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Synthesis of Fluoroazaindolines by an Uncommon Radical *ipso* Substitution of a Carbon−Fluorine Bond

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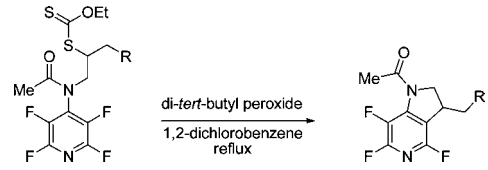
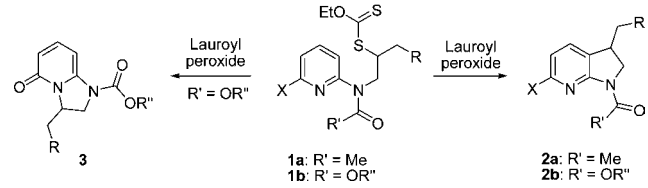
ABSTRACT



Rare examples of a synthetically useful radical *ipso* substitution of a carbon−fluorine bond are reported. Highly functionalized fluoroazaindoline structures have thus been prepared with use of cheap and readily available substrates and reagents.

In chemistry, minor and seemingly harmless modifications can have a profound effect on reactivity. We recently made such a remarkable and very surprising observation while studying a new approach to azaindolines and related substances.[1] We found that whereas *N*-acetyl-protected xanthate **1a** underwent the expected ring-closure to give azaindoline **2a** in good yield, the corresponding *N*-Boc derivative **1b** gave only a very small amount of the analogous azaindoline **2b**. The major product turned out to be pyridinone **3**, which was formed by a hitherto undocumented radical attack on the pyridine nitrogen (Scheme 1).[2] While further work indicated that the Boc group may be replaced by another carbamate motif and the chlorine in the pyridine ring could be exchanged for a fluorine, no completely satisfactory rationale for this curious reactivity has yet emerged.[3] In an attempt to expand the scope of the process and perhaps gain some additional mechanistic insight, we examined the behavior of fluorinated derivative **6** (Scheme 2). This compound was readily obtained by radical addition of xanthate **5a** to Boc-protected 2-*N*-allylamine pyridine **4**.[4] The latter was accessible from commercially available pentafluoropyridine through substitution, first with dimethylamine then with *N*-allylamine, followed by reaction with Boc anhydride.[5]

Scheme 1. Divergent Radical Cyclization on a Pyridine Ring



(1) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671.
(2) El Qacemi, M.; Ricard, L.; Zard, S. Z. *Chem. Commun.* **2006**, 4422.
(3) We wish to acknowledge in this respect our collaboration on the theoretical aspects with Dr. Michelle Coote at the Australian National University.

(4) For reviews on xanthate chemistry, see: (a) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (c) Zard, S. Z. In *Radical in Organic Chemistry*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 90−108. (d) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus Sulfur Silicon* **1999**, *153−154*, 137–154. (e) Quiclet-Sire, B.; Zard, S. Z. *J. Chin. Chem. Soc.* **1999**, *46*, 139. (f) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.
(5) Pentafluoropyridine usually reacts with amines first at the 4-position then at the 2-position. See for example: Hargreaves, C. A.; Sanford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. *Tetrahedron* **2007**, *63*, 5204. The reactivity of pentafluoropyridine and other fluorinated derivatives is extensively discussed in ref 6j.

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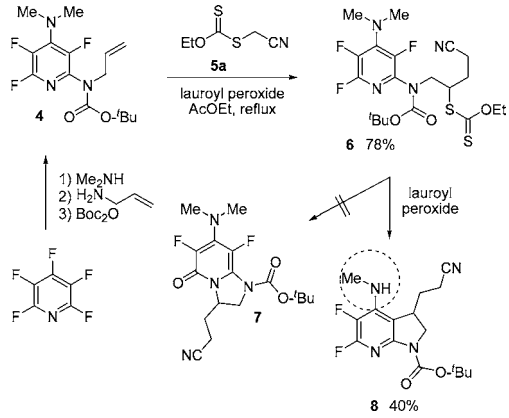
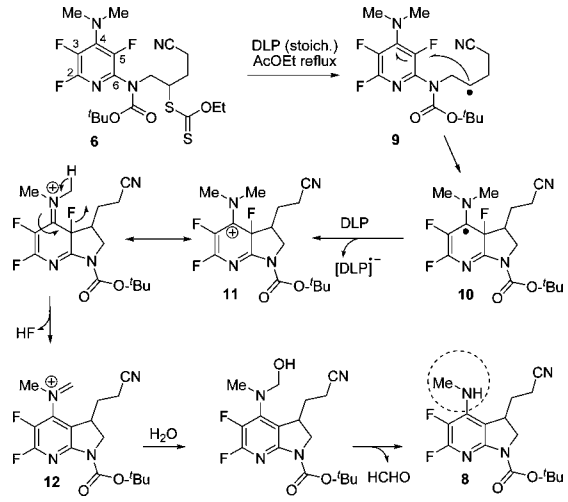
Scheme 2. Unexpected Radical *ipso* Cyclization−Demethylation



