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Highly stereoselective ring expansion of enantiopure α-hydroxyalkyl azetidines

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Abstract—Stereodefined α-hydroxyalkyl azetidines, prepared in a few steps from enantiopure β-amino alcohols, are chlorinated or transformed into methanesulfonyloxymethyl derivatives in good yields. Heating of these compounds in chloroform or dimethylformamide induces a stereospecific ring enlargement to give 3-chloro or 3-methanesulfonyloxy pyrrolidines. The ease of this rearrangement depends on the nature of the migrating group (Cl^- or MsO^-), of the class of the starting alcohol (primary or secondary) and of the relative stereochemistry of the starting material.

Ring enlargements of nitrogen heterocycles are useful reactions because they can provide an original access to target molecules which are otherwise difficult to prepare.[1] These reactions frequently involve strained nitrogen rings in which the strain release acts as a driving force for the enlargement. As a result, numerous examples of aziridine expansions have been reported.[2] Recent work has shown that five- to six-membered ring enlargement can also produce functionalized piperidines in an enantiospecific way[3] and this was successfully applied to the preparation of (–)-parotexine[4a] or zamifenamicin.[4b] The strain release in these reactions is not always necessary and expansion of larger nitrogen heterocycles has also been reported through various pathways.[5] The azetidine ring however, despite its strain which is a favourable factor for a ring expansion, has been less studied. Some scarce reports describe the Pd-catalysed rearrangement of *N*-tosyl-2-alkenyl azetidines into piperidines (4 to 6 enlargement),[6] the four to six-membered ring enlargement of 2-thioacetal azetidines under the action of a Lewis acid,[7] and the use of *N*-tosyl azetidines as a 1,4 dipole in cycloaddition reactions (4 to 6 enlargement).[8] These isolated examples reflect the difficulty of access to azetidines, especially in enantiomerically pure form.[9] Very recently,[10] the thermic ring enlargement of racemic 2-halomethylazetidines into 3-halopyrrolidines was reported (Fig. 1). This prompted us to disclose herein our asymmetric version of this rearrangement.

In order to study this ring expansion, we prepared a series of primary, secondary and tertiary α-hydroxyalkyl azetidines from 2-cyano azetidines, for which we have recently described an efficient preparation starting from commercially available enantiomerically pure β-amino alcohols.[11]

Primary α-hydroxyalkyl azetidines **1**–**4** were prepared in good yields from the corresponding 2-cyano azetidines following a two-step sequence involving transformation into the corresponding ethyl ester, followed by $LiAlH_4$-mediated reduction. No detectable epimerisation could be observed during this sequence. Secondary *anti*-α-hydroxyalkyl azetidines **5** and **6** were prepared as previously reported[12] through the diastereoselective reduction of the intermediate ketone. Finally, tertiary azetidinic alcohol **8** was prepared by addition of methylmagnesium bromide to the corresponding ester **7** whilst **9** was prepared as previously described[12] (Scheme 1).

Having in hand the required substrates, we next began to investigate their ring enlargements. Chlorination of primary alcohols **3** and **4** gave good yields of the corresponding chlorides **10** and **11** as stable com-

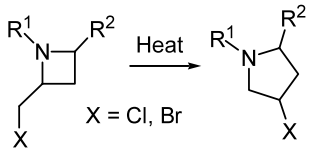

Figure 1.

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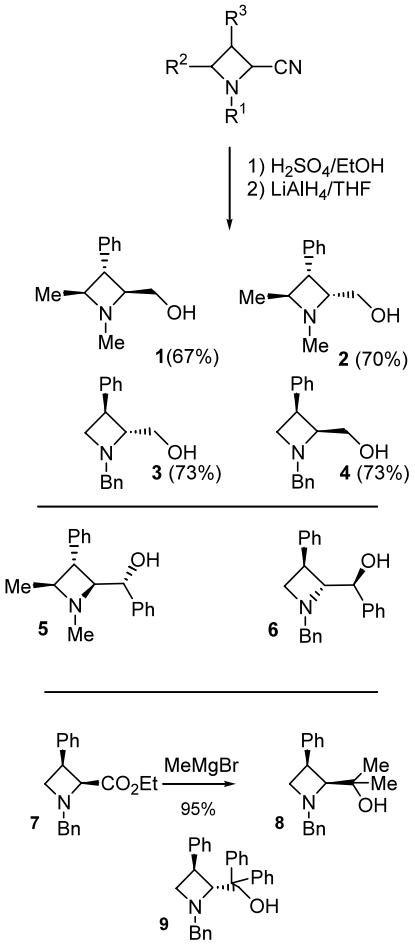
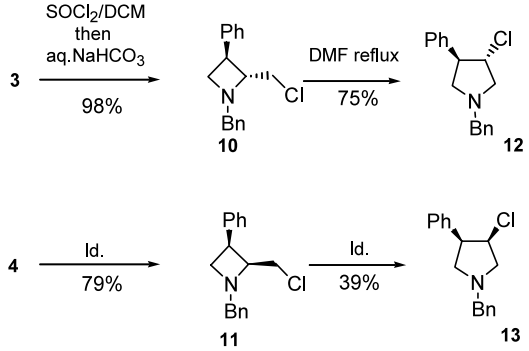


