Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1027–1031

Chemo- and regioselective reductive opening of azetidinium ions

François Couty,* Olivier David and François Durrat

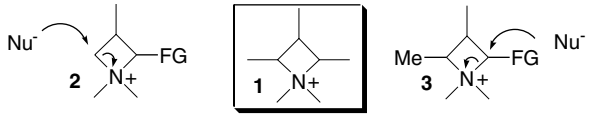
Institut LAVOISIER, UMR CNRS 8180, Université de Versailles, 45, avenue des Etats-Unis, 78035 Versailles Cédex, France

Received 26 October 2006; revised 23 November 2006; accepted 29 November 2006
Available online 22 December 2006

Abstract—Enantiomerically pure azetidinium trifluoromethanesulfonates were opened by various hydride reagents. $LiAlH_4$ and $NaBH_3CN$ reacted with a complete regioselectivity and the latter reagent also reacted in a chemoselective way, leaving unaffected an ester or a cyano moiety present in the substrate. This reaction provides 1,2-diamines, 1,2- and 1,4-amino alcohols or α-amino esters by combining proper choice of substrate and hydride reagent.

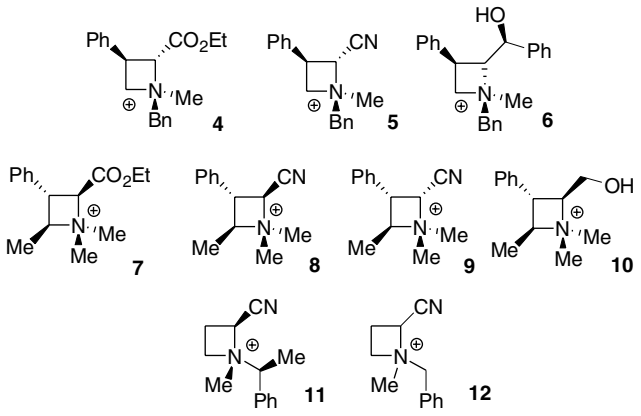
Azetidinium ions **1** are electrophilic synthons[1] able to react with a range of heteronucleophiles such as amines,[2] azide anions,[3] acetate anions,[3] thiols,[4] sodium thiosulfate[5] and phosphorous-containing nucleophiles,[6] leading to the corresponding opened product in a good yield. Recently, we have studied in details the regioselectivity of this nucleophilic opening starting with enantiopure functionalized azetidines such as **2** (FG = CN, CO_2Et) or **3**, and we have demonstrated that heteronucleophiles (azide and acetate anions or amines) preferably attack at the unsubstituted position in **2** and at the carbon bearing the functional group in type **3** substrates[3] (Scheme 1).

Considering the new methodologies available for the synthesis of functionalized azetidines in enantiomerically pure form,[7] and the efficiency in terms of yield and regioselectivity associated with the above reaction, it is surprising to note that only scarce examples of such nucleophilic opening involving carbon nucleophiles[8] or hydrides[9] have been reported so far. In this letter, in continuation with our interest in the reactivity of azetidinium ions,[10] we wish to report some examples involving the reductive opening of azetidinium ions, (i.e., $Nu^- = H^-$ in Scheme 1), a reaction that proceeds in a highly chemo- and regioselective manner giving rise to enantiopure functionalized amines.



Scheme 1. Azetidinium ions are regioselectively opened by heteronucleophiles.

In order to determine the scope of this reduction we first selected a series of azetidinium ions (trifluoromethanesulfonate salts) and these substrates can be divided into three categories. Compounds **4**–**6**, derived from (*R*)-phenyl glycinol are bearing a representative set of moieties at C-2 and are unsubstituted at C-4. On the contrary, compounds **7**–**10** prepared from (−)-ephedrine are substituted at C-4. Finally, compounds **11** and **12** (prepared respectively from (*S*)-phenylethylamine or benzylamine) are unsubstituted at C-3,4. All these substrates were prepared from the corresponding azetidine by



Scheme 2. Selected azetidinium trifluoromethanesulfonates for reductive opening.

