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Reduction of 4-(Haloalkyl)azetidin-2-ones with $LiAlH_4$ as a Powerful Method for the Synthesis of Stereodefined Aziridines and Azetidines

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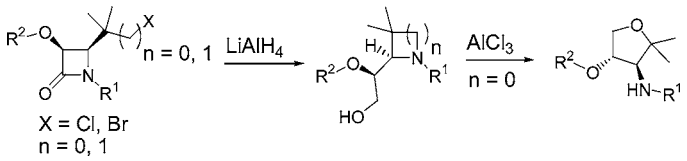
ABSTRACT



A new synthesis of stereodefined aziridines and azetidines, starting from 4-(1- or 2-haloalkyl)azetidin-2-ones, is described. Treatment of the latter compounds with $LiAlH_4$ gave 1,2-fission of the β-lactam, followed by an intramolecular nucleophilic substitution of the halogen, giving rise to the formation of 2-(1-alkoxy-2-hydroxyethyl)aziridines in the case of 4-(1-haloalkyl)azetidin-2-ones and of 2-(1-alkoxy-2-hydroxyethyl)-azetidines in the case of 4-(2-haloalkyl)azetidin-2-ones. The resulting 2-(1-alkoxy-2-hydroxyethyl)aziridines were transformed into the corresponding trans-3,4-substituted oxolanes via an intramolecular nucleophilic ring opening, triggered by $AlCl_3$.

The use of $LiAlH_4$ as a reductive agent of azetidin-2-ones has been shown not to be predictive, as both direct reduction of the carbonyl function[1−4] (leading toward azetidines) and 1,2-fission of the β-lactam core[4−8] (leading toward γ-amino alcohols) may occur. In addition, the former reaction predominantly occurs with N-unsubstituted β-lactams, whereas the 1,2-fission is mostly described for azetidin-2-ones bearing an electron-withdrawing group (Boc, sulfonyl) or an aryl at the nitrogen.

4-(1- or 2-Haloalkyl)azetidin-2-ones consist of an interesting class of azaheterocyclic compounds because the presence of ring strain and a halogen in these compounds makes them attractive for further reactions. In addition, these β-lactams are now readily available by performing a Staudinger reaction between α-chlorinated imines and different ketenes (prepared in situ from the corresponding acid chlorides and triethylamine). Investigating the reactivity of these compounds toward $LiAlH_4$ seems interesting, as treatment of 4-(1-haloalkyl)azetidin-2-ones **1** with $LiAlH_4$ may give rise to the formation of 2-(1-haloalkyl)azetidines **3** or 2-(1-alkoxy-2-hydroxyethyl)aziridines **2** depending on whether reduction of the β-lactam carbonyl or 1,2-fission of the β-lactam amide

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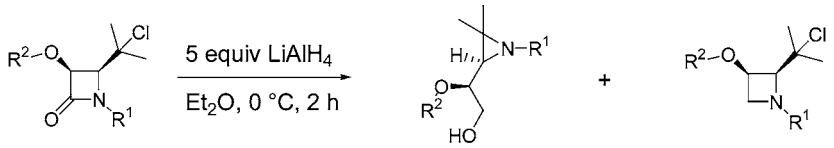
Scheme 1. Stereoselective Synthesis of 2-Hydroxyaziridines **2**



1a R^1 = *i*Pr, R^2 = Bn
1b R^1 = Bn, R^2 = Bn
1c R^1 = Bn, R^2 = Me
1d R^1 = allyl, R^2 = Bn
1e R^1 = allyl, R^2 = Me
1f R^1 = cHex, R^2 = Me

2a R^1 = *i*Pr, R^2 = Bn (57%)
2b R^1 = Bn, R^2 = Bn (62%)
2c R^1 = Bn, R^2 = Me (55%)
2d R^1 = allyl, R^2 = Bn (43%)
2e R^1 = allyl, R^2 = Me (51%)
2f R^1 = cHex, R^2 = Me (52%)

