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Ring Transformation of 2-(Haloalkyl)azetidines into 3,4-Disubstituted Pyrrolidines and Piperidines

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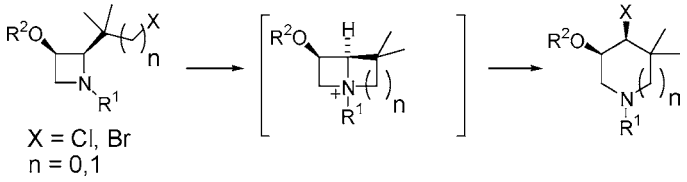
ABSTRACT



Reduction of 4-(haloalkyl)azetidin-2-ones with chloroalane (AlH_2Cl) afforded new 2-(haloalkyl)azetidines in high yields. The latter compounds proved to be very useful starting materials for rearrangements toward stereospecifically defined five- and six-membered azaheterocycles, such as 3,4-*cis*-disubstituted pyrrolidines and piperidines. During these reactions, bicyclic azetidinium intermediates were formed which were ring opened by a variety of nucleophiles. Hereby, reactions proceeding via 1-azoniabicyclo[2.2.0]hexanes are reported for the first time.

Pyrrolidine and piperidine substructures are common skeletons found in many biologically interesting compounds and natural products. Therefore, a continuous interest exists in the isolation and new syntheses of compounds containing these five- and six-membered azaheterocycles.[1−6] 2-(1-Haloalkyl)azetidines have been proven to be suitable starting materials to perform rearrangements toward pyrrolidines because of the presence of both ring strain and a leaving group.[7−10] In the present report, a straightforward pathway from β-lactams toward pyrrolidines is reported. Efforts have been made in the present study to provide evidence that these rearrangements progress via azetidinium ions. Rearrangements of 2-(2-haloalkyl)azetidines have not yet been reported, although these reactions could afford the development of new pathways toward 4-substituted piperidines. Accordingly, efforts have been performed to unravel this novel pathway toward piperidines by rearrangement of 2-(2-haloalkyl)-azetidines.

Treatment of β-lactams with chloroalane (AlH_2Cl) has already been proven to be a suitable method for the synthesis of azetidines.[11−13] In the present report, reductions of highly functionalized β-lactams were performed successfully. Treatment of 4-(1-haloalkyl)azetidin-2-ones **1**, synthesized by [2+2] cyclocondensation of the corresponding novel halogenated imines and ketenes (formed in situ from the corresponding acid chlorides by treatment with triethyl-

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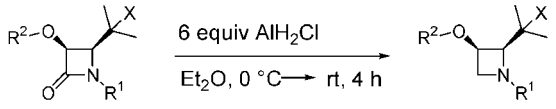
amine), in benzene[14,15] afforded the corresponding azetidines **2** in high yields. It was necessary to perform an inverse addition by adding 4-(haloalkyl)azetidin-2-ones **1** to 6 molar equiv of AlH_2Cl, prepared in situ from $LiAlH_4$ and $AlCl_3$ (Scheme 1).

Scheme 1. Synthesis of 2-(1-Haloalkyl)azetidines **2**

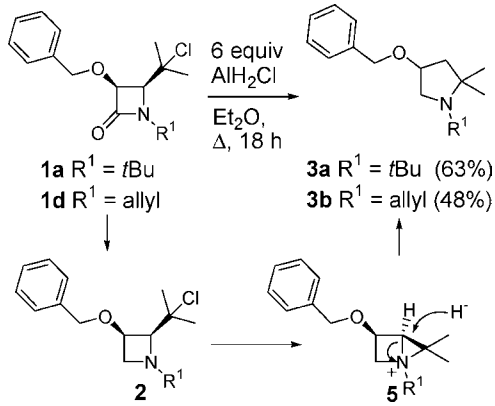


1a R^1 = *t*Bu, R^2 = Bn, X= Cl
1b R^1 = Bn, R^2 = Bn, X= Cl
1c R^1 = Bn, R^2 = Me, X= Cl
1d R^1 = allyl, R^2 = Bn, X= Cl
1e R^1 = allyl, R^2 = Me, X= Cl
1f R^1 = *t*Bu, R^2 = Bn, X= Br

