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# Opening of azetidinium ions with C-nucleophiles

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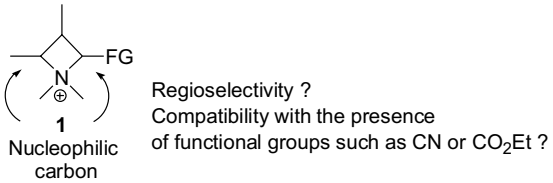
**Abstract**—The nucleophilic opening of functionalized azetidinium ions by C-nucleophiles was screened. Malonate and cyanide anions reacted in a highly regio- and chemoselective way leading to functionalized pure amines. The success of this reaction was found to be highly dependent on the basicity of the involved nucleophiles and the competitive reactions induced by too basic reagents were identified.


The versatility of aziridines as significant building blocks has been extensively demonstrated.[1] Not only are these strained nitrogen heterocycles able to react with a wide range of heteronucleophiles but they can also be opened by C-nucleophiles such as Grignard reagents,[2] enolates,[3] enamines[4] and alkenes[5] leading to the corresponding opened product with concomitant C–C bond formation, thus opening avenues for the synthesis of nitrogen-containing compounds. In contrast, their higher homologues, the azetidines, including an additional carbon atom, have been much less studied as electrophilic synthons. Two main reasons can explain this point: first, due to the lower strain of the four-membered ring compared to the three-membered ring, nucleophilic opening requires strong activation of the intracyclic nitrogen atom. Secondly, efficient synthetic access to these heterocycles, particularly in enantiomerically pure form, has not been developed to the same extent as for aziridines.[6]

In our continuing interest in the chemistry of azetidines and azetidinium ions, we have recently studied in detail the regioselectivity of the nucleophilic opening of substituted azetidinium ions **1** bearing functional groups (FG: CN, $CO_2Et$) with various heteronucleophiles such as amines, azide anions and acetate anions.[7] In these strained ammoniums, the activation of the nitrogen atom is sufficient to allow smooth opening by an external nucleophile in a regioselective manner. We also demonstrated that these valuable building blocks could be reductively opened in a regio- and chemoselective manner by different sources of hydride.[8] In continuation, considering that the formation of a C–C bond is of utmost importance in organic synthesis, we decided to explore the possibility of the nucleophilic opening of such azetidinium ions by a nucleophilic carbon atom (Scheme 1) since this reaction would give access to original amino acids. Such nucleophilic openings have been very scarcely reported, and the isolated examples in the literature concern carbanions stabilized by adjacent phosphorous moieties[9] or butyllithium.[10] In addition, the question of regioselectivity or compatibility with other functional groups present on the azetidinium ring has never been addressed, to our knowledge.

The intrinsic problem associated with the above reaction is the basicity of the carbon nucleophile, that can lead to a competitive abstraction of the proton on the carbon of the azetidinium bearing the functional group, thus leading to a nitrogen ylide. Such ylides have been recently studied by us.[11] To address this problem, we first selected azetidinium trifluoromethanesulfonate **2**,[11] bearing a nitrile moiety, and we reacted this compound




**Scheme 1.** Can functionalized azetidinium ions be opened by C-nucleophiles?

*Keywords*: Azetidines; Azetidinium ions; Strain.
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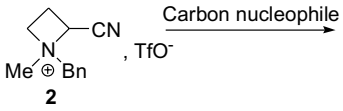
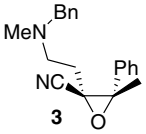
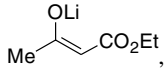
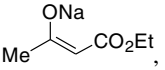
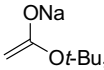
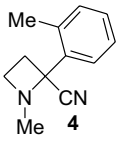
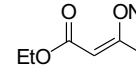
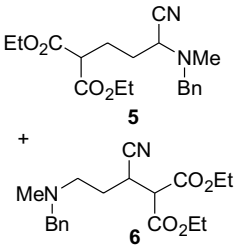
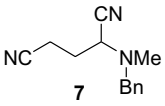
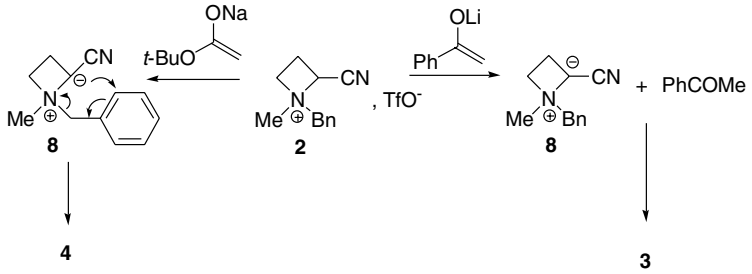
**Table 1.** Reaction of azetidinium ion **2** with C-nucleophiles