Our anticipation was that the ring-closure on such a structure could only take place on the pyridine nitrogen to give **7** since the other position was blocked by a fluorine atom. In the event, none of compound **7** could be observed upon treatment of xanthate **6** with lauroyl peroxide (DLP). Instead, azaindoline **8** was isolated in modest yield. Not only did the ring-closure take place on carbon, with loss of a fluorine atom, *but a methyl group was also lost from the dimethylamino group on C-4*.

A plausible mechanism for this unexpected transformation is pictured in Scheme 3. Radical **9**, derived from xanthate

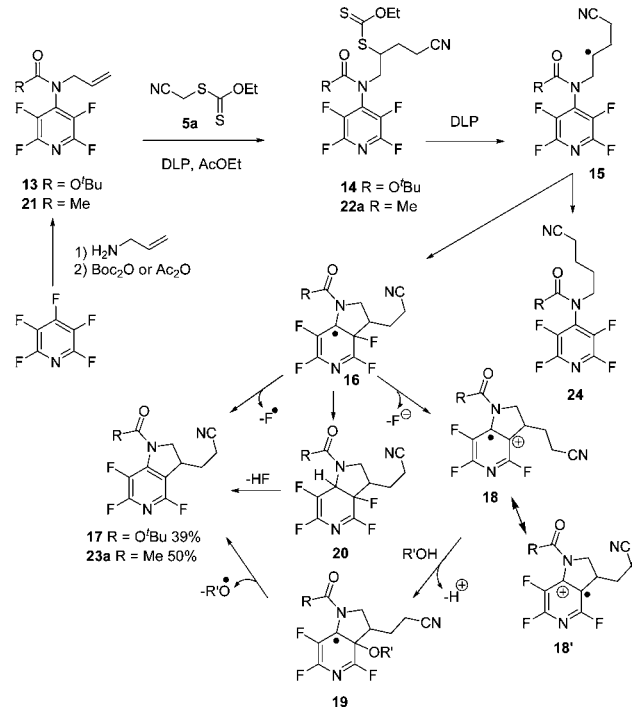
Scheme 3. Plausible Mechanism for Radical *ipso* Cyclization−Demethylation



6, undergoes an *ipso* substitution on C-5 to give intermediate **10**, which is then converted into the corresponding allylic cation **11** by electron transfer to the peroxide. This species is destabilized by the adjacent electron-withdrawing fluorine atoms but stabilized by the two exocyclic nitrogen substituents. Loss of hydrogen fluoride then furnishes iminium derivative **12**. This species is readily hydrolyzed upon workup to furnish novel difluoroazaindoline **8**.

The possibility of an *ipso* closure on carbon bearing fluorine on the pyridine ring raised the question of the fate of the cyclized radical in the absence of a second nitrogen substituent to stabilize the corresponding cation. We therefore examined the reaction of xanthate **14** derived from *N*-Boc-*N*-allyl-4-aminotetrafluoropyridine **13**. Upon treatment with DLP in refluxing ethyl acetate, a new trifluoroazaindoline **17** was produced in about 40% crude NMR yield (Scheme 4).

Scheme 4. Azafluoroindoline by a Radical *ipso* Cyclization and Fluorine Atom Elimination



