**Application of 3-bromo-3-ethylazetidines and 3-ethylideneazetidines for the synthesis offunctionalized azetidines**

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**Abstract**.The synthetic utility of 3-bromo-3-ethylazetidines was shown by the straightforward preparation of 3-alkoxy-, 3-aryloxy-, 3-acetoxy, 3-hydroxy-, 3-cyano-, 3-butyl-, 3-carbamoyl- and 3-amino-3-ethylazetidines. In addition, 3-bromo-3-ethylazetidines were successfully deployed as precursors for a convenient synthesis of 3-ethylideneazetidines, which served as starting materials for the preparation of novel functionalized azetidines and spirocyclicazetidine building blocks.

Aziridines and azetidines belong to an intriguing group of small-ring azaheterocycles with interesting properties and a great potential from both a synthetic[[2]](#endnote-2) and a biological[[3]](#endnote-3) point of view.Azetidines, which have been studied to a lesser extent than aziridines, are accessible via established synthetic routes including ring closure of γ-halo amines and reduction of β-lactams,1j,k,[[4]](#endnote-4)although also other general approaches such as addition of nucleophiles across β-haloimines followed by ring closure[[5]](#endnote-5)and Mannich-type reactions of functionalized imines[[6]](#endnote-6) have been designed.3-Alkylideneazetidines are strained cyclic allylamines, and very limited information on the reactivity of this peculiarclass of azetidinecompounds is available in the literature.[[7]](#endnote-7) In most cases, the 3-alkylideneazetidine moiety has been incorporated in the structure of more complex molecules,[[8]](#endnote-8) and no special attention has been devoted to the chemical nature and synthetic applicability of these systems so far. The two main literature approaches to introduce an alkylidene functionality atthe 3-position of an azetidine ring comprise Wittig olefination of the corresponding azetidin-3-ones6b,6d,6eand dehydrohalogenation of 3-halo-3-(haloalkyl)azetidines.6d

In continuation of our interest in the study of 3-haloazetidines as synthons in organic chemistry,[[9]](#endnote-9) 3-bromo-3-ethylazetidines were prepared in this work and evaluated as suitable substrates to enable nucleophilic bromide displacement toward functionalized 3-ethylazetidines and dehydrobromination as an entry toward novel 3-ethylideneazetidines. Furthermore, the behavior of this 3-ethylideneazetidine scaffold was then assessed with respect to different reagents in order to reveal new synthetic pathways toward functionalized azetidines.It should be mentioned that the synthesis and reactivity study of structurally related 2-alkylideneazetidines, which behave as cyclic enamines, has been the subject of previous reports.[[10]](#endnote-10),[[11]](#endnote-11) These azetidineshave been shown to be eligible substrates in various cycloaddition reactions and ring rearrangements.

However, it is expected that 3-alkylideneazetidines, which can be regarded as cyclic allylamines, will exhibit a totally different reactivity profile as compared to 2-alkylideneazetidines due to the presence of a rather inactive and stericallyhindered double bond. The reactivity of both the azetidine ring and the olefenic moiety will be assessed in this study.

In accordance with the previously described synthesis of 3-bromo-3-methylazetidines, 3-bromo-3-ethylazetidines **3a,b**were prepared starting from 2-bromomethyl-2-ethylaziridines **2a,b**, obtained through a three-step approach[[12]](#endnote-12) involving bromination of 2-ethylpropenal **1**usingBr2 in CH2Cl2, imination with primary*N*-(arylmethyl)amines in the presence of TiCl4and Et3N in Et2O, and reduction of the corresponding α,β-dibromoimines by means of NaBH4 in MeOH(Scheme 1).Heating of aziridines**2** in MeCN under reflux for 15 hours afforded the contemplated new 3-bromo-3-ethylazetidines **3a,b** in nearly quantitative yields. A similaraziridine to azetidine ring rearrangement of 2-bromomethyl-2-methylaziridines has previously been shown to occur via intermediacy of bicyclic aziridinium species, which were opened at the more hindered carbon atom to provide the corresponding 3-bromo-3-methylazetidines.11

In contrast to the synthesis of 1-arylmethyl-3-bromo-3-ethylazetidines **3**, obtained through rearrangement of 2-bromomethyl-2-ethylaziridines **2**, the formation of 3-bromo-1-*tert*-butyl-3-ethylazetidine **5** proceeded via β,γ-dibromoamine**4**, formed through consecutive treatment of 2-ethylpropenal **1** with bromine, *tert*-butylamine and sodium borohydride (Scheme 2). Heating a solution of the latter β,γ-dibromoamine**4** in iPrOH under reflux for 16 h induced cyclization to the premised 3-bromo-3-ethylazetidine **5**.