2a R^1 = *t*Bu, R^2 = Bn, X= Cl (63%)
2b R^1 = Bn, R^2 = Bn, X= Cl (75%)
2c R^1 = Bn, R^2 = Me, X= Cl (67%)
2d R^1 = allyl, R^2 = Bn, X= Cl (65%)
2e R^1 = allyl, R^2 = Me, X= Cl (61%)
2f R^1 = *t*Bu, R^2 = Bn, X= Br (61%)

Reaction conditions proved to be important during this reduction, as pyrrolidines **3** were obtained when the same reaction mixture was refluxed for 18 h instead of keeping it at 0 °C to room temperature for 4 h (Scheme 2). In these

Scheme 2. Synthesis of Pyrrolidines **3**



cases, azetidines **2** reacted further toward bicyclic azetidinium ions **5**, which could be ring opened by attack of a hydride, resulting in the formation of 3-alkoxy substituted pyrrolidines **3**.

Although previous research concerning possible ring transformations of 2-(1-chloro-1-methylethyl)azetidines did not provide the expected 3-chloropyrrolidines,[9] reflux of 2-(1-chloro-1-methylethyl)azetidines **2d** and **2e** in acetonitrile afforded 3-chloropyrrolidines **4a** and **4b** in moderate yields (Table 1). Addition of several nucleophiles to azetidines **2** in DMSO resulted in 3,4-disubstituted pyrrolidines **4c**, **4d**, and **4e**. Although the yields (44−52%) are not excellent, they are very acceptable because of the ready access to stereo-

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Table 1. Transformations of 2-(1-Chloroalkyl)azetidines **2** toward Pyrrolidines **4**

reactant	R^1	R^2	reaction conditions	product	Nu	yield (%)
2d	allyl	Bn	Δ, MeCN, 18 h	**4a**	Cl	46
2e	allyl	Me	Δ, MeCN, 18 h	**4b**	Cl	44
2a	*t*Bu	Bn	10 equiv NaOH, 100 °C, 18 h, DMSO	**4c**	OH	46
2d	allyl	Bn	10 equiv KCN, 100 °C, 18 h, DMSO	**4d**	CN	44
2d	allyl	Bn	10 equiv NaN_3, 100 °C, 18 h, DMSO	**4e**	N_3	52

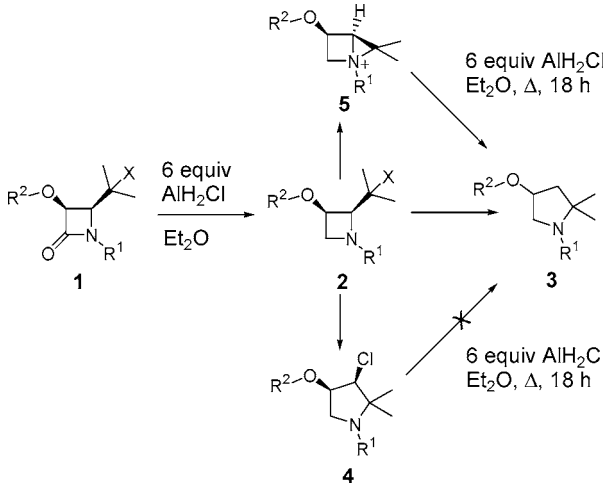
defined pyrrolidines **4** from β-lactams in two steps. Furthermore, these results constitute the first examples of a stereodefined addition of different nucleophiles to pyrrolidines **4** starting from 2-(1-haloalkyl)azetidines **2**.

The stereochemistry of pyrrolidines **4** was shown to be cis, on the basis of nOe experiments, coupling constants, and the reaction mechanism. Nuclear Overhauser effects of 4% between the two hydrogens at C3 and C4 of **4a** were observed ($CDCl_3$). The coupling constants between the two hydrogens at C3 and C4 of **4** were in the order of 8 Hz. These results are in accordance with literature data.[9]