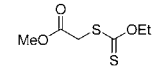
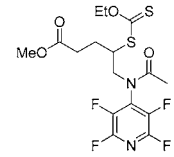
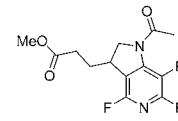
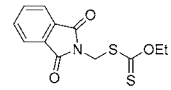
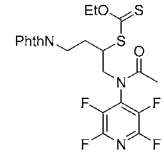
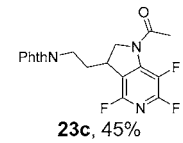
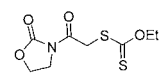
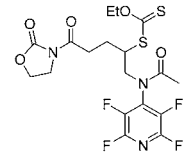
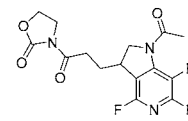
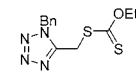
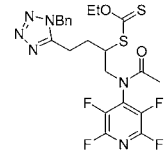
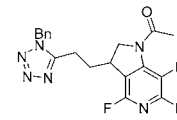
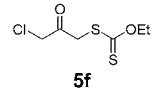
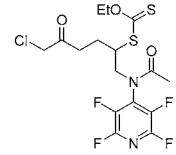
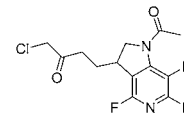
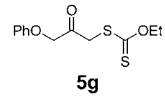
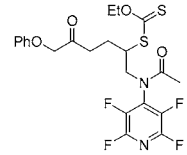
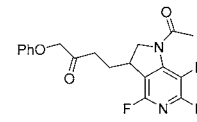
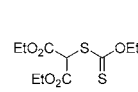
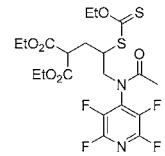
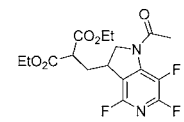
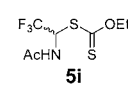
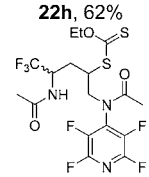
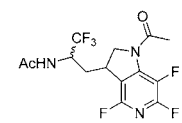
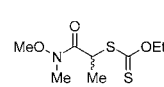
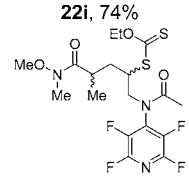
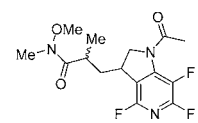
The formation of an azaindoline implies apparently the loss of a fluorine atom by a *homolytic rupture of a very strong C−F bond* in intermediate **16**. As far as we know, such a fragmentation under comparably mild conditions is quite rare. The decomposition of peroxides in perfluorinated aromatic derivatives (normally used as the solvent) has been reported to give products which could arise by a homolytic *ipso* substitution of a carbon−fluorine bond. The yields were generally low and considerable amounts of dimers of the intermediate perfluorocyclohexadienyl radicals were ob-

(6) (a) Brooke, G. M. *J. Fluorine Chem.* **1997**, *86*, 1, and references cited therein. We thank one of the referees for pointing out this reference to us. β-Scission of chlorides, bromides, and iodides is well known: (b) Struss, J. A.; Sadeghipour, M.; Tanko, J. M. *Tetrahedron Lett.* **2009**, *50*, 2119. (c) Maddess, M. L.; Mainetti, E.; Harrak, Y.; Brancour, C.; Devin, P.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Chem. Commun.* **2007**, 936. (d) Kim, S.; Kim, N.; Chung, W.-J.; Cho, C. H. *Synlett* **2001**, 937. (e) Tanko, J. M.; Sadeghipour, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 159. (f) Huval, C. C.; Singleton, D. A. *Tetrahedron Lett.* **1993**, *34*, 3041. (g) Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741. (h) Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397. (i) Meijs, G. F.; Rizzardo, E.; Tang, S. H. *Polym. Bull.* **1990**, *24*, 501. (j) For a review on C−F bond activation, see: Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.

served.[6] In our case, a favorable entropic term and the rearomatization of the pyridine ring may constitute a sufficient driving force for expelling a fluorine atom. Furthermore, the nucleophilic character of the adduct radical and the electrophilic character of the pyridine ring are complementary and may aid the radical cyclization. Previous studies, especially by Walton and Studer, have demonstrated the possibility of breaking strong C−C and C−O bonds under similar circumstances.[7] Cleavage in the same manner of the stronger C−F bond, while obviously more difficult, is not therefore unrealistic. An alternative pathway can be envisaged involving first a solvolysis to give radical-cation **18**-**18′** and a fluoride anion, followed by quenching with a nucleophile in a medium such as water or lauric acid (R′OH) leading to radical **19**.[8] This is then followed by β-scission to give the observed azaindoline **17**. Even if it cannot yet be discounted, this variant seems unlikely, however, in view of the poor leaving group ability of the fluoride anion and the low dielectric constant of the solvent, which disfavors normally a heterolytic process.[9] Yet another pathway involves abstraction by intermediate radical **16** of a hydrogen atom from the solvent to give derivative **20**, which can then ionically lose hydrogen fluoride to furnish the observed product **17**. However, radical **16** is highly stabilized (it is not only both tertiary and allylic, but further stabilized by the lone pair of the nitrogen) and its reaction with the solvent would be expected to be very endothermic and in fact quite unlikely. The possibility of a prior ionic elimination of HF from **16** followed by hydrogen abstraction from the solvent is even less likely. Ionic elimination of HF from **16** in the absence of a base in a nonpolar solvent is too slow in comparison with the lifetime of the radical; moreover, the resulting radical species would still be too stabilized and incapable of hydrogen abstraction from the solvent.