Keywords: Azetidines; Azetidinium ions; Strain; Reduction.
* Corresponding author. Tel.: +33 139254455; fax: +33 139254452; e-mail: couty@chimie.uvsq.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.175

Table 1. Reaction of azetidinium ions with hydride donors

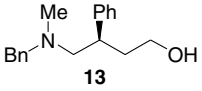
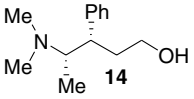
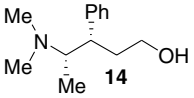
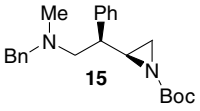
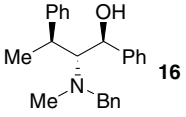
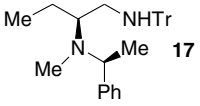
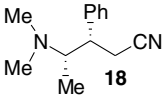
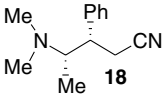
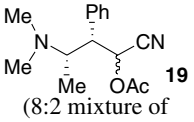
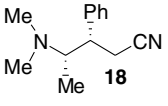
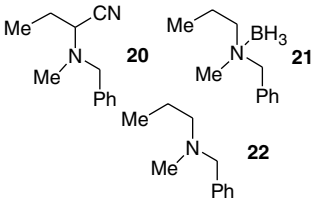
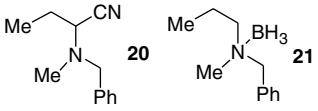
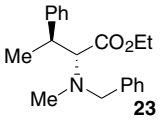
Entry	Substrate	Conditions	Product(s)	Yield[a] (%)
1	**4**	$LiAlH_4$, 2 equiv, THF, 0 °C, 1 h	 **13**	40
2	**7**	$LiAlH_4$, 2 equiv, THF, 0 °C, 1 h	 **14**	34
3	**10**	$LiAlH_4$, 2 equiv, THF, 0 °C, 1 h	 **14**	42
4	**5**	$LiAlH_4$, 2 equiv, THF, 0 °C, 1 h, then Boc_2O, AcOEt, reflux	 **15**	59
5	**6**	$LiAlH_4$, 2 equiv, THF, 0 °C, 1 h	 **16**	49
6	**9**	$LiAlH_4$, 2 equiv, THF, 0 °C, 1 h, then Boc_2O, AcOEt, reflux	—	[b]
7	**11**	$LiAlH_4$, 2 equiv, THF, 0 °C, 1 h, then TrCl, Et_3N	 **17**	82
8	**9**	$NaBH_4$, 2 equiv, THF, rt, 6 h	 **18**	39
9	**9**	$NaBH_3CN$, 5 equiv, THF, reflux, 48 h	 **18**	73
10	**9**	$NaBH(OAc)_3$, 5 equiv, THF, reflux, 24 h	 **19** (8:2 mixture of stereoisomers)	Quant.
11	**8**	$NaBH_3CN$, 5 equiv, THF, reflux, 48 h	 **18**	67
12	**12**	$NaBH_3CN$, 5 equiv, THF, reflux, 48 h	 **20** **21** **22**	63[c] (Ratio **20**:**21**:**22** = 1:4:3)

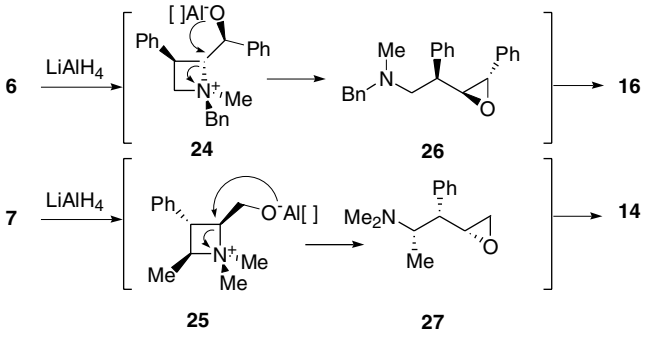
Table 1 (*continued*)

Entry	Substrate	Conditions	Product(s)	Yield[a] (%)
13	**12**	$NaBH_3CN$, 5 equiv, THF, reflux, 2 h	 **20** **21**	75[d] (Ratio **20**:**21** = 2:1)
14	**4**	$NaBH_3CN$, 5 equiv, THF, reflux, 48 h	 **23**	67

[a] Yield of isolated product.
[b] A complex mixture was obtained.
[c] Combined yields. Compounds **20**/**21** on one side and **21**/**22** on the other side were obtained as mixtures.
[d] These compounds were obtained as mixtures.

methylation with methyltrifluoromethanesulfonate[11] (Scheme 2).

