# Regioselective Nucleophilic Opening of Azetidinium Ions

François Couty,* François Durrat, Gwilherm Evano

SIRCOB, UMR 8086, Université de Versailles, 45, Avenue des Etats-Unis, 78035, Versailles Cedex, France
E-mail: couty@chimie.uvsq.fr

*Received 14 April 2005*

**Abstract:** Azetidinium ions bearing different substitution patterns were reacted with nitrogen nucleophiles (sodium azide and benzylamine) and oxygenated nucleophiles (sodium acetate and alkoxides). High regioselectivity of nucleophilic opening was observed in both cases: the nucleophile reacting on the unsubstituted carbon in the case of α-substituted azetidinium salts and on the carbon bearing an ester or cyano moiety in the case of α,α′-substituted azetidinium salts.

**Key words:** azetidiniums, nitrogen, heterocycles, ring opening, asymmetric synthesis

The reactivity of small cycles towards nucleophilic opening is a cornerstone of organic synthesis. Although the ring-opening of aziridines[1] and aziridinium ions[2] are well established synthetic tools, this reaction with their higher homologues azetidines and azetidinium ions has been under-utilized. In this area, after the pioneering work of Gaertner[3] and Leonard[4] in the early sixties showing that these strained ammonium ions can react with a range of nucleophiles leading to ring opening, Illuminati et al.[5] clearly brought into light through an elegant study the particular reactivity of these cyclic ammoniums compared to their higher homologues: in these ions, the ring strain strongly favors the substitution reaction versus the classical Hofmann elimination. Notwithstanding, the use in synthesis of these original building blocks has not been developed and only few and isolated examples report the use of these ammonium ions in synthesis.[6] This is most probably due to the lack of easy access to these heterocycles, particularly in enantiomerically pure form. In addition, issues with regioselectivity of the nucleophilic opening of α-substituted or α,α′-disubstituted azetidinium ions have seldom been addressed (Figure 1): scarce examples report the regioselective opening with a carboxylate,[6m] an amine[6f] or a phenol[6d] at the unsubstituted carbon ($R^1$ = H, path a), or the regioselective opening at a benzylic position ($R^1$ = H, $R^3$ = Ph, path b),[6d] but no systematic study has been conducted so far.

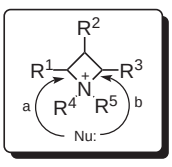



**Figure 1**

*SYNLETT* 2005, No. 11, pp 1666–1670
Advanced online publication: 14.06.2005
DOI: 10.1055/s-2005-871537; Art ID: D08505ST


We recently reported a very efficient access to enantiomerically pure functionalized azetidines, using β-amino alcohols as starting materials.[7] This allowed us to prepare a range of azetidines bearing different substitution patterns and permitted us to undertake different studies of their reactivity.[8] We wish to present in this Letter our preliminary results concerning the nucleophilic opening of a series of azetidinium ions which demonstrates that high regioselectivity can be attained in such processes, therefore considerably enhancing their synthetic usefulness.

The azetidinium triflate salts **1**–**10** necessary to conduct this study were prepared by alkylation of the corresponding azetidine with methyltrifluoromethanesulfonate (Figure 2). The yield of this reaction was uniformly high and this alkylation proceeded with high stereoselectivity in the case of *N*-benzyl azetidines.[8c] The azetidine precursors are derived from either (1*R*,2*S*)-ephedrine or (*R*)-phenyl glycinol and have been described earlier,[7,8] expect the precursor of salt **10**. These azetidinium ions can be divided into two classes: α-substituted compounds, derived from (*R*)-phenylglycinol (**1**–**5**) and bearing different moieties at C-2, and α,α′-disubstituted azetidiniums (**6**–**10**), bearing different moieties at C-2, and a methyl substituent at C-4. The latter compounds are derived from (1*R*,2*S*)-ephedrine, or (1*R*,2*S*)-norephedrine (for **10**).