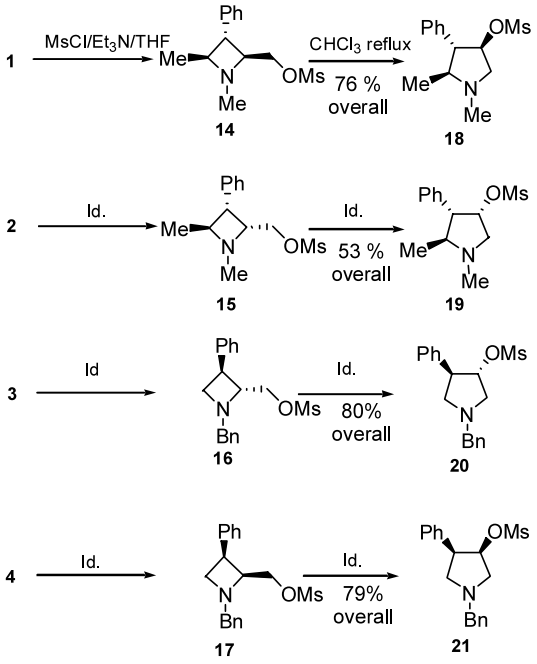
Scheme 1. Synthesis of α-hydroxyalkyl azetidinic substrates.

pounds. Overnight heating of these chlorides in refluxing chloroform left them unchanged whilst heating in DMF (120°C, 10 h) smoothly gave 3-chloropyrrolidines **12** and **13** in fair to modest yields (Scheme 2).

On the other hand, mesylation of **1**–**4** gave the corresponding mesylates **14**–**17** with trace amounts (10–15%) of rearranged mesylates **18**–**21**. In this case, heating of these mixtures in chloroform completed the ring expansion to give 3-mesyloxy pyrrolidines in good overall yields (Scheme 3).

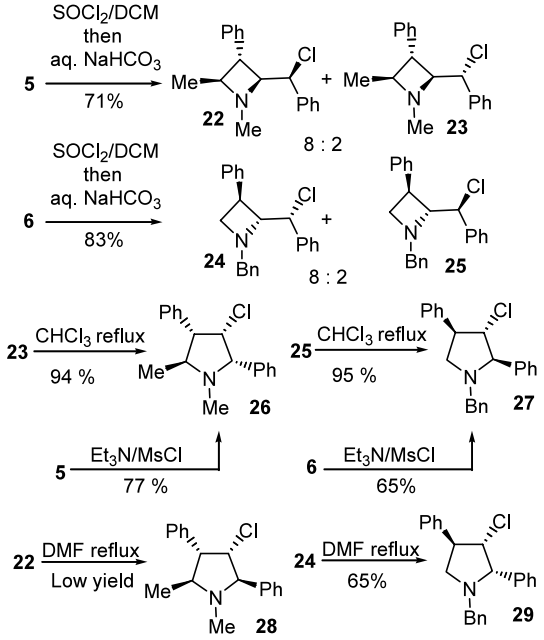


Scheme 2. Chlorination of primary alcohols followed by ring expansion.



Scheme 3. Mesylation of primary alcohols followed by ring expansion.

The behavior of the secondary alcohols was somewhat different (Scheme 4). Chlorination of benzylic alcohols **5** and **6** was not stereoselective and gave unrearranged chlorides **22**–**25**. In both cases chlorination occurred predominantly with inversion of configuration to give *syn*-chlorides **22** and **24** as major products. The *syn* and *anti* isomers could be separated by chromatography and showed a different reactivity with regard to the ring expansion. Indeed, heating a solution of the minor *anti*-isomer **23** or **25** in chloroform induced the ring



Scheme 4. Chlorination or mesylation of secondary alcohols followed by ring expansion.

expansion to give **26** or **27**, respectively, but left the *syn*-isomers **22** and **24** unchanged. However, upon heating in refluxing DMF, compound **24** rearranged to give **29**, whilst **22** gave trace amounts of rearranged pyrrolidine **28** along with unidentified byproducts. On the other hand, mesylation of **5** and **6** afforded directly rearranged chlorides **26** and **27** with no detectable amount of the corresponding intermediate mesylate.