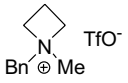
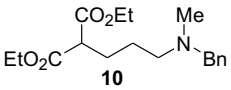
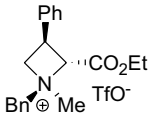
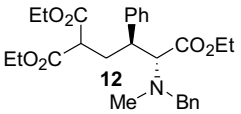
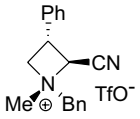
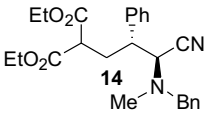
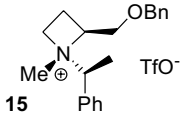
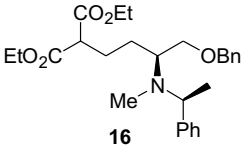
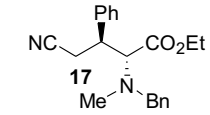
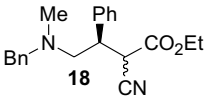
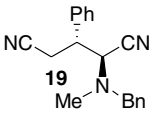
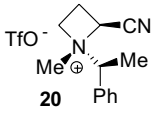
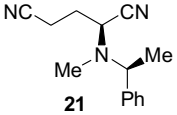
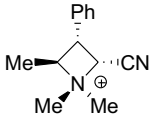
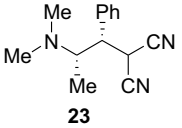
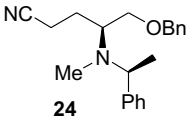

| Entry | Conditions | Product(s) | Yield[a] (%) |
|---|---|---|---|
| 1 |  1.5 eq. Generated from LDA, -40 °C to rt, THF |  **3** | 32 |
| 2 |  1.5 eq. Generated from LiHMDS, -40 °C 2 h, THF | **3** | 44 |
| 3 |  , 1.5 eq. Generated from LiHMDS rt, 1 h, THF | [b] | — |
| 4 |  , 1.5 eq. Generated from NaH DMF, 0 °C, 1 h | [b] | — |
| 5 |  , 1.5 eq. Generated from NaHMDS -20 °C to rt, 12 h, THF | [b] | — |
| 6 |  , 3 eq. Generated from NaHMDS -20 °C to rt, 1 h, THF/DMF |  **4** | 31 |
| 7 |  , 2 eq. Generated from NaHMDS rt, 15 h, THF |  **5** + **6** | 95[c] (ratio **5**:**6** = 75:25) |
| 8 | KCN, 3 equiv DMF, 1 h, rt |  **7** | 99 |

[a] Yield of isolated product.
[b] A complex mixture was obtained.
[c] Combined yields.




**Scheme 2.** Ketone and ester enolates deprotonate azetidinium ion **2**.

**Table 2.** Reaction of azetidinium trifluoromethanesulfonate salts with the enolate derived from diethyl malonate[a] and KCN[b]

| Entry | Substrate | Product(s) | Yield[c] (%) |
|---|---|---|---|
| *Reactions with sodium diethylmalonate* | | | |
| 1 |  **9** |  **10** | 57 |
| 2 |  **11** |  **12** | 41 |
| 3 |  **13** |  **14** | 90 |
| 4 |  **15** |  **16** | 69 |
| *Reactions with potassium cyanide* | | | |
| 5 | **11** |  +  **18** | 98 (ratio **17**:**18** = 43:57) |
| 6 | **13** |  **19** | 88 |
| 7 |  **20** |  **21** | 66[d] |
| 8 |  **22** |  **23** | 91[e] |
| 9 | **15** |  **24** | 78 |

Conditions:

[a] Sodium salt of diethyl malonate (generated from NaHMDS), 2 equiv, THF, rt, 15 h.

[b] KCN, 3 equiv, DMF, 0 °C, 1 h.

[c] Yield of isolated product.

[d] Contaminated by 12% of an inseparable regioisomer.

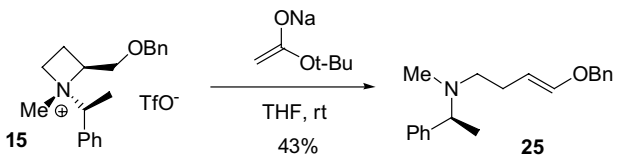
[e] Crude yield. This compound evolves to a zwitterion.

with a series of carbon nucleophiles. The results of these experiments are collected in Table 1.

This first set of experiments demonstrated that this reaction is indeed possible but seems to be restricted to a narrow range of C-nucleophiles. In fact, only the sodium enolate derived from diethyl malonate and the cyanide anion efficiently opened the azetidinium compound (entries 7 and 8). In the first case, the reaction smoothly occurred in THF at rt, with a fair regioselectivity in favour of C-4 attack, while the opening with cyanide anion was run in DMF and gave **7** with total regioselectivity and almost quantitative yield. In contrast, the sodium enolate derived from ethylacetoacetate, *tert*-butyl acetate or acetophenone gave complex mixtures (entries 1–6) from which epoxide **3** (entries 1 and 2) or azetidine **4** (entry 6) could be isolated. The formation of these products unambiguously proves that deprotonation of the azetidinium salt by the reacting enolate occurs with these nucleophiles. As a matter of fact, epoxide **3** results from a reaction between azetidinium ylide **8** derived from **2** and acetophenone, as previously described,[12] and azetidine **4** results from a Sommelet–Hauser rearrangement of the intermediate ylide **8**,[13] as depicted in Scheme 2.