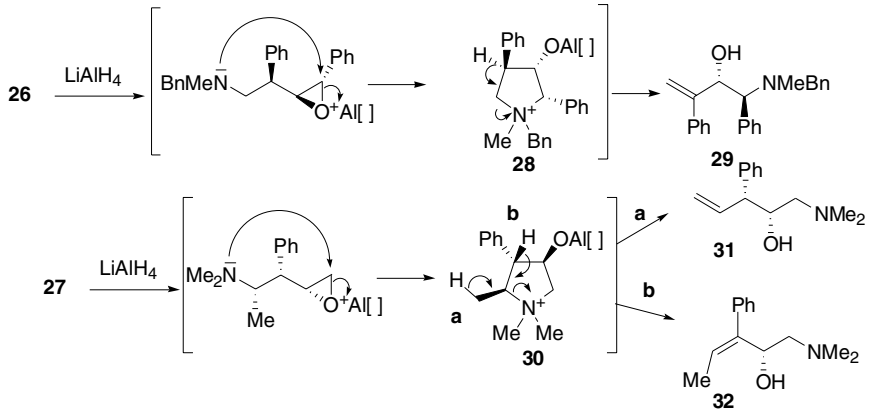
Two sources of hydride ions were then selected in order to test the reductive opening with these substrates. $LiAlH_4$ was first chosen since it has been previously described to open azetidinium[9] or aziridinium ions.[12] Then, $NaBH_4$[13] and related reagents $NaBH(OAc)_3$ and $NaBH_3CN$ were next tested in order to determine whether some chemoselectivity (i.e., reductive opening of the azetidinium ion without reduction of the ester or cyano moiety) could be achieved. The issues of these experiments are collected in Table 1.



Scheme 3. Reduction of azetidinium ions might proceed through an intermediate epoxide.

These results first bring one general comment: except entries 6, 12, 13 a single compound is obtained resulting from the regioselective opening of the four-membered ring by a hydride ion. This demonstrates that both reagents are able to perform the reductive opening of the azetidinium ring. The yields of reduced compounds are quite low (especially when $LiAlH_4$ is used, mostly because of the highly polar nature of the produced compounds) to fair. In all cases, no significant amount of regioisomer other than the one depicted in Table 1 could be detected in the crude reaction mixture. Whereas $LiAlH_4$ leads to a concomitant reduction of the adjacent moiety (ester or nitrile) at C-2, the use of $NaBH_4$ (or more efficiently $NaBH_3CN$: compare entries 8 and 9) permits to preserve these moieties in the substrate. However, $NaBH(OAc)_3$ induces an opening of the azetidinium by an acetate anion, as previously observed (entry 10).[3]

The regioselectivity of the opening depends both on the substitution pattern of the azetidinium ring and on the nature of the hydride reagent. Hence, when boron-derived reagents $NaBH_4$ and $NaBH_3CN$ are used, the regioselectivity follows the one previously observed with



Scheme 4. Reduction of γ-epoxy amines **26** and **27** produces alkenes.

heteronucleophiles, which is summarized in Scheme 1: azetidinium ions **9** and **8** substituted at C-4 are regioselectively opened at C-2 (entries 8, 9 and 11) and azetidiniums **12** or **4**, devoid of substituents at C-4 are also opened at this position (entries 12–14). It should be noticed that in the case of substrate **12**, this reduction is not totally chemoselective, since the produced aminonitrile **20** undergoes further reductive decyanation[14] by $NaBH_3CN$ to give the corresponding amine **22**, accompanied by its BH_3 complex **22**. This overreduction can however be minimized by running the reduction for 2 h instead of 48 h (entry 13).

When $LiAlH_4$ is used as the reducing agent, the regioselectivity is less simple to explain due to the concomitant reduction of the functional group linked to the azetidinium ring. Compounds **4**, **7** and **10** (entries 1–3) are all resulting from a regioselective opening at C-2 and a concomitant reduction of the ester moiety (for **4** and **7**). On the other hand, compounds **6** and **11** are exclusively opened at C-4 (entries 5 and 7) and in the latter case, the cyano moiety is reduced into a primary amine, to give (after tritylation), diamine **17** in a good yield. Although these regioselectivities are most often in agreement with the one summarized in Scheme 1, it is unexpected with substrate **4** that would logically be opened at C-4 considering the precedent outcomes. As a matter of fact the different issues of regioselectivity for substrates **4** (opening at C-2, entry 1) and **6** (opening at C-4, entry 5) are rather intriguing and suggest a strong directing effect of the produced aluminium alkoxide for the nucleophilic opening by the hydride. This directing effect is however radically different when the alkoxide is produced by the reduction of an ester (compound **4**) or from a secondary alcohol (compound **6**). The intervention of the reduced moiety at C-2 is further illustrated by entry 4. In this case, the aluminium amide resulting from the reduction of the nitrile by $LiAlH_4$ is nucleophilic enough to override the opening by an hydride ion, and aziridine **15** is isolated in a fair yield, after N-protection. The success of this opening probably depends on subtle parameters, because when this reaction was attempted with the closely related substrate **9**, then a complex mixture was obtained in a low yield (entry 6), suggesting the occurrence of various competitive pathways. Moreover, this nucleophilic opening does not compete with substrate **11** (entry 7).

