. A-Chem.,* 2009, **299**, 18; (k) E. Torregiani, G. Seu, A. Minassi, G. Appendino, *Tetrahedron Lett.,* 2005, **46**, 2193; (l) B.P. Bandgar, V.T. Kamble, V.S. Sadavarte, L.S. Uppalla, *Synlett,* 2002, **5**, 735; (m) E.C. Taylor, G.W. McLay, A. McKillop, *J. Am. Chem. Soc.,* 1968, **90**, 2422

4 B.C. Ranu, S.S. Dey, A. Hajra, *Green Chemistry,*2003, **5**, 44.

5 (a) A.A. Kulkarni, K.P. Zeyer, T. Jacobs, A. Kienle, *Ind. Eng. Chem. Res.,*2007, **46**, 5271; (b) X.J. Yao, J.F. Yao, L.X. Zhang, N.P. Xu, *Catal. Lett.,* 2009, **132**, 147; (c) R. Becker, K. Koch, P.J. Nieuwland, F.P.J.T. Rutjes, *Chim. Oggi,*2011, **29**, 47; (d) J.W. Swarts, P. Vossenberg, M.H. Meerman, A.E.M. Janssen, R.M. Boom, *Biotechnol. Bioeng.,* 2008, **99**, 855; (e) A. Pohar, I. Plazl, P. Znidarsic-Plazl, *Lab Chip,*2009, **9**, 3385; (f) P. Znidarsic-Plazl, I. Plazl, *Process Biochem.,*2009, **44**, 1115; (g) F. Benito-Lopez, R.M. Tiggelaar, K. Salbut, J. Huskens, R.J.M. Egberink, D.N. Reinhoudt, H.J.G.E. Gardeniers, W. Verboom, *Lab Chip,*2007, **7**, 1345; (h) O. Naef, M. Roch, T. Chappuis, *Chimia,*2010, **64**, 889; (i) J. Jovanovic, W. Hengeveld, E.V. Rebrov, T.A. Nijhuis, V. Hessel, J.C. Schouten, *Chem. Eng. Technol.,*2011, **34**, 1691.