From a synthetic standpoint, we found this reaction capricious, giving variable and often low yields (hence the crude NMR yield given above for azaindoline **17**). The observation of unidentified side products where the Boc group had apparently been lost indicated a likely detrimental effect of the hydrogen fluoride produced by either mechanistic pathway. We therefore replaced the Boc group in **14** with the more robust acetyl group. Working with analogue **22a** allowed us to operate at the much higher temperature of refluxing *o*-dichlorobenzene (175 °C) and thus improve the chances of the intrinsically slow cyclization, as well as the high entropy fragmentation step.[10] At this temperature, it is necessary to replace the lauroyl peroxide with di-*tert*-butyl peroxide, which has a much longer lifetime. Under these conditions, the reaction was more reproducible and cleaner, furnishing the desired trifluoroazaindoline **23a** in 50% yield along with 25% of prematurely reduced material (**24**, R = Me).

Table 1. Preparation of Fluoroazaindolines **23**

xanthate	addition product	cyclisation product
 **5b**	 **22b**, 80%	 **23b**, 45%
 **5c**	 **22c**, 78%	 **23c**, 45%
 **5d**	 **22d**, 95%	 **23d**, 40%
 **5e**	 **22e**, 60%	 **23e**, 27%
 **5f**	 **22f**, 60%	 **23f**, 43%
 **5g**	 **22g**, 80%	 **23g**, 50%
 **5h**	 **22h**, 62%	 **23h**, 32%
 **5i**	 **22i**, 74%	 **23i**, 41% (1:1.5)
 **5j**	 **22j**, 74%	 **23j**, 51% (1:1.5)

(7) For a review, see: Walton, J. A.; Studer, A. *Acc. Chem. Res.* 2005, *38*, 794.

(8) (a) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273. (b) Crich, D.; Brebion, F.; Suk, D.-H. *Top. Curr. Chem.* **2006**, *263*, 1.

(9) Shoute and Mittal generated a radical-anion from hexafluorobenzene through radiolysis and noted the relative difficulty of eliminating a fluoride anion. Eliminating fluoride from a simple free radical should therefore be even more difficult. See: Shoute, L. C. T.; Mittal, J. P. *J. Phys. Chem.* **1993**, *97*, 379. Interestingly, these authors also remarked on the "considerable resistance" of hexafluorobenzene to radical addition. Both of these observations make our present cyclization and extrusion of a fluorine atom all the more unique.

In the same manner, various trifluoroazaindolines were prepared as shown by the results collected in Table 1. Xanthates **5a**−**j** bearing various functional groups added readily to the allyl group in **21** allowing ultimately access to a broad assortment of novel trifluoroazaindolines. Furthermore, the presence of easily replaceable fluorines at positions C-2 and C-6 of the pyridine ring opens countless opportunities for further modification of these structures.[11] Azaindolines and related derivatives are emerging as important motifs in medicinal chemistry, especially as kinase inhibitors in the treatment of cancer.[12] This is reflected by the constantly increasing flux of recent publications dealing with their synthesis. More generally, fluorine-containing heterocycles represent a particularly interesting class for the pharmaceutical and agrochemical industry.[13]

The present work complements existing methods and highlights the hitherto unsuspected possibility of using a fluorine atom as a radical leaving group. It also documents an example of an unusual demethylation reaction in the conversion of **6** into **8**. Even if the yields are still relatively modest because of the competing premature reduction of the intermediate radical, it must be realized that such cyclizations would be very hard, if not impossible, to accomplish with existing methodology.

Acknowledgment. We respectfully dedicate this paper to Professor A. Vasella (ETH, Switzerland). Y.L. and L.P. thank Ecole Polytechnique and Laboratoires Servier, respectively, for a studentship.

Supporting Information Available: Experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101240F

(10) For an example of the use of high temperature to force a difficult cyclization on an aromatic ring, see: Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun.* **2002**, 2306.

(11) The use of ring-fused trifluoropyridine systems in further synthetic transformations has recently been described. See for example: (a) Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. *J. Org. Chem.* **2005**, *70*, 7208. (b) Cartwright, M. W.; Convery, L.; Kraynck, T.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D. *Tetrahedron* **2010**, *66*, 519.

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