3a R^1 = *i*Pr, R^2 = Bn (3%)
3b R^1 = Bn, R^2 = Bn (4%)
3c R^1 = Bn, R^2 = Me (4%)
3d R^1 = allyl, R^2 = Bn (2%)
3e R^1 = allyl, R^2 = Me (3%)
3f R^1 = cHex, R^2 = Me (5%)

bond occurs. The former compounds are very attractive starting materials to perform rearrangements toward 3-halopyrrolidines,[9−12] whereas the latter serve as excellent building blocks in a variety of syntheses.[13−19] Treatment of 4-(2-haloalkyl)azetidin-2-ones **11** with $LiAlH_4$ may afford in the same way 2-(2-haloalkyl)azetidines **12** or 2-(1-alkoxy-2-hydroxyethyl)azetidines **13**. In general, azetidines constitute an interesting class of four-membered heterocycles, both from synthetic and from medicinal viewpoints.[20−27]

The present research will focus on the reactivity of $LiAlH_4$ toward 4-(1- or 2-haloalkyl)azetidin-2-ones **1** and **11** to develop new pathways for synthetically interesting aziridines and azetidines.

To investigate the reaction of $LiAlH_4$ with 4-(1-haloalkyl)-azetidin-2-ones **1**, synthesized by [2+2] cyclocondensation of the corresponding halogenated imines and ketenes (formed in situ from the corresponding acid chlorides by treatment with triethylamine) in benzene,[28,29] the latter compounds were added to a mixture of 5 molar equiv of $LiAlH_4$ in diethyl ether at 0 °C. After 2 h, a reaction mixture of mainly 2-(1-alkoxy-2-hydroxyethyl)aziridines **2** and little 2-(1-haloalkyl)-azetidines **3** (2−5%) was obtained. Separation of these two compounds by flash chromatography proved to be very easy, as both compounds seriously differ in polarity. After purification, the 2-(1-alkoxy-2-hydroxyethyl)aziridines **2** were isolated in good to high yields (Scheme 1). It has to be noted that the order of addition turned out to be very important during this reduction. Addition of $LiAlH_4$ to a mixture of 4-(1-haloalkyl)azetidin-2-ones **1** in diethyl ether gave a very substantial decrease of yields, and many side products were formed, indicated by the complex reaction mixtures obtained after workup.

As can be seen in Scheme 1, ring transformation of 4-(1-chloroalkyl)azetidin-2-ones **1** toward aziridines **2** proceeds with retention of stereochemistry. The 1,2-fission of the azetidin-2-ones **1** explains the obtained syn stereochemistry observed in aziridines **2**. The proposed mechanism proceeds via an initial reduction of the amide functionality into an hemiaminal **4**. Coordination of lithium to nitrogen triggers ring opening of azetidinium salt **5**, leading to the formation of the intermediate aminoaldehyde complex **6**. Reduction of the formyl group and nucleophilic substitution of the chlorine by nitrogen leads to the formation of 2-(1-alkoxy-2-hydroxy-ethyl)aziridines **2** (Scheme 2).[4] The obtained stereochemistry of aziridines **2** was proven by the observation that the vicinal coupling constants (J = 8.6 Hz; ^{1}H NMR; $CDCl_3$) between the NCH of the aziridine ring and the R^2OCH in all cases were similar to coupling constants found in the literature for aziridines with analogous stereochemistry.[29]

The formation of small amounts of azetidines **3** could be due to two reasons. Alane, formed after initial reaction of