The participation of aluminium alkoxide **24** or **25**, resulting from the treatment of azetidinium **6** and **7** by $LiAlH_4$ could indeed result from the formation of an intermediate epoxide **26** or **27** that would undergo further regioselective reduction to furnish **16** and **14** (Scheme 3) rather than a direct hydride opening of the azetidinium ring.

This hypothesis was discarded, running the following experiments: we subjected epoxides **26** and **27**[3] to $LiAlH_4$ reduction, but no traces of **16** or **14** were detected in the crude reaction mixture. Instead, alkene **29** could be isolated (49%) when starting from **26**, and alkenes **31** and **32** from **27** (16%). The formation of these alkenes can be explained by the formation of intermediate pyrrolidinium ions **28** or **30** that undergo β-elimination reactions. These results demonstrate that epoxides **26** and **27** are probably not produced in the course of the reduction of **6** and **7** by $LiAlH_4$ and that a direct opening of the aziridinium ion by the hydride ion is operating (Scheme 4).

In conclusion, we have shown that azetidinium ions can be reductively opened in a highly chemo- and regioselective way by hydride ions. By an appropriate choice of the substrate and hydride reagent, this reaction affords functionalized enantiomerically pure amines of high synthetic relevance, such as α-amino ester **23**, 1,2-diamine **17**, 1,2- and 1,4-amino alcohols **16** and **13**. Synthetic applications of this methodology are in progress in our group.

Acknowledgment

CNRS is acknowledged for the generous support.

Supplementary data

Experimental procedures and characterization for compounds **13**–**16**, **18** and **23**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.175.

References and notes

1. For a review, see: Couty, F.; Durrat, F.; Evano, G. In *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, 2005; Vol. 9, pp 186–210.
2. (a) Bernstein, S.; Heller, M. *J. Org. Chem.* **1971**, *36*, 1386–1389; (b) Szmuszkovicz, J.; Kane, M. P. *J. Org. Chem.* **1981**, *46*, 3728–3730.
3. Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar, S.; Marrot, J.; Vargas-Sanchez, M. *Eur. J. Org. Chem.* **2006**, 3479–3490.
4. Hata, Y.; Watanabe, M. *Tetrahedron* **1987**, *43*, 3881–3888.
5. Jeziorna, A.; Heliński, J.; Krawiecka, B. *Synthesis* **2003**, *2*, 288–294.
6. (a) Heliński, J.; Skrzypczyński, Z.; Michalski, J. *Tetrahedron Lett.* **1995**, *36*, 9201–9204; (b) Bakalarz, A.; Heliński, J.; Krawiecka, B.; Michalski, J.; Potrzebowski, M. J. *Tetrahedron* **1999**, *55*, 12211–12226; (c) Bakalarz-Jeziorna, A.; Heliński, J.; Krawiecka, B. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1086–1090; (d) Jeziorna, A.; Heliński, J.; Krawiecka, B. *Tetrahedron Lett.* **2003**, *44*, 3239–3243; (e) Krawiecka, B.; Jeziorna, A. *Tetrahedron Lett.* **2005**, *46*, 4381–4384.
7. For a review, see: Couty, F.; Evano, G.; Prim, D. *Mini Reviews in Organic Chemistry* **2004**, *1*, 133–148.
8. For some isolated example, see: Refs. 6a,c (opening with phosphorous-stabilized C-nucleophiles). See also: Wills, M. T.; Wills, I. E.; Von Dollen, L.; Butler, B. L.; Porter, J.; Anderson, A. G. *J. Org. Chem.* **1980**, *45*, 2489–2498 (opening with BuLi).
9. For a single example, involving LAH as hydride source, see: Kikuchi, T.; Uyeo, S. *Chem. Pharm. Bull.* **1967**, *15*, 549–570.

10. Couty, F.; Durrat, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2006**, 4214–4223.
11. For the preparation of these substrates, see: Ref. 3 and references cited therein.
12. See for examples: (a) Bernhard, H. O.; Snieckus, V. *Tetrahedron* **1971**, *27*, 2091–2100; (b) Malpass, J. R.; White, R. *J. Org. Chem.* **2004**, *69*, 5328–5344.
13. For an example of reductive opening of tetrahydroisoquinolinium methiodide induced by $NaBH_4$, see: Hara, H.; Kaneko, K.; Endoh, M.; Uchida, H.; Hoshino, O. *Tetrahedron* **1995**, *37*, 10189–10204.
14. For an example of reductive decyanation of an amino nitrile by $NaBH_4$, see: Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.