Scheme 1

Itshould be mentioned that 3-bromo-3-ethylazetidines **3** representeligible substrates for nucleophilic bromide displacements, as it was the case for their structurally related 3-bromo-3-methylazetidines.8a

For example, the reactions of **3a,b** with oxygen nucleophiles, such asmethoxide (2 equiv NaBH4, MeOH, Δ, 2d), phenoxide (2.2 equivPhOH, 5 equiv K2CO3, MeCN, Δ, 1d),sodium acetate (5 equivNaOAc, MeCN, Δ, 3-5d) andkalium hydroxide (5 equiv KOH, H2O/CH2Cl2 (7/1), Δ, 15-20 h),provided the corresponding 3-alkoxy-, 3-aryloxy-, 3-acetoxy- and 3-hydroxy-3-ethylazetidines**6a-d** (Nu = OMe, OPh, OAc, OH) (Scheme 2). The reaction of **3a** with n-propylamine furnished 3-propylaminoazetidine **6e**(Nu = nPrNH; 5 equiv nPrNH2, MeCN, Δ, 1 d), while azetidines**3a,b** gave 3-cyanoazetidines **6f,f’**by treatment with potassium cyanide (1.5 equiv KCN, MeCN, Δ, 1 d).

Further reaction of azetidine-3-carbonitrile **6f**with 5 equiv of KOH in EtOH/H2O (10/1) under microwave irradiation (10 min, 150°C, 150 W) resulted in amide **7** as the major compound (77%), next to a small amount of the corresponding amino acid **8** (19%) (Scheme 2). The formation of carboxylic acid **8** was acknowledged upon neutralization of the reaction mixture to pH = 7 using1M HCl. Attempts toward the selective synthesis of amino acid **8** by prolonging the reaction time (up to 2 hours) proved to be unsuccessful.

In summary, the above-described ﬁndings acknowledge the suitability of 3-bromo-3-ethylazetidines as substrates for nucleophilic substitutions by different oxygen-, nitrogen- and carbon-centered nucleophiles.



Scheme 2

In the next part, the eligibility of 3-bromo-3-ethylazetidines as substratesfor the preparation of the corresponding new 3-ethylideneazetidines was investigated. Whereas the dehydrobromination of 3-bromo-1-*tert*-butylazetidine **5**utilizing 1.5 equiv of KOtBu in THF afforded1-*tert*-butyl-3-ethylideneazetidine **9**in a good yield (Scheme 3), the synthesis of 1-arylmethyl-3-ethylideneazetidines **10a,b** starting from 3-bromo-3-ethylazetidines **3a,b** was not as straightforward as initially anticipated, and several attempts were performed to optimize the reaction conditions. Treatment of azetidine**3a** with different bases such as KOtBu, LDA and NaH in THF at room temperature or under reflux gave no reaction, and addition of KOtBu in tBuOHunder refluxresulted in a mixture of different compounds. Eventually, the use of 1.5 equiv of KOtBu in THF and heating under microwave irradiation for 10 min at 120 °C selectively provided 3-ethylideneazetidines **10a,b** in excellent yields (Scheme 3).[[13]](#endnote-13)