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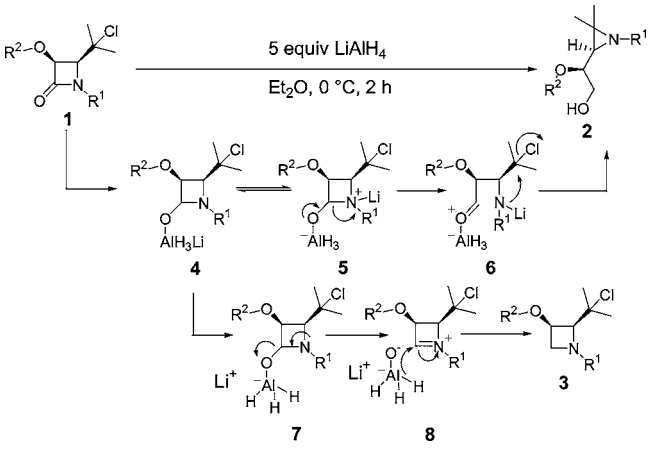
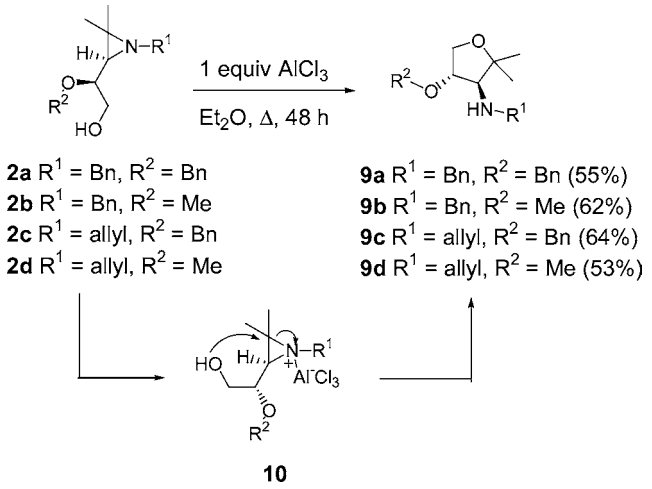
Scheme 2. Reduction Reaction Mixtures of 2-(1-Haloalkyl)azetidines **3**



$LiAlH_4$ with azetidin-2-ones **1**, could be responsible for reduction of the latter compounds into azetidines **3**.[4] On the other hand, formation of an azetidinium ion **8** can also give rise to the formation of azetidines **3** (Scheme 2). The observation that the use of more equivalents of $LiAlH_4$ did not result in a diminishing amount of azetidines **3** proved that alane was not responsible for the formation of 2-(1-haloalkyl)azetidines **3**. Reduction of intermediately formed azetinium salts **8** is more suitable to explain the observed results (Scheme 2).

Aziridines have been shown to serve as excellent building blocks in organic synthesis.[13−19] Also, aziridines **2** proved to be very useful intermediates toward the synthesis of highly substituted oxolanes. Therefore, 2-(1-alkoxy-2-hydroxyethyl)aziridines **2** were treated with $AlCl_3$ in ether under reflux for 48 h, affording *trans*-tetrahydrofurans **9** in good isolated yields (Scheme 3). The stereochemistry was clearly shown

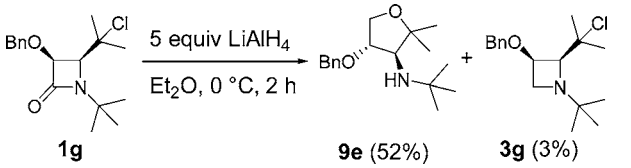
Scheme 3. Stereoselective Synthesis of 3,4-*trans*-Tetrahydrofurans **9**



to be trans, as coupling constants of 4 Hz were observed between the two protons at C3 and C4 (^{1}H NMR; $CDCl_3$). The reaction mechanism is explained by an initial complexation of $AlCl_3$ with nitrogen. In this way, the activation of the aziridine ring renders a more facile ring opening after intramolecular nucleophilic attack of the hydroxyl function, leading toward oxolanes **9**. Recently, unusual dideoxynucleosides received increasing interest because of their antiviral activity.[30,31] More specifically, *trans*-3-hydroxy-4-uracyloxolane proved to show HCMV inhibitory activity.[31]

It has to be noted that, when 3-benzyloxy-1-*tert*-butyl-4-(1-chloro-1-methylethyl)azetidin-2-one **1g** was treated with 5 molar equiv of $LiAlH_4$ at 0 °C for 2 h, no 2-(hydroxyethyl)-aziridine **2** could be obtained, as only the corresponding oxolane **9e** was isolated, next to small amounts of azetidine **3g** (Scheme 4). Apparently, in this case, the *tert*-butyl group

Scheme 4. Reduction of Azetidin-2-one **1g**



exerts too much strain onto the intermediate 2-(hydroxyethyl)aziridine to be stable under these reaction conditions, and intramolecular attack of the hydroxyl function leads toward the formation of oxolane **9e**.

