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Radical *ipso*-Substitution of a Carbon−Fluorine Bond Leading to Fluoro-7-azaindolines and Fluoro-7-azaindoles

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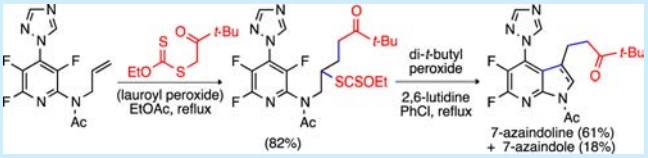
Supporting Information

ABSTRACT: Rare examples of a synthetically useful radical *ipso*-substitution of a carbon−fluorine bond are reported, leading to highly functionalized 5,6-difluoro-7-azaindolines. An unexpected hydrogen atom translocation and fragmentation with loss of molecular nitrogen and formation of a nitrile were observed in the case of an *N*-benzyl-tetrazole derivative.



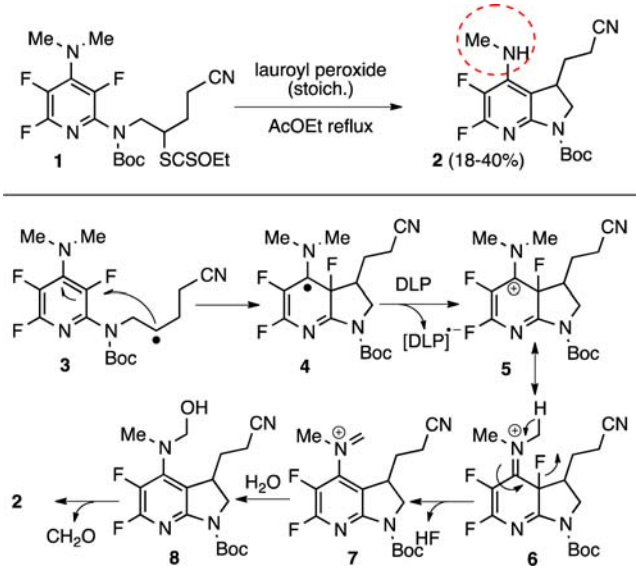
Azaindoles and related derivatives have attracted much synthetic effort in recent years.[1] These molecular scaffolds are akin to the enormously important indoles and constitute particularly privileged structures in medicinal chemistry.[2] While aza-analogues of indole-based active compounds usually exhibit improved solubility and bioavailability, synthetic routes to these derivatives are often much more troublesome than in the indole series. In fact, the classical indole syntheses are not easily transposed to their aza analogues, either because of the limited availability of the requisite precursors or because of reactivity problems. Thus, when applied to the pyridines, the powerful and widely used Fischer indole synthesis often results in poor yields and sometimes even completely fails.[3] In addition, very few pyridylhydrazines are commercially available.

As part of our more general exploration of the potential of the xanthates for constructing heteroaromatic structures,[4,5] we recently described a radical based approach for fusing various sized rings around the pyridine and pyrimidine nuclei.[6] In the course of this work, we made a surprising observation while studying a radical ring closure leading to fluoroazaindolines.[7] We found that treatment of xanthate **1** with lauroyl peroxide resulted in the formation of an azaindoline with the loss of a fluorine atom and the unexpected loss of a methyl group on the 4-dimethyamino substituent to give difluoroazaindoline **2** as the major isolated product (Scheme 1).

The reaction was not very clean, and the yield was variable but generally modest (18−40%). A plausible mechanism for this unusual transformation is briefly outlined in Scheme 1. Radical **3** arising from fragmentation of the xanthate undergoes ring closure into **4**. This intermediate is reluctant to expel a fluorine atom and prefers to react with the peroxide by electron transfer to furnish the corresponding cation **5**, which may be drawn as mesomer **6** and which can aromatize into final product **2** via intermediates **7** and **8** through loss of a hydrogen fluoride and formaldehyde.

In an attempt to gain a better understanding of the mechanism and perhaps to expand the scope of the process, we examined the behavior of other 4-amino-substituted fluoropyridines. In particular, by studying cyclic amine substituents we hoped to avoid the hydrolysis step and capture

Scheme 1. An Unexpected Demethylation



the iminium intermediate corresponding to **7** in a synthetically more useful way.