With a set of enantiomerically pure azetidinium salts showing various α,α′-substitution patterns in hand, we first examined the reactivity of these compounds towards nitrogen nucleophiles such as sodium azide and benzylamine. Thus, compounds **1**, **2**, **4**–**8** were reacted in DMF at room temperature with an excess of sodium azide (5 equiv) and compounds **1** and **6** were reacted with benzylamine. The structure of the obtained adducts is detailed hereafter (Table 1).

Important trends concerning the opening of these aziridinium ions can be outlined through these experiments. First, these reactions occur in a stereospecific way through an exclusive $S_N2$ pathway, as shown by the diastereoisomeric homogeneity of the ring-opened products. The yields are excellent in most cases and no competitive elimination was detected as a side reaction. The regioselectivity of the opening is high and strongly depends on the substitution pattern of the ring: while attack of the nucleophile occurs on the unsubstituted side in the case of phenyl glycinol derived azetidinium ions (entries 1, 2, 7), this regioselectivity is reversed in the case of disubstituted substrates derived from ephedrine. In those cases, the nucleophile attacks the carbon bearing the CN or $CO_2Et$ moiety (entries 4–6, 8). The substrate **5**, bearing an alkene substituent, is

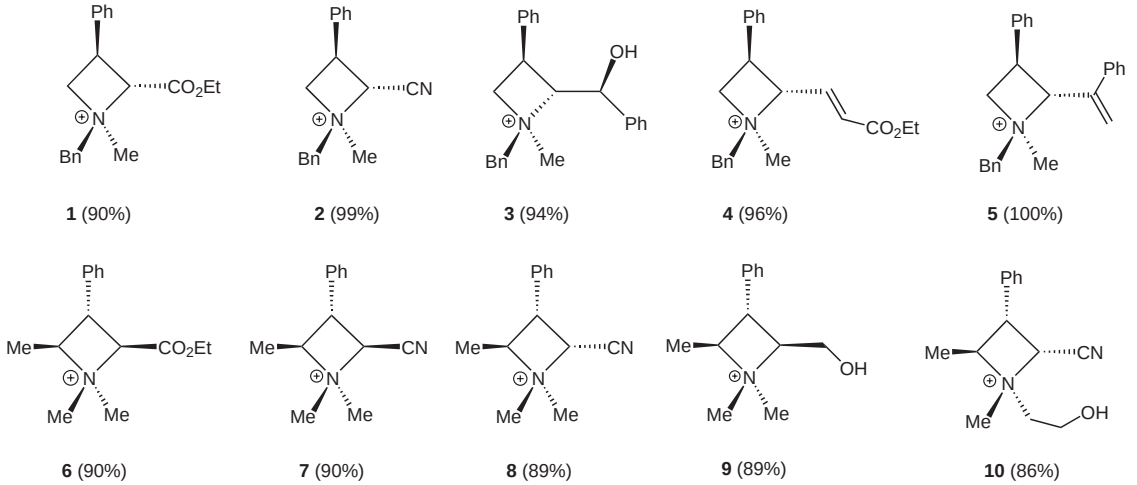
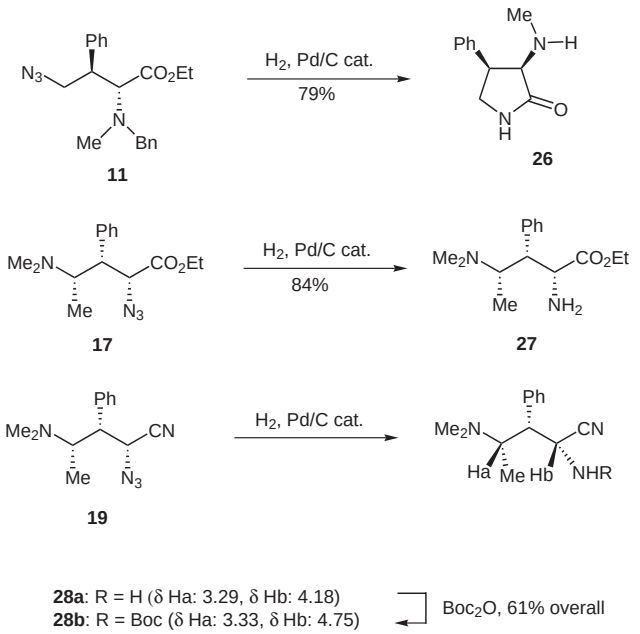



**Figure 2**

a special case. With this compound, exclusive $S_N2'$ reaction was observed, and yielded the trisubstituted alkene **15** as a mixture of isomers. This reaction gave a more complex mixture in case of salt **4**.