The reactivity study of 3-ethylideneazetidines was expected to be a quite challenging task bearing in mind the sterically hindered and poorly reactive double bond. Prior to evaluating the intrinsic reactivity of this olefinic moiety, the propensity of the azetidine ring to undergo ring openingwas investigated.Due to the presence of an electron-donating alkyl group at nitrogen, activation of the azetidine ring toward an azetidinium species is necessary to effect ring-opening processes.*N*-Acetylation of alkylideneazetidine**10a** with 1.5 equiv of acetyl chloride in CH2Cl2 and subsequent ring opening by the expelled chloride ion afforded a mixture of *E*- and *Z*-allylamine**12**(E = CH3CO, X = Cl, *E*/*Z* = 1/1) after 15 hours under reflux (Table 2, Scheme 3). In a similar way, the reaction of **10a**with 1 equivof benzyl bromide in MeCN gave the corresponding allylamine**13** (Table 2, E = Bn, X = Br, *E*/*Z* = 3/2 or *vice versa*) after 15 hours under reflux. These reactions were straightforward and resulted in a complete conversion of the starting material, although chromatographically inseparable *E*/*Z*-mixtures were obtained. In addition, treatment of azetidines**10a,b** with 1.5 equiv of methyl chloroformate in MeCN for 15 hours under reflux resulted in a *E*/*Z*-mixture of 4-aminobut-2-enes**14**(E = COOMe, X = Cl, *E*/*Z* = 1/1). Upon heating of this mixture under microwave irradiation (140 °C, 30 min, 150 W) in DMF, the corresponding new cyclic carbamates**16** were obtained through 6-*exo*-*tet* cyclization.[[14]](#endnote-14)These cyclic carbamates can be regarded as interesting compounds with a variety of applications, most notably as precursors for γ-amino alcohols,[[15]](#endnote-15) as chiral auxiliaries,[[16]](#endnote-16) and as the core substructure in a number of biologically active compounds.[[17]](#endnote-17)When azetidine**10a**was added to a mixture of 1.3 equiv of benzyloxy- or methoxyacetyl chloride and 3 equiv of Et3N in CH2Cl2 and stirred at room temperature for 15 hours in an attempt to effect cycloaddition, the corresponding ring-opened amides **15a,b** (E = MeOCH2CO or E = BnOCH2CO, X = Cl, *E*/*Z* = 1/1) were formed instead. Apparently, the initial attack of the nucleophilic nitrogen atomacross the *in situ* formed ketene and subsequent ring opening of the azetidine moiety prevailed over the premised cycloaddition reaction.



Scheme 3

Table 2. Activation and ring opening of 3-ethylideneazetidines **10a,b** toward functionalizedallylamines

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Substrate** | **Reaction conditions** | **E** | **X** | **Product (yield, *E*/*Z*)** |
| **10a** | 1.5 equivAcCl, CH2Cl2, Δ, 15 h | CH3CO | Cl | **12** (R = H, 100%, *E*/*Z* = 1/1) |
| **10a** | 1 equivBnBr, MeCN, Δ, 15 h | Bn | Br | **13** (R = H, 100%, *E*/*Z* = 3/2or*vice versa*) |
| **10a** | 1.5 equivClCOOMe, MeCN, Δ, 15 h | COOMe | Cl | **14a** (R = H, 100%, *E*/*Z* = 1/1) |
| **10b** | 1.5 equivClCOOMe, MeCN, Δ, 15 h | COOMe | Cl | **14b** (R = Me, 100%, *E*/*Z* = 1/1) |
| **10a** | 1.3 equiv MeOCH2COCl3 equiv Et3N, CH2Cl2, r.t., 15 h | MeOCH2CO | Cl | **15a** (R = H, 78%, *E*/*Z* = 1/1) |
| **10a** | 1.3 equiv BnOCH2COCl3 equiv Et3N, CH2Cl2, r.t., 15 h | BnOCH2CO | Cl | **15b** (R = H, 75%, *E*/*Z* = 1/1) |

The reactivity of 3-ethylideneazetidines **10**with respect to electrophilic additions across the exocyclic double bond was evaluated in the next part. The attempts to prepare halohydrines by treatment of azetidine**10a**with 1 equiv of NBS in water/THF (1/1) for 10 min to 2 days proceeded sluggishly and gave mixtures of multiple products.The outcome of this reaction was shown to be hardly controllable and also dependent on the purity of NBS.On the other hand, a selective access to the functionalized dibrominatedazetidine**17**was realized by the reaction of azetidine**10a**with 2 equiv of NBS in CHCl3 or CH2Cl2 under reflux for 15-24 hours. Apparently, the small amount of bromine, released from NBS, was able to react with azetidine**10a**to afford 3-bromo-3-(1-bromoethyl)azetidine**17**(X = Br), however, in variable yields (30-70%) dependent on the purity of NBS (Scheme 4).In another approach, the azetidine nitrogen atom was protonated by introducing gaseous HCl to the solution of azetidine**10a**in CH2Cl2 for 10 min, after which 1 equiv of *m*CPBA was added. Instead of the expected spirocyclicazetidinyl epoxide**20a**, 3-chloro-3-(1-chloroethyl)azetidine**18** (X = Cl) was obtained in 92% yield (Scheme 4), probably as the result of the electrophilic addition of *in situ* formed Cl2to the double bond.[[18]](#endnote-18) The vicinallydihalogenatedazetidines**17**and **18**were subsequently subjected to reactions with benzylamineor KCN in MeCN in the presence of a catalytic amount of Ag2CO3 or NaI. Unfortunately, these reactions resulted in the recovery of the starting materials or gave complex mixtures as a result of decomposition.

