Rearrangement of 2-Hydroxyalkylazetidines into 3-Fluoropyrrolidines

Bruno Drouillat, François Couty,* Olivier David, Gwilherm Evano, Jérome Marrot

UniverSud Paris, Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles Saint Quentin en Yvelines, 45 avenue des Etats-Unis, 78035 Versailles Cedex, France
Fax +33(1)39254452; E-mail: couty@chimie.uvsq.fr

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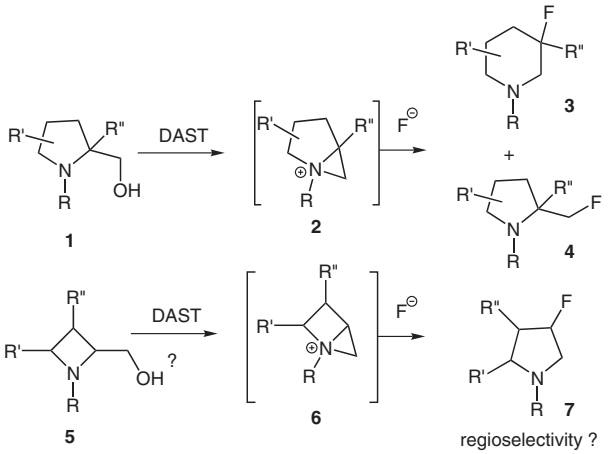
Abstract: Upon treatment with DAST (diethylaminosulfur trifluoride) enantiopure 2-hydroxyalkylazetidines rearrange into 3-fluoropyrrolidines. The reaction is stereospecific and involves a bicyclic 1-azoniabicyclo[2.1.0]pentane intermediate which is regioselectively opened by a fluoride anion.

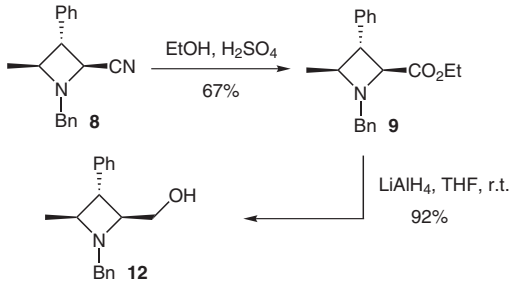
Key words: fluorination, DAST, pyrrolidines, azetidines

The replacement of a hydrogen atom by a fluorine atom in a molecule deeply modifies its electronic and lipophilic properties while maintaining its overall geometry. This strategy is now commonly used in medicinal chemistry since up to 18% of the new drugs released contain at least one fluorine atom; this percentage has increased to 30% for agrochemicals.[1] New methods for the selective introduction of a fluorine atoms into pyrrolidines, a ubiquitous skeleton in bioactive molecules are therefore highly desirable. Up to now, most 3-fluoro (or difluoro) pyrrolidines have been prepared by electrophilic fluorination of available 3-hydroxy (or oxo) pyrrolidines,[2] nucleophilic opening of suitably functionalized 3,4-epoxypyrrolidines,[3] reduction of the corresponding pyrrolidinone,[4] 1,3-dipolar cycloaddition with 3-fluoroacrylates,[5] or radical cyclization[6] and they have found application in medicinal chemistry after their incorporation in bioactive molecules such as ACE inhibitors,[7] antibacterials,[8] calcium-sensing receptor antagonists,[9] di- and tripeptidyl peptidase inhibitors,[10] or antitumour agents.[11] Therefore, a general synthesis of stereodefined enantiomerically pure 3-fluoropyrrolidines with additional substituents on the nitrogen ring would certainly find applications in medicinal chemistry.

Stimulated by the recent report from Cossy and coworkers[12] describing the rearrangement of 2-hydroxyalkylpyrrolidines **1** to 3-fluoropiperidines **3** via aziridinium intermediate **2** (Scheme 1) and in continuation of our studies related to the ring expansions of azetidines,[13] we decided to investigate whether such a transformation would be possible starting from 2-hydroxyalkylazetidines **5**. The success of this reaction involving azetidinols would mostly depend on two parameters. First, the energy of strained 1-azoniabicyclo[2.1.0]pentane **6** should be much higher than that of **2** and a competing S_N1 process could in this case hamper the stereospecificity of the rearrangement. Secondly, the nonregioselective opening of this putative intermediate by the fluoride anion may lead to mixtures of fluorinated pyrrolidines **7** and azetidines, as reported by Cossy with pyrrolidinols who obtained mixtures of **3** and **4**.



Scheme 1 Can the DAST-induced rearrangement of pyrrolidinols be transposed to azetidinols?