Regioselectivity of these openings was confirmed through chemical transformation (reduction of the azido group) on **11**, **17** and **19**. Upon reduction of **11**, lactam **26** was obtained after spontaneous lactamization and N-debenzylation. In contrast, the same reaction carried out on **17** and **19** yield α-aminoester or α-aminonitrile, respectively, the latter being protected as a carbamate (Scheme 1). Careful analysis of $^1$H NMR spectra (relevant chemical shifts are depicted in Scheme 1) unambiguously allowed for identification of the regioisomer formed during these reactions.



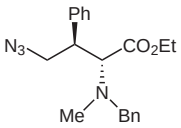
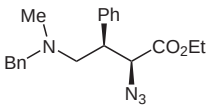
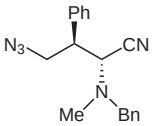
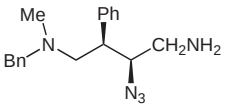
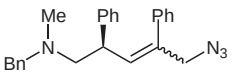
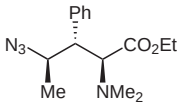
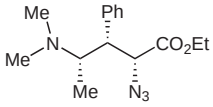
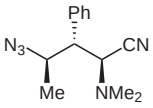
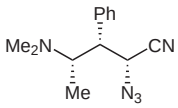
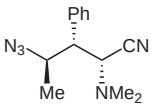
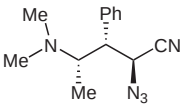
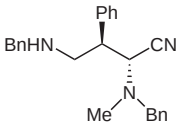
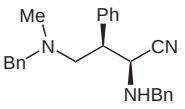
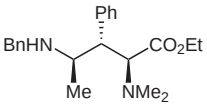
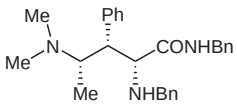

**Scheme 1**

We studied next the reaction of oxygen nucleophiles, and sodium acetate as well as benzyl alkoxide were selected for this study as external nucleophiles. We also experimented with an alkoxide as an internal nucleophile, starting from azetidinium ions **3**, **9** and **10**. The results are summarized in Table 2.

The same trend of regioselectivity is observed: the acetate anion exclusively reacts at the unsubstituted carbon (entry 1), with a regioselectivity even higher than in the previous case involving an azide anion (compare entry 2 in Table 1 and entry 1 in Table 2). In the case of a disubstituted substrate, the acetate anion regioselectively attacks the carbon bearing the ester, but, with this less reactive nucleophile, the yield is lower than with an azide anion and we had to switch to the more nucleophilic cesium salt (entries 3, 4) to induce the opening. However, even under these conditions, the yield of different trials was not consistent. Benzyl alkoxide was inactive in an intermolecular reaction (entry 2), but alkoxides generated with the aim of inducing intramolecular ring-opening proceeded well and gave the corresponding unstable epoxides **33** and **34** (entries 5, 6) if the alkoxide was generated from an hydroxymethyl substituent at C-2. The degradation observed in entry 7, involving an hydroxylated side chain branched on the nitrogen of the azetidine ring can be explained by the requirement of a difficult 5-*endo-tet* process for the intramolecular ring opening.[9]

Although the general trends are well delineated by this set of experiments, i.e., regioselective attack on the unsubstituted site and regioselective attack on the site substituted by an electron-withdrawing group in case of α,α′-disubstituted salts, more subtle influences on the efficiency of this reaction need further comments. This is the case with entries 5 and 6 in Table 1, highlighting a strong influence of the relative stereochemistry of the substituents on the substrate. The very efficient reaction of the 2,3-*cis* azetidinium salt **8**, compared to the 2,3-*trans* isomer **7**, giving the corresponding opened product **19** in only 27% yield in a reproducible way, can be explained by considering the