The relative configurations in the produced pyrrolidines were determined by careful NOE experiments. As examples, some observed NOE enhancements for compounds **19**, **27**, and **29** are shown in Figure 2. The determination of the relative configurations of pyrrolidines **26**–**29** allowed the determination of the stereochemistries of the chlorinated stereocentre in the starting azetidines **22**–**25**.

Finally, tertiary alcohols also showed a different behavior. Treatment of **8** with thionyl chloride, followed by alkaline workup gave in fair yield (60%) a roughly equimolar mixture of alkene **31** and amino ketone **33** (Scheme 5). The formation of the compound **31** can be explained by the occurrence of a transient carbenium species **30** that undergoes elimination, whilst a 1,2-hydride shift giving an iminium ion **32** followed by ring opening accounts for the formation of **33**. Under the same conditions, diphenyl substrate **9** gave only starting material as an isolable compound: clearly the stable carbenium species does not rearrange, but gives the corresponding chloride that undergoes hydrolysis upon workup.

The relative reactivity of these substrates with regard to the ring expansion can be explained as follows. The difference of reactivity between methanesulfonyloxymethyl derivatives (most reactive) and chlorides is in accordance with the higher leaving group ability of the methanesulfonate anion compared to the chloride. The ease of the rearrangement is further enhanced if the leaving group is held at a benzylic position (note the facile production of **26** and **27** without isolation of the intermediate unrearranged methanesulfonate derivatives). Furthermore, the difference of reactivity between *syn*-**22**, **24** and *anti*-**23**, **25** benzylic chlorides can be easily explained by examination of the corresponding rearrangement transition states, depicted in Figure 3 for the rearrangements of **24** and **25**. It is clear that if the phenyl group is oriented in an *endo* position, such as for the rearrangement involving **24**, the steric strain is important, and the reaction will require higher thermic activation.

The above discussion supposes that this rearrangement involves a concerted pathway and not a transient azetidinium ion (**34** in Fig. 4) resulting from intramolecular alkylation. A similar intermediate (**35** in Fig. 4) was postulated in a related ring expansion involving pyrrolidinemethanol derivatives.[3a]

Our preliminary experimental observations are consistent with a concerted mechanism. First, AM1 calculations performed on both of these bicyclic ammonium ions show a very high energy difference, reflecting the steric strain of the azabicyclo [2.1.0] pentane frame, although this skeleton was reported in one case.[13] We feel that, unlike **35**, the strained ion **34** is not produced.

Furthermore, we were not able to detect by NMR such azetidinium ions upon treatment of unrearranged benzylic chloride **24** with $AgBF_4$ in $CDCl_3$. Another experimental observation in favor of the concerted pathway is the absence of rearrangement when α-azetidine carbenium species are involved. Although further experimen-

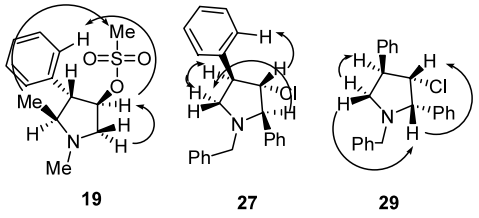
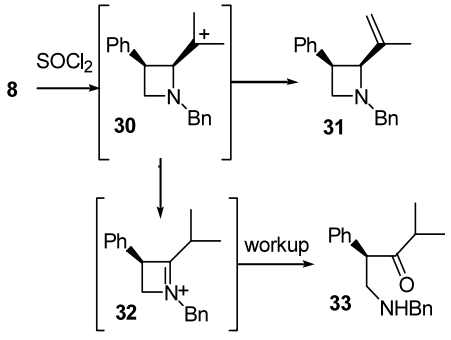


Figure 2.



Scheme 5. Chlorination of a tertiary alcohols: no ring expansion takes place.

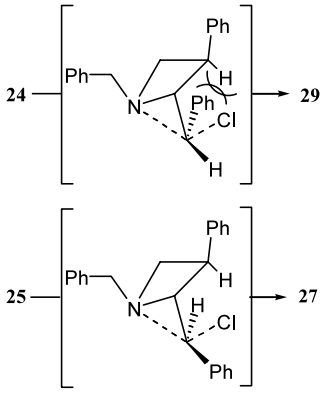


Figure 3.