Having established that sodium diethylmalonate and potassium cyanide are suitable reagents to achieve our goal, we next examined the scope of this reaction with a range of different azetidinium ions. These results are gathered in Table 2.

Except for azetidinium ion **11** reacting with cyanide anion (entry 5), all the substrates studied here were opened with a total to fair regioselectivity. This regioselectivity is in accordance with our previous observations involving heteronucleophiles,[7] that is, regioselective opening at C-4 with substrates free of substituent at this position (entries 2–4, 6–7 and 9) and opening at C-2 with substrate **22**, bearing a methyl group at C-4 (entry 8). The low regioselectivity observed with **11** reacting with cyanide ion (entry 5) was previously observed with acetate anion as nucleophile.[7] This substrate reacted however with sodiomalonate in a highly regioselective manner (entry 2), as proven by examination of the $^1$H NMR of the crude reaction mixture, thus highlighting the crucial importance of the nucleophile involved in the reaction. Importantly, in both experiments involving cyanide or malonate anion, no epimerization at the stereocentre of the azetidinium bearing the ester or the cyano moiety could be observed. This demonstrates that, under such conditions, these nucleophiles are either unable to deprotonate the azetidinium salts or that the rate of nucleophilic opening is much higher than deprotonation. Another experiment demonstrates the crucial importance of the p$K_a$ value of the involved C-nucleophile: the treatment of azetidinium ion **15** with the sodium enolate of *t*-butyl acetate gives enol ether **25** as the major product. This azetidinium substrate, unable to produce an ylide, undergoes a Hofmann elimination with this basic nucleophile (Scheme 3).




**Scheme 3.** Hofmann elimination competes with nucleophilic opening.

Another parameter governing the efficiency of this reaction is the degree of substitution of the azetidine ring. This parameter can influence the regioselectivity of the reaction (compare the exclusive C-4 attack by the cyanide anion in substrates **2** and **13** and the slight drop of regioselectivity with substrate **20**), or even the reactivity (substrate **22** did not react with malonate anion, leading to decomposition products after protracted reaction time). These hardly predictable results may reflect subtle steric interactions generated during the $S_N2$ process.

In conclusion, we have shown that azetidinium ions can be opened in a highly regioselective way by malonate and cyanide anions, and we have delineated the crucial parameters for the success of this reaction. Synthetic applications of this methodology are in progress in our group.

## Acknowledgement

CNRS is acknowledged for generous support.

## Supplementary data

Supplementary data (experimental procedures and characterization of compounds resulting from the nucleophilic opening of azetidinium ions by cyanide and malonate anions) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.105.

## References and notes

1. Hu, E. X. *Tetrahedron* **2004**, *60*, 2701.
2. Nenajdenko, V. G.; Karpov, A. S.; Balenkova, E. S. *Tetrahedron: Asymmetry* **2001**, *12*, 2517.
3. Vicario, J. L.; Badia, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801.
4. Nishikawa, T.; Ishikawa, M.; Wade, K.; Isobe, M. *Synlett* **2001**, 945.
5. Lapinsky, D. J.; Bergmeier, S. C. *Tetrahedron* **2002**, *58*, 7109.
6. For a review, see: Couty, F.; Evano, G.; Prim, D. *Mini Rev. Org. Chem.* **2004**, *1*, 133.
7. Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar, S.; Marrot, J.; Vargas-Sanchez, M. *Eur. J. Org. Chem.* **2006**, 3479.
8. Couty, F.; David, O.; Durrat, F. *Tetrahedron Lett.* **2007**, *48*, 1027.
9. (a) Heliński, J.; Skrzypczyński, Z.; Michalski, J. *Tetrahedron Lett.* **1995**, *36*, 9201; (b) Bakalarz-Jeziorna, A.; Heliński, J.; Krawiecka, B. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1086.

10. Wills, M. T.; Wills, I. E.; Von Dollen, L.; Butler, B. L.; Porter, J.; Anderson, A. G. *J. Org. Chem.* **1980**, *45*, 2489.
11. Couty, F.; David, O.; Larmanjat, B.; Marrot, J. *J. Org. Chem.* **2007**, *72*, 1058.
12. Alex, A.; Larmanjat, B.; Marrot, J.; Couty, F.; David, O. *Chem. Commun.* **2007**, *24*, 2500.
13. For an example of Sommelet–Hauser rearrangement involving an azetidinium ion, see: Anderson, A. G.; Wills, M. T. *J. Org. Chem.* **1968**, *33*, 3046.