**Table 1** Reaction of Azetidinium Ions with Nitrogen Nucleophiles

| Entry | Substrate | Conditions | Products | | | Yield (%)[a] |
|---|---|---|---|---|---|---|
| | | | C-4 Attack | | C-2 Attack | |
| 1 | **1** | $NaN_3$ (5 equiv), DMF |  **11** | + 93:7 |  **12** | Quant. |
| 2 | **2** | $NaN_3$ (5 equiv), DMF |  **13** | + 82:12 |  **14** | Quant. |
| 3 | **5** | $NaN_3$ (5 equiv), DMF |  **15** 6:4 isomeric mixture | | | 88 |
| 4 | **6** | $NaN_3$ (5 equiv), DMF |  **16** | + 14:86 |  **17** | Quant. |
| 5 | **7** | $NaN_3$ (5 equiv), DMF |  **18** | + >2:98 |  **19** | 27 |
| 6 | **8** | $NaN_3$ (5 equiv), DMF |  **20** | + >2:98 |  **21** | Quant. |
| 7 | **2** | Benzylamine (5 equiv), $CH_2Cl_2$ |  **22** | + >98:2 |  **23** | 89 |
| 8 | **6** | Benzylamine (5 equiv), $CH_2Cl_2$ |  **24** | + >2:98 |  **25** | 68 |

[a] Yield of pure isolated product.

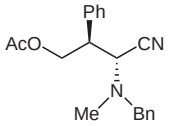
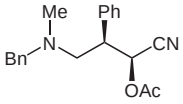
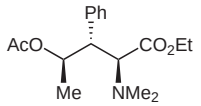
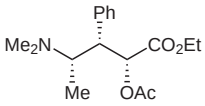
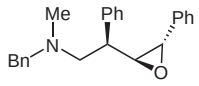
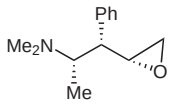
conformation of the involved substrate. Figure 3 illustrates the conformational equilibrium in diasteroisomeric salts **7** and **8**. In compound **7**, the equilibrium should strongly favor conformer **7a**, in which all substituents are in *pseudo*-equatorial positions. However, this conformer appears to be less reactive towards nucleophilic opening, due to steric shielding of the aromatic ring in the trajectory of the nucleophile. In this case, it appears that the strongly disfavored conformer **7b**, presenting severe 1,3-diaxial interactions between the substituents, is the reactive one. If the diastereomeric salt **8** is now considered, conformer **8b**, which is also the reactive conformer for the same reasons, is now more stable due to the equatorial position of the cyano moiety. In this case, the kinetics of the reaction should be less hampered by an unfavorable pre-conformational equilibrium.

In conclusion, we have shown that high regioselectivities of nucleophilic ring-opening can be obtained with these original and readily accessible electrophilic synthons.[10] Generalization with other nucleophiles and synthetic applications of this methodology are under investigation.

## Acknowledgment

The CNRS is acknowledged for generous financial support (ATIP jeune équipe).

**Table 2** Reaction of Azetidinium Ions with Oxygenated Nucleophiles

| Entry | Substrate | Conditions | Products | | | Yield (%)[a] |
|---|---|---|---|---|---|---|
| | | | C-4 Attack | | C-2 Attack | |
| 1 | **2** | AcONa (5 equiv), DMF |  **29** | + >98:2 |  **30** | Quant. |
| 2 | **2** | $PhCH_2ONa$ (5 equiv), DMF | | – | | Decomposition |
| 3 | **6** | AcONa (5 equiv), DMF | | – | | Decomposition |
| 4 | **6** | AcOCs (5 equiv), DMF |  **31** | + >2:98 |  **32** | 21–67 |
| 5 | **3** | KHMDS (1.2 equiv), THF, –78 °C to r.t. |  **33** | | | –[b] |
| 6 | **9** | KHMDS (1.2 equiv), THF, –78 °C to r.t. |  **34** | | | –[b] |
| 7 | **10** | KHMDS (1.2 equiv), THF, –78 °C to r.t. | | – | | Decomposition |

[a] Yield of pure isolated product.
[b] These epoxides were not purified since they were unstable on silica gel. Exclusive formation of the epoxide was observed in the crude reaction mixture.