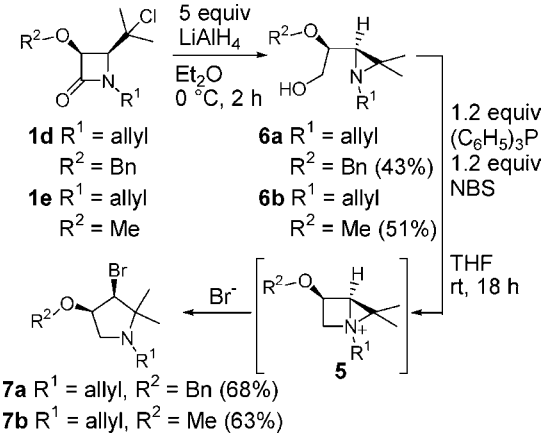
The reaction mechanism of ring transformations of 2-(1-haloalkyl)azetidines toward 3-halopyrrolidines has been proposed to proceed via a concerted mechanism.[9] The following results will prove that this proposition is wrong, and it will be shown that bicyclic azetidinium intermediates occur during ring enlargements of 2-(1-haloalkyl)azetidines **2** toward pyrrolidines **4**.

To investigate the reaction mechanism, 3-chloropyrrolidine **4a** was refluxed in ether for 18 h in the presence of 6 molar equiv of AlH_2Cl (Scheme 3).

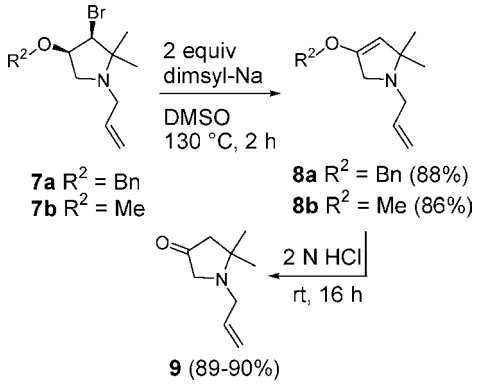
Scheme 3. Intermediacy of Bicyclic Azetidinium Intermediates **5**



Scheme 4. Synthesis of 3-Bromopyrrolidines **7**



Scheme 5. Synthesis of Pyrrolidin-3-ones **9**



As shown in Scheme 2, the same reaction conditions afforded pyrrolidines **4**, starting from 4-(1-haloalkyl)azetidin-2-ones **1**. If ring transformations of 2-(1-chloro-1-methylethyl)azetidines proceed in a concerted way, this should mean that, in the synthesis of pyrrolidines **3**, 3-chloropyrrolidines should be intermediates. Furthermore, these intermediates should be convertible toward pyrrolidines **3**. The observation that reflux of 3-chloropyrrolidine **4a** in ether for 18 h in the presence of 6 molar equiv of AlH_2Cl did not yield pyrrolidine **3b** proved that ring transformations of 2-(1-chloro-1-methylethyl)azetidines proceed via bicyclic azetidinium intermediates **5**.

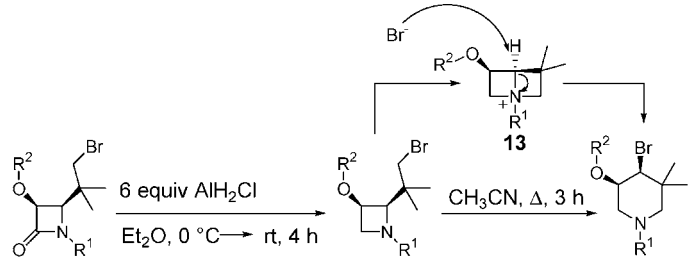
To provide additional proof, 2-(2-hydroxyethyl)aziridines **6** were synthesized by reduction of 4-(1-haloalkyl)azetidin-2-ones **1** with $LiAlH_4$.[16] The former compounds were subjected to Mitsunobu conditions to substitute the hydroxyl function with a bromine (Scheme 4). After workup, this reaction afforded 4-oxygenated 3-bromopyrrolidines **7**. The fact that pyrrolidines **7** were obtained with stereochemistry similar to that observed in pyrrolidines **4** after reaction via the bicyclic azetidinium intermediate **5** gave additional proof in favor of the occurrence of a similar intermediate **5** during ring transformations of 2-(1-chloro-1-methylethyl)azetidines **2** toward 3-halopyrrolidines **4**.