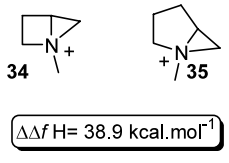


Figure 4.

tal work will be needed, we therefore think that this ring expansion occurs through a concerted pathway.

In conclusion, we have described in this letter a straightforward access to enantiopure 2-halomethyl or 2-methanesulfonyloxymethyl azetidines and 3-chloro[14] or 3-methanesulfonyloxy pyrrolidines, and we have examined the scope of the rearrangement of the former four- into five-membered rings. Further functionalisation of these heterocycles is under active investigation in our group.

Acknowledgements

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References

1. Hesse, M. *Ring Enlargements in Organic Chemistry*; VCH: Weinheim; New York; Basel; Cambridge, 1991.
2. For some recent examples see: (a) Papa, C.; Tomasini, C. *Eur. J. Org. Chem.* **2000**, 1569–1576; (b) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887–5890; (c) Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801–1812; (d) Friedolin, W.; Eberbach, W. *Tetrahedron* **2001**, *57*, 4349–4358; (e) Ducray, R.; Ciufolini, M. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4688–4691.
3. (a) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693–1699; (b) Calvez, O.; Chiaroni, A.; Langlois, N. *Tetrahedron Lett.* **1998**, *39*, 9447–9450.
4. (a) Cossy, J.; Mirguet, O.; Gomez Pardo, D.; Desmurs, J.-R. *Tetrahedron Lett.* **2001**, *42*, 5705–5707; (b) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1343–1344.
5. (a) Wasserman, H. H.; Robinson, R. P.; Matsuyama, H. *Tetrahedron Lett.* **1980**, *21*, 3493–3497; (b) Lednicer, D.; Hauser, C. R. *J. Am. Chem. Soc.* **1957**, *79*, 4449–4451; (c) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 669–673.
6. Fugami, K.; Miura, K.; Morizawa, Y.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1989**, *45*, 3089–3098.
7. Alcaide, B.; Almendros, P.; Aragoncillo, C.; Salgado, N. R. *J. Org. Chem.* **1999**, *64*, 9596–9604. See also references cited therein for other 4 to 5 ring enlargements.
8. Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *J. Chem. Commun.* **2001**, 958–959.
9. (a) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2002**, *43*, 4633–4636; (b) Carlin-Sinclair, A.; Couty, F.; Rabasso, N. *Synlett* **2003**, 726–729.
10. Outurquin, F.; Pannecoucke, X.; Berthe, B.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 1007–1014.
11. Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, 297–302.
12. Couty, F.; Prim, D. *Tetrahedron: Asymmetry* **2002**, *13*, 2619–2624.
13. Joucla, M.; Fouchet, B.; Hamelin, J. *Tetrahedron* **1985**, *41*, 2707–2715.
14. Selected data: Compound **27**: ^{1}H NMR (300 MHz): 3.01 (t, $J=9.5$ Hz, 1H, H_5), 3.19 (d, $J=13.1$ Hz, 1H, C*H*HPh), 3.26 (dd, $J=9.5$ and 3.3 Hz, 1H, $H_{5'}$), 3.50 (ddd, $J=3.3$, 7.1, 9.5 Hz, 1H, H_4), 3.73 (d, $J=8.5$ Hz, 1H, H_2), 3.96 (d, $J=13.1$ Hz, 1H, CH*H*Ph), 4.03 (dd, $J=7.1$ and 8.4 Hz, 1H, H_3), 7.21–7.48 (m, 13H, Ar), 7.63 (d, $J=7.5$ Hz, 2H, Ar). Compound **29**: ^{1}H NMR (300 MHz): 2.48 (t, $J=9.8$ Hz, 1H, H_5), 3.21 (d, $J=13.1$ Hz, 1H, C*H*HPh), 3.50 (dd, $J=9.5$ and 7.5 Hz, 1H, $H_{5'}$), 3.66 (ddd, $J=6.5$, 7.5, 9.5 Hz, 1H, H_4), 4.01 (d, $J=13.1$ Hz, 1H, CH*H*Ph), 4.07 (d, $J=7.9$ Hz, 1H, H_2), 4.52 (dd, $J=6.5$ and 7.9 Hz, 1H, H_3), 7.21–7.60 (m, 15H, Ar).