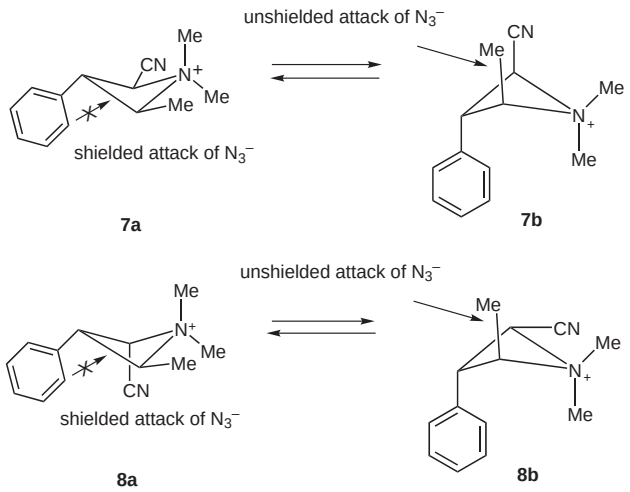



**Figure 3**

## References


(1) Hu, E. X. *Tetrahedron* **2004**, *60*, 2701.
(2) For recent examples, see: (a) Mulvihill, M. J.; Cesario, C.; Smith, V.; Beck, P.; Nigro, A. *J. Org. Chem.* **2004**, *69*, 5124. (b) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555; and references cited therein. (c) Rowlands, G. J.; Barnes, W. K. *Tetrahedron Lett.* **2004**, *45*, 5347. (d) Periasamy, M.; Seenivasaperumal, M.; Dharma Rao, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3847.
(3) (a) Gaertner, V. R. *Tetrahedron Lett.* **1967**, *4*, 343. (b) Gaertner, V. R. *J. Org. Chem.* **1968**, *33*, 523.
(4) Leonard, N. J.; Durand, D. A. *J. Org. Chem.* **1968**, *33*, 1322.
(5) Cospito, G.; Illuminati, G.; Lilloci, C.; Petride, H. *J. Org. Chem.* **1981**, *46*, 2944.
(6) (a) O'Brien, P.; Phillips, D. W.; Towers, T. D. *Tetrahedron Lett.* **2002**, *43*, 7333. (b) Concellón, J. M.; Riego, E.; Bernard, P. L. *Org. Lett.* **2002**, *4*, 1303. (c) Concellón, J. M.; Bernard, P. L.; Pérez-Andrés, J. A. *Tetrahedron Lett.* **2000**, *41*, 1231. (d) Higgins, R. H.; Faircloth, W. J.; Baughman, R. G.; Eaton, Q. L. *J. Org. Chem.* **1994**, *59*, 2172. (e) Guidicelli, M.-B.; Picq, D.; Anker, D. *Tetrahedron Lett.* **1992**, *48*, 6033. (f) Kane, M. P.; Szmuszkovicz, J. *J. Org. Chem.* **1981**, *46*, 3728. (g) Heller, M.; Bernstein, S. *J. Org. Chem.* **1971**, *36*, 1386. (h) Jeziorna, A.; Heliński, J.; Krawiecka, B. *Synthesis* **2003**, 288. (i) Jeziorna-Bakalarz, A.; Heliński, J.; Krawiecka, B. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1086. (j) Heliński, J.; Skrzypczynski, Z.; Michalski, J. *Tetrahedron Lett.* **1995**, *36*, 9201. (k) Jeziorna, A.; Heliński, J.; Krawiecka, B. *Tetrahedron Lett.* **2003**, *44*, 3239. (l) Bakalarz, A.; Heliński, J.; Krawiecka, B.; Michalski, J.; Potrzebowski, M. J. *Tetrahedron* **1999**, *55*, 12211. (m) Sudo, A.; Iitaka, Y.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1912.