In a final attempt to produce the synthetically challenging spirocyclicazetidinyl epoxides**20**, the azetidine nitrogen atom in structures **10** was protected by addition of 1 equiv of *p*TsOH in CH2Cl2. Subsequent addition of 1.5 equiv of *m*CPBA and heating under reflux for 15 hours afforded highly unstable azetidin-3-ols **19a,b**. However, immediate treatment of these alcohols**19**with 1 equiv of NaH in THF for 15 hours at room temperature provided the target 1-oxa-5-azaspiro[2.3]hexanes **20a,b** in excellentyields (Scheme 4).[[19]](#endnote-19) These novel strained spirocyclic systems showed a considerable stability as they were purified by means of column chromatography on basic Al2O3 to provide analytically pure samples. The synthesis of the spiranicazetidinyl epoxide moiety has received only very limited attention in the literature.[[20]](#endnote-20)However, these compounds have been shown to be useful intermediates for the preparation of different biologically active molecules.[[21]](#endnote-21) In general, the synthesis and reactivity of different azaspirocyclic scaffolds represent a challenging task for organic chemists and has lately been the subject of significant interest.19a,[[22]](#endnote-22)



Scheme 4

Bearing in mind that a number of azaspirocyles containing an azetidine moiety can be considered as structural surrogates of commonly employed saturated heterocycles with beneficial inherent structural features, further efforts were devoted to expand the family of novel spiroazetidine building blocks. In analogy with the epoxidation of azetidines**10**, the direct aziridination of the double bond could provide an access to novel spirocyclic 1,5-diazaspiro[2.3]hexanes,[[23]](#endnote-23) althoughthe treatment of azetidine**10a** with NBS and Chloramine-Tasnitrene precursor[[24]](#endnote-24) in MeCN afforded only small amounts of 3-bromo-3-(1-bromoethyl)azetidine**17** and no traces of the corresponding spiro compounds. Usingphenyltrimethylammoniumtribromide (PTAB) and Chloramine-T in MeCN, a complex mixture was also obtained.[[25]](#endnote-25)An alternative route to the synthesis of the spiro-fusedaziridinylazetidine core structure could comprise the ring opening of epoxides **20** with an appropriate amine (iPrNH2) in the presence of BF3·Et2O, followed by subsequent ring closure of the resulting amino alcohols under Mitsunobu conditions. Although the epoxide ring opening was shown to be successful, the drawback of this procedure involved the very low stability of the obtained β-amino alcohol, which underwent immediate decomposition.On the other hand, the ring opening of epoxides**20**with 3 equiv of NaN3 and 2 equiv of NH4Cl in acetone/water (8/1) did afford the corresponding azide**21**after 15 hours under reflux (Scheme 4). However, the subsequent ring closure of **21** utilizing Ph3P in THF gave only complex reaction mixtures. In addition, dihydroxylation of the double bond in azetidines**10a,b** with 1.1 equiv of *N*-methylmorpholine-*N*-oxide (NMO) and OsO4 (5 mol%) in acetone/water (4/1) for 4 hours at room temperature, followed by an aqueous work up, furnished dihydroxyazetidines**22a,b** in good yields (Scheme 4). In order to provide an entry to a different class of azaspirocyclic building blocks, azetidine**22b**was treated with 1.1 equiv of *p*TsOH and 5 equiv of CuSO4 in acetone to successfully afford the corresponding novel 5,7-dioxa-2-azaspiro[3.4]octane **23**after stirring under reflux for 1 day (Scheme 4). This spirocyclic core structure was found to be present in a number of spiro lactams, suitable for further chemical transformations.[[26]](#endnote-26)