Scheme 2 Synthesis of azetidinol **12**

A set of representative azetidinols bearing a primary, secondary or tertiary alcohol function and presenting various substitution patterns on the azetidine ring was thus prepared following our reported procedure.[14] Primary alcohols **10–14** were obtained in excellent yields by $LiAlH_4$-mediated reduction of the corresponding ethyl ester, itself prepared from the corresponding 2-cyano azetidine. Scheme 2 exemplifies the synthesis of novel alcohol **12**, starting from (1*R*,2*S*)-norephedrine as chiral source.[14e]

The *anti* secondary alcohols **19–21** were prepared as previously reported,[14b] from the diastereoselective reduction of the corresponding ketone, itself prepared by addition of

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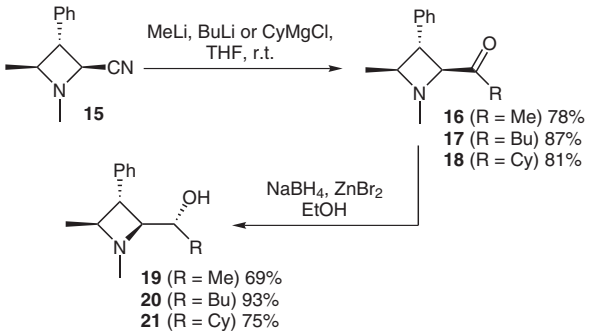
the appropriate organometallic reagent onto the corresponding 2-cyano azetidine. Scheme 3 highlights the preparation of novel compounds **19**–**21**. Finally, tertiary alcohols **23**–**25** were prepared by addition of phenyl- or methylmagnesium bromide onto the corresponding ester.



Scheme 3 Synthesis of azetidinols **19**–**21**

Having in hand a representative set of azetidinol substrates, they were treated under standardized conditions with DAST (1.5 equiv, CH_2Cl_2, 0 °C 1 h, then r.t., 1 h), followed by alkaline workup. Results are given in Table 1.

Table 1 Fluorination of 2-Hydroxyalkylazetidines

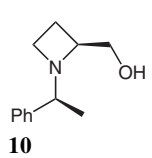
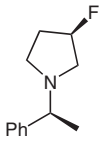
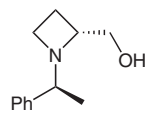
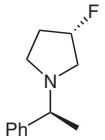
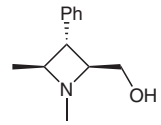
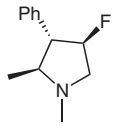
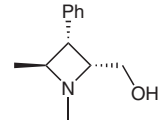
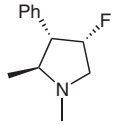
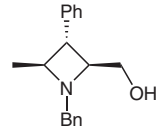
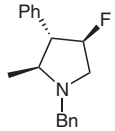
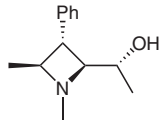
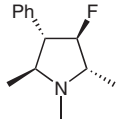
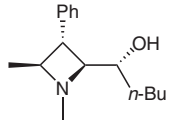
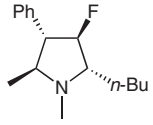
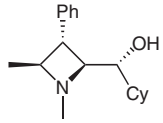
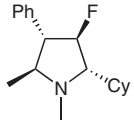
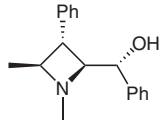
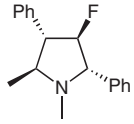
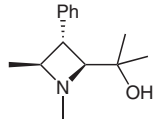
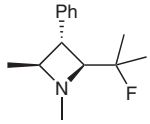
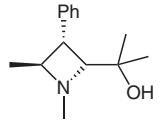
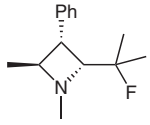
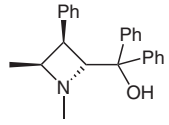
Entry	Substrate	Product(s)	Yield (%)[a]
1	 **10**	 **26**	81
2	 **11**	 **27**	58
3	 **12**	 **28**	68
4	 **13**	 **29**	45
5	 **14**	 **30**	79

Table 1 Fluorination of 2-Hydroxyalkylazetidines (continued)

Entry	Substrate	Product(s)	Yield (%)[a]
6	 **19**	 **31**	69
7	 **20**	 **32**	78[b]
8	 **21**	 **33**	80
9	 **22**	 **34**	62
10	 **23**	 **35**	37[c]
11	 **24**	 **36**	32[d]
12	 **25**	**25**	–[e]

[a] Yield of isolated products.
[b] This compound was contaminated with 12% of unrearranged isomer **37** (see text).
[c] Elimination product **38** (37%) was isolated in this experiment (see text).
[d] An unseparable elimination product **39** (40%) was produced in this experiment.
[e] A complex crude mixture was obtained in which starting material was the major product. No characteristic signals of a rearranged 3-fluoropyrrolidine could be detected.