The stereochemistry of 4-oxygenated 3-bromopyrrolidines **7** (Scheme 4) was determined by determination of the coupling constants (around 8 Hz) between the two hydrogens at C3 and C4, similar to those observed in pyrrolidines **4**. Also, the fact that dehydrobromination occurred upon treatment of pyrrolidines **7** with dimsylsodium in DMSO at 130 °C for 2 h indicated a cis relationship between the C3 and C4 substituents, which is required to obtain a trans elimination. The obtained cyclic enol ethers **8** could be easily hydrolyzed into the corresponding pyrrolidin-3-one **9** by reaction with 2 N hydrogen chloride at room temperature overnight (Scheme 5).

Pyrrolydin-3-ones constitute a class of compounds of great interest concerning their potential HIV inhibitory activity[17,18] and are considered as pharmacophores in pharmaceutical sciences.

To investigate the scope of the ring transformation of 2-(haloalkyl)azetidines, 4-(2-bromoalkyl)azetidin-2-ones **10** were 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.[15] The resulting β-lactams **10** were treated with 6 molar equiv of

Scheme 6. Synthesis of 4-Bromopiperidines **12**

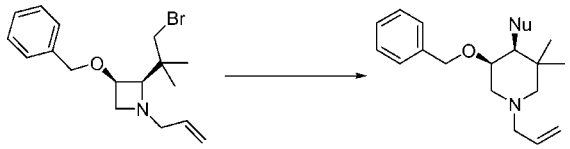


10a R^1 = *t*Bu, R^2 = Bn
10b R^1 = Bn, R^2 = Bn
10c R^1 = Bn, R^2 = Me
10d R^1 = allyl, R^2 = Bn
10e R^1 = cHex, R^2 = Bn

11a R^1 = *t*Bu, R^2 = Bn (95%)
11b R^1 = Bn, R^2 = Bn (65%)
11c R^1 = Bn, R^2 = Me (63%)
11d R^1 = allyl, R^2 = Bn (57)
11e R^1 = cHex, R^2 = Bn (95%)

12a R^1 = *t*Bu, R^2 = Bn (98%)
12b R^1 = Bn, R^2 = Bn (97%)
12c R^1 = Bn, R^2 = Me (92%)
12d R^1 = allyl, R^2 = Bn (95%)
12e R^1 = cHex, R^2 = Bn (95%)

Table 2. Transformations of 2-(2-Bromoalkyl)azetidine **10d** toward Piperidines **14**



10d **14**

reactant	reaction conditions	product	Nu	yield (%)
10d	10 equiv NaOH, 100 °C, 18 h, DMSO	**14a**	OH	86
10d	10 equiv KCN, 100 °C, 18 h, DMSO	**14b**	CN	92
10d	10 equiv NaN_3, 100 °C, 18 h, DMSO	**14c**	N_3	72

AlH_2Cl, affording the corresponding 2-(2-bromoalkyl)azetidines **11**. The latter compounds were converted into *cis*-3-alkoxy-4-bromopiperidines **12** in very high yields through reflux in acetonitrile for 3 h (Scheme 6).

No ring transformations of azetidines toward piperidines, proceeding via 1-azoniabicyclo[2.2.0]hexanes, have been reported until now. Again, the obtained cis stereochemistry is explained by the occurrence of a bicyclic azetidinium intermediate **13** during the reaction. Attack of bromide at the bridgehead carbon of this azetidinium salt **13** affords *cis*-3-alkoxy-4-bromopiperidines **12**.

The ability of introducing nucleophiles other than bromine was again tested through the addition of sodium azide, potassium cyanide, and sodium hydroxide onto azetidine **10d** in DMSO. The corresponding 4-substituted piperidines were obtained in high to very high yields (Table 2).

The present results indicate that ring transformations toward piperidines **12** and **14** run more easily than toward pyrrolidines **4**. This is probably due to a less energetic transition state of **13** compared to the transition state of **5**.

In conclusion, 2-(haloalkyl)azetidines proved to be useful starting materials to perform rearrangements toward five- and six-membered azaheterocycles in high yield. The latter reactions via 1-azoniabicyclo[2.2.0]hexanes have not yet been described in the case of 2-(2-haloalkyl)azetidines, and the present results allow the development of a wide variety of highly functionalized five- and six-membered heterocycles.

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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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