In conclusion, 3-bromo-3-ethylazetidines were shown to easily undergo nucleophilic substitution with different nucleophiles, providing a convenient method for the preparation of new 3-alkoxy-, 3-aryloxy-, 3-acetoxy-, 3-hydroxy-, 3-cyano-, 3-butyl-, 3-carbamoyl- and 3-amino-3-ethylazetidines.Furthermore,3-bromo-3-ethylazetidines were used as suitable substrates for the preparation of 3-ethylideneazetidines, which, in spite of the presence of a rather inactive double bond, were shown to represent valuable compounds for the preparation of novel functionalized azetidines andspirocyclicazetidinebuilding blocks.

**References**

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13. 3-Ethylidene-1-(4-methylbenzyl)azetidine**10b**. To an ice-cooled solution of 3-bromo-3-ethyl-1-(4-methylbenzyl)azetidine**3b** (1.34 g, 5 mmol) in dry THF (30 mL), KOtBu (0.84 g, 1.5 equiv) was added and the mixture was subjected to microwave heating (150W) for 10 min at 120 °C. Afterward, the reaction mixture was cooled to room temperature, filtered, poured into water (20 mL) and extracted with Et2O (3 × 20 mL). The combined organic extracts were washed with H2O (2 × 15 mL) and brine (20 mL). Drying (MgSO4), filtration of the drying agent and evaporation of the solvent in vacuo afforded azetidine**10b**(0.88 g, 94%), which was purified by silica gel column chromatography to obtain an analytically pure sample. Light**-**yellow oil, *R*f*=* 0.22 (petroleum ether/ethyl acetate 4/1), Yield 94%. 1H NMR (300 MHz, ref = CDCl3) δ 1.46-1.51 (3H, m), 2.33 (3H, s), 3.68 (2H, s), 3.79-3.82 (4H, m), 5.16-5.24 (1H, m), 7.11-7.14 and 7.18-7.21 (4H, m). 13C NMR (75 MHz, ref = CDCl3) δ 13.6, 21.2, 60.8, 62.2, 63.5, 115.1, 128.5, 129.1, 131.8, 135.7, 136.7. IR (neat) *ν*max= 2917, 2805, 1514, 1439, 1358, 1273, 1176, 1042, 1021, 806, 780, 753 cm-1. MS *m/z* (%) 188 (M+ + 1, 100).HRMS m/z (ESI) calculated for C13H18N [MH]+ 188.1434, found 188.1435. [↑](#endnote-ref-13)
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19. 5-Benzyl-2-methyl-5-aza-1-oxaspiro[2.3]hexane **20a**. To an ice-cooled solution of 1-benzyl-3-hydroxy-3-(1-tosyloxyethyl)azetidine**19a**(0.19 g, 0.5 mmol) in dry THF (15 mL), NaH (60% suspension) (0.02 g, 1 equiv) was slowly added and the mixture was stirred for 15 hours at room temperature. The reaction mixture was poured into water (20 mL) and extracted with Et2O (3 × 20 mL). The combined organic extracts were washed with H2O (2 × 15 mL) and brine (20 mL). Drying (MgSO4), filtration of the drying agent and evaporation of the solvent in vacuo afforded spirocycle**20a**(0.10 g, 95%), which was purified by means of column chromatography on basic aluminium oxide in order to obtain an analytically pure sample. Light-yellow oil, *R*f = 0.22 (petroleum ether/ethyl acetate 4/1), Yield 95%. 1H NMR (300 MHz, CDCl3) δ 1.23 (3H, d, *J =* 5.5 Hz), 3.07 (1H, q, *J =* 5.5 Hz), 3.35-3.38 and 3.43-3.46 (2H, 2 x m), 3.60-3.66 (2H, m), 3.76 (2H, s), 7.23-7.36 (5H, m). 13C NMR (75 MHz, ref = CDCl3) δ 15.5, 56.2, 59.5, 60.4, 61.6, 64.1, 127.3, 128.6, 138.2. IR (neat) *ν*max = 2925, 2831, 1495, 1453, 1363, 1161, 826, 725, 697 cm−1. MS m/z (%) 190 (M+ + 1, 100). HRMS m/z (ESI) calculated for C12H15NO [MH]+ 190.1232, found 190.1232. [↑](#endnote-ref-19)
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