As depicted in the Table 1, all primary and secondary alcohols rearranged into 3-fluoropyrrolidines in fair to good yields (entries 1–9). In all cases, only one diastereoisomer was produced, as proven by examination of the ^{19}F NMR spectra. The identity of the rearranged product could be easily determined by analysis of the coupling constants in both ^{19}F and ^{1}H NMR spectra. For example, in compound **26**, the ^{1}H NMR spectrum displayed a characteristic signal at $\delta = 5.13$ (dt, $^{2}J_{HF} = 54.0$ Hz, $^{3}J_{HH} = 6.0$ Hz) while the

^{19}F NMR spectrum showed one sharp signal at δ = –168.2 (app sept, $^{2}J_{HF}$ = 80.7 Hz, $^{3}J_{HF}$ = 30.0 Hz), in accordance with a CH_2CHFCH_2 pattern. In only one case (entry 7, substrate **20**) 12% of a minor inseparable compound contaminated the pyrrolidine product. On the basis of MS and NMR spectroscopy, the structure of this minor compound **37** was shown to be the nonrearranged fluoroazetidine. Particularly relevant signals indicative of this structure are: (i) a doublet in the ^{13}C NMR spectrum at δ = 30.6 ($^{3}J_{CF}$ = 21.0 Hz) indicative of a CH_2CHF pattern and, (ii) a doublet of multiplets in the ^{1}H NMR spectrum at δ = 4.45, also in accordance with this feature. On the other hand, tertiary alcohols **23**–**25** did not rearrange at all. The only fluorinated compound produced were determined to be **35** and **36** and these products were accompanied by significant amounts of elimination products **38** and **39** (ratios **35**:**38** and **36**:**39** ca. 6:4). The yield and ratio remained exactly the same when **23** was reacted with Deoxofluor instead of DAST. Finally, an attempt to treat 2-acylazetidine **40** (Figure 1) under the same conditions (DAST, CH_2Cl_2, r.t.) aiming to produce a 3,3-difluoropyrrolidine[15] failed and the starting material was recovered.

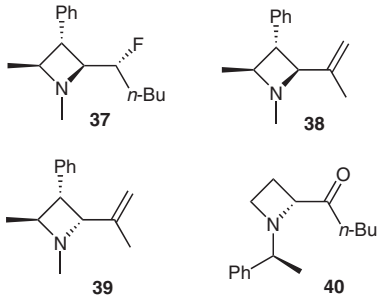


Figure 1 Structure of compounds **37**–**40**

The relative configuration of the substituents in the produced 3-fluoropyrrolidines was unambiguously determined by X-ray crystallography of compound **30**, whose ORTEP diagram is depicted in Figure 2.[16] The 2,3-*trans* relationship between the fluorine atom and the adjacent phenyl group and the observed stereospecificity of the rearrangement is fully consistent with the mechanism outlined in Scheme 4 starting with **14** and involving an intermediate 1-azoniabicyclo[2.1.0]pentane **42**. Considering the poor nucleofugacity of the fluoride anion, this reaction is expected to be under kinetic control[17] and the chemoselectivity (2-fluoroalkylazetidine vs. rearranged 3-fluoropyrrolidine) arises from the regioselective attack of the fluoride anion at the C-2 carbon in the intermediate azetidinium ion **42**. This high regioselectivity contrasts with the results obtained by Cossy for the higher homologues (Scheme 1), since in this case, the regioselectivity was poorer and was found to depend on the substitution pattern of the starting 2-hydroxyalkylpyrrolidine. The highly strained nature of intermediate **42** probably discriminates here to a larger extent between the two possible attacks of the fluoride anion. The absence of rearrangement in the case of tertiary alcohols can be ascribed to the formation of an intermediate carbonium ion (supported by the competitive formation of elimination products **41** and **42**), that is faster than the initial nucleophilic displacement leading to the bicyclic ammonium ion.

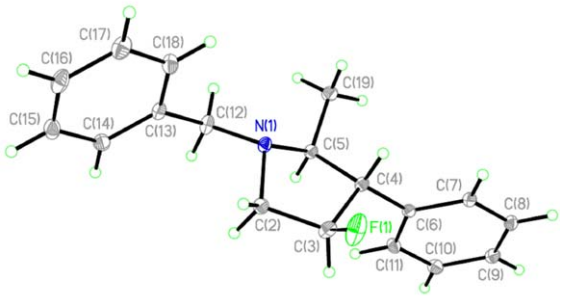
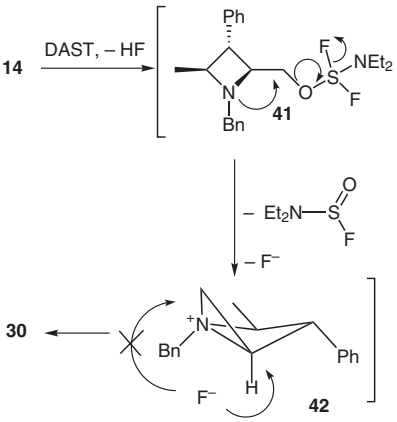