Treatment of 4-(2-bromoalkyl)azetidin-2-ones **11**, prepared by [2+2] cyclocondensation of the corresponding *N*-(3-bromo-2,2-dimethylpropylidene)alkylamines and ketenes (formed in situ from the corresponding acid chlorides by treatment with triethylamine) in benzene[29] with 5 molar equiv of $LiAlH_4$, gave analogous results as with 4-(1-chloroalkyl)-azetidin-2-ones **1**. However, because of the extended carbon chain, 1,2-fission of the starting material followed by a nucleophilic substitution of bromide led toward the formation of 2-(1-alkoxy-2-hydroxyethyl)azetidines **12** next to small amounts of *cis*-4-(2-bromoalkyl)azetidines **13** (1−5%), obtained by reduction of the carbon−oxygen double bond of 4-(2-bromoalkyl)azetidin-2-ones **11** (Scheme 5). Again, the obtained syn stereochemistry of azetidines **12** was proven by the observation that coupling constants (J = 9.4 Hz; $CDCl_3$) between the NCH of the azetidine ring and the R^2-OCH units were similar to coupling constants found in the literature for azetidines with analogous stereochemistry.[29]

Attempts to perform ring enlargements of 2-(hydroxyethyl)azetidines **12** toward pyranes were not successful.

In conclusion, 4-(haloalkyl)azetidin-2-ones were proven to be useful synthons in the synthesis of new functionalized aziridines and azetidines. Treatment of 4-(haloalkyl)azetidin-2-ones with $LiAlH_4$ gave 1,2-fission of the β-lactam core, followed by a nucleophilic substitution of the halogen, giving

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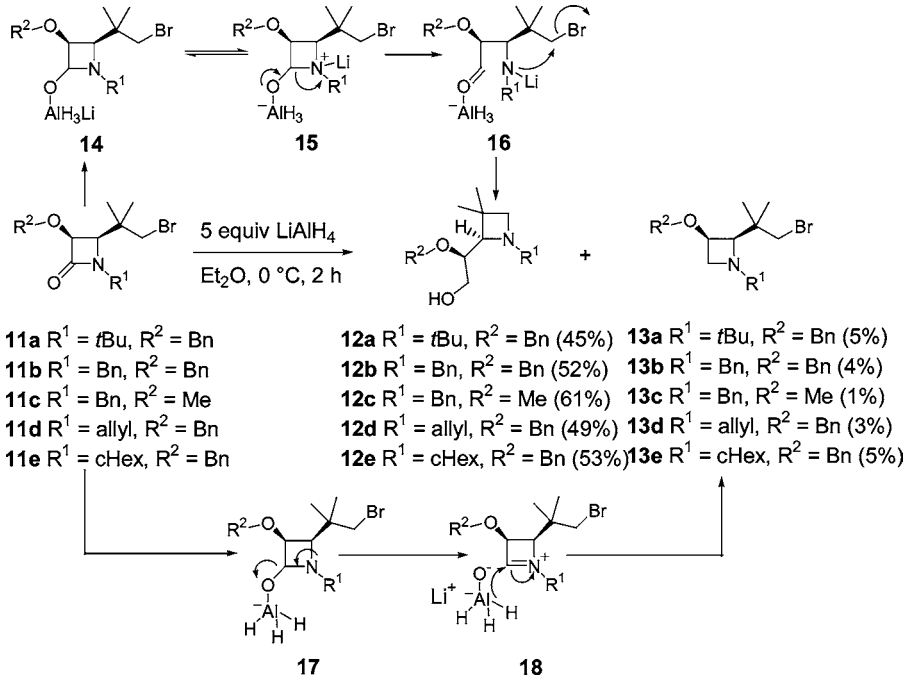
Scheme 5. Stereoselective Synthesis of 2-(1-Alkoxy-2-hydroxyethyl)azetidines **12**



rise to the formation of stereodefined 2-(1-alkoxy-2-hydroxyethyl)aziridines in the case of 4-(1-haloalkyl)azetidin-2-ones and of 2-(1-alkoxy-2-hydroxyethyl)azetidines in the case of 4-(2-haloalkyl)azetidin-2-ones. In all cases, very small amounts of azetidines, originating from the reduction of the carbonyl function on the β-lactam core, were formed as side products. Furthermore, 2-(1-alkoxy-2-hydroxyethyl)aziridines could be transformed into the corresponding trans-3,4-substituted oxolanes via an intramolecular nucleophilic ring opening, triggered by $AlCl_3$.

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Supporting Information Available: General information and all spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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