(7) (a) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297. (b) Carlin-Sinclair, A.; Couty, F.; Rabasso, N. *Synlett* **2003**, 726. (c) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2002**, *43*, 4633.
(8) (a) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209. (b) Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Eur. J. Org. Chem.* **2004**, 3893. (c) Couty, F.; Durrat, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2004**, *45*, 7525.
(9) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846.
(10) All new compounds were characterized by $^1$H NMR, $^{13}$C NMR spectroscopy, mass spectra analysis, and for most relevant compounds, by elementary analysis. Typical procedure for the preparation of an azetidinium salt is given below:
To a solution of the azetidine (2.0 mmol) in $CH_2Cl_2$ (10 mL), cooled at 0 °C, was added dropwise methyltrifluoromethanesulfonate (0.45 mL, 4 mmol). The reaction mixture was stirred for 1 h at r.t., and the solvent was evaporated under reduced pressure. The crude salt was washed thoroughly with small quantities of dry $Et_2O$, and dried under vacuum.
Compound **2**: yield 99%; $[\alpha]_D^{25}$ –34 (*c* 0.5, acetone); mp 116 °C. MS (ESI Pos): *m/z* = 263.2 $[M - OTf]^+$. $^1$H NMR [300 MHz, $(CD_3)_2CO$]: δ = 7.89–7.82 (m, 2 H, Ph), 7.67–7.42 (m, 8 H, Ph), 6.34 (d, *J* = 9.3 Hz, 1 H, H-2), 5.31–5.14 (m, 4 H, H-3, H-4, H-6, H-6′), 4.91–4.81 (m, 1 H, H-4′), 3.70 (s, 3 H, H-5) ppm. $^{13}$C NMR [75 MHz, $(CD_3)_2CO$]: δ = 133.9 ($C_{ipso}$ Ph), 133.1, 131.9, 130.5, 129.9, 129.8, 128.4 (CH Ph), 128.3 ($C_{ipso}$ Ph), 112.3 (CN), 69.3, 69.2 (C-4, C-6), 65.3 (C-2), 46.9 (C-5), 39.6 (C-3) ppm. Anal. Calcd for $C_{19}H_{19}F_3N_2O_3S$: C, 55.33; H, 4.64; N, 6.79. Found: C, 55.23; H, 4.66; N, 6.74.
Typical procedure for the reaction of an azetidinium salt with sodium azide is given below:
To a solution of azetidinium triflate (2.0 mmol) in DMF (10 mL) was added sodium azide (650 mg, 10.0 mmol) and the suspension was stirred overnight at r.t. Partition between $Et_2O$ and $H_2O$ was followed by usual work-up. The crude residue was examined by NMR, and the major compound was purified by flash chromatography.
Compound **11**: purified by flash chromatography ($Et_2O$–cyclohexane, 10:90, 20:80, 40:60); yield 93%; clear oil; $R_f$ = 0.61 ($Et_2O$–petroleum ether, 3:7); $[\alpha]_D^{25}$ –90 (*c* 0.75, $CH_2Cl_2$). MS (IC $NH_3$ Pos): *m/z* = 353 $[M + H]^+$. $^1$H NMR [300 MHz, $(CD_3)_2CO$]: δ = 7.38–7.19 (m, 10 H, Ph), 4.67 (d, *J* = 4.2 Hz, 1 H, H-2), 4.17 (q, *J* = 7.1 Hz, 2 H, H-7), 3.66 (d, *J* = 13.1 Hz, 1 H, H-6), 3.54–3.47 (m, 2 H, H-3, H-6′), 3.01 (t, *J* = 11.9 Hz, 1 H, H-4), 2.47 (dd, *J* = 4.2, 12.3 Hz, 1 H, H-4′), 2.28 (s, 3 H, H-5), 1.22 (t, *J* = 7.1 Hz, 3 H, H-8) ppm. $^{13}$C NMR [75 MHz, $(CD_3)_2CO$]: δ = 170.2 (C-1), 138.9, 138.1 ($C_{ipso}$ Ph), 129.2, 128.9, 128.5, 128.4, 127.6, 127.3 (CH Ph), 64.3 (C-2), 62.9 (C-6), 61.7 (C-7), 59.3 (C-4), 45.2 (C-3), 42.5 (C-5), 14.2 (C-8) ppm. Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.03; H, 6.91; N, 15.80.