Figure 2 ORTEP structure of fluoropyrrolidine **30**



Scheme 4 Mechanism of the rearrangement

In summary, we have developed an efficient and straightforward synthesis of stereodefined 3-fluoropyrrolidines[18] in enantiomerically pure form, that takes advantage of the reactivity of functionalized azetidines based on the strain in this heterocycle.[19]

Acknowledgment

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(15) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(16) Crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 676883.
(17) The kinetic control invoked here is also supported by the chemical stability of **36**, which does not rearrange when heated at 100 °C in toluene for 8 h.
(18) **General Procedure for the Reaction of Azetidinols with DAST**: To a solution of the required 2-hydroxyalkylazetidine (1 mmol) in anhyd CH_2Cl_2 (7 mL) cooled at 0 °C under argon was added dropwise diethylaminosulfur trifluoride (245 μL, 2 mmol). The resulting solution was allowed to reach r.t. (1 h) and was stirred for 1 h. The reaction mixture was then basified with 1 M NaOH (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). Drying over $MgSO_4$, filtration, and evaporation of the solvent under reduced pressure gave a residue that was purified by flash chromatography.
Selected data: Compound **26**: yield (from **10**): 81%; colorless oil; R_f 0.75 (EtOAc); $[\alpha]_D^{25}$ –46.1 (c = 0.57, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 1.40 (d, J = 6.6 Hz, 3 H, Me), 1.80–2.15 (m, 2 H, H4, H4′), 2.50–3.75 (m, 3 H, H2, H5, H5′), 2.79 (dd, J = 12.0, 30.0 Hz, 1 H, H2′), 3.21 (q, J = 6.6 Hz, 1 H, C*H*Me), 5.13 (dt, $^2J_{HF}$ = 54.0 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H, H3), 7.13–7.28 (m, 5 H, Ar). ^{13}C NMR (75 MHz): δ = 23.1 (Me), 32.8 (d, $^3J_{C-F}$ = 23.0 Hz, C2), 50.9 (C4), 59.6 (d, $^3J_{CF}$ = 23.0 Hz, C4), 65.4 (*C*HMe), 92.5 (d, $^2J_{CF}$ = 176.0 Hz, C3), 127.0, 128.1, 128.4 (CHAr), 145.1 (CqAr). ^{19}F NMR (188 MHz): δ = –168.2 [qd (false hept), $^2J_{HF}$ = 80.7 Hz, $^3J_{HF}$ = 30.0 Hz, 1 F]. MS (CI, NH_3 gas): m/z = 194 (100) [MH^+]. Compound **30**: yield (from **14**): 79%; colorless solid; mp 69 °C; R_f 0.85 (EtOAc–pentane, 1:9); $[\alpha]_D^{25}$ +119.8 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 1.29 (d, J = 6.0 Hz, 3 H, Me), 2.48–2.72 (m, 2 H, H2, H5), 3.16 (ddd, $^3J_{HH}$ = 3.0, 9.0 Hz, $^3J_{HF}$ = 36.0 Hz, 1 H, H5′), 3.27 (d, J = 12.0 Hz, 1 H, NC*H*HPh), 3.35 (dd, $^3J_{HH}$ = 12.0 Hz, $^3J_{HF}$ = 21.0 Hz, 1 H, H3), 4.22 (d, J = 12.0 Hz, 1 H, NCH*H*Ph), 5.10 (dm, $^2J_{HF}$ = 57.0 Hz, 1 H, H4), 7.22–7.41 (m, 10 H, Ar). ^{13}C NMR (75 MHz): δ = 16.0 (Me), 57.4 (N*C*H_2Ph), 60.3, 60.8 (d, $^3J_{CF}$ = 23.0 Hz, C3, C5), 67.2 (d, $^4J_{CF}$ = 2.2 Hz, C2), 98.3 (d, $^2J_{CF}$ = 182.0 Hz, C4), 127.1, 127.2, 127.4, 128.1, 128.4, 128.8, 128.9 (CHAr), 138.4, 140.5 (CqAr). ^{19}F NMR (188 MHz): δ = –164.4 to –165.2, (m, 1 F). MS (ESI, +ve): m/z = 270.3 (100) [MH^+].
(19) Couty, F.; Durrat, F.; Evano, G. *Targets in Heterocyclic Systems – Chemistry and Properties*, Vol. 9; Attanasi, O. A.; Spinelli, D., Eds.; Italian Society of Chemistry: Rome, **2005**, 186.