Compound **11a** was therefore prepared by lauroyl peroxide (DLP) initiated radical addition of xanthate **10a** to carbamate-protected 2-*N*-allylamine pyridine **9a**, a substrate easily accessible from commercially available and cheap pentafluoropyridine (Scheme 2).[8] Upon treatment with stoichiometric amounts of di-*tert*-butyl peroxide (DTBP), pyrrolidine substituted azaindoline **12a** was produced in a small yield (17%), along with an even smaller yield of the corresponding pyrrole **13a** (10%; see discussion of mechanism below). The addition of 2,6-lutidine resulted in a much cleaner reaction and significantly improved the yield of both pyrroline **12a** and pyrrole **13a** to a 56% combined yield. The lutidine most likely

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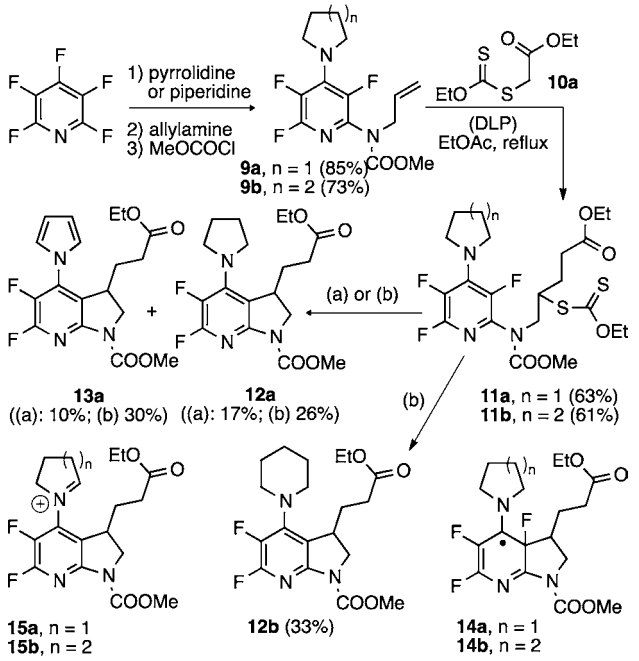
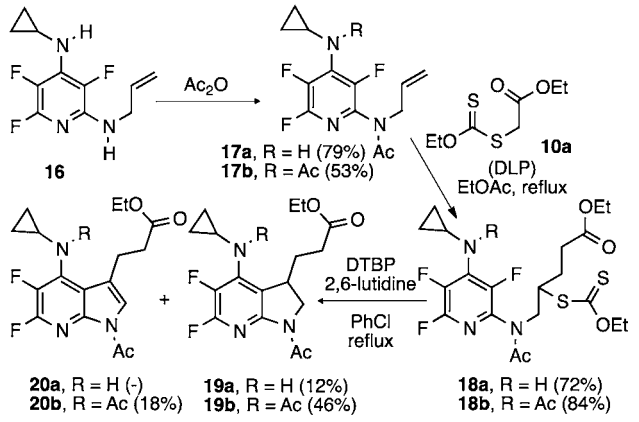
Scheme 2. Synthesis of 7-Azaindolines



acts by neutralizing any hydrogen fluoride produced and limits its destructive effect. With the higher piperidine homologue **11b**, the main product was azaindoline **12b** (33%). In this case, the corresponding iminium **15b** cannot evolve into a stable aromatic structure and this pathway does not lead to identifiable products.

In a further attempt to divert the reaction from its initial course, we examined the transformation of adducts **18a** and **18b**, prepared from cyclopropylamine derivative **17a** and its acetylated analogue **17b** (Scheme 3; yields for **17a** and **17b** are

Scheme 3. 7-Azainolines and 7-Azaindoles



overall from pentafluoropyridine). The former, **18a**, gave rise disappointingly to a complex mixture, from which azaindoline **19a** was isolated in a very poor yield (12%). In stark contrast, the reaction of the latter was much cleaner and furnished azaindoline **19b** in 46% yield. Furthermore, a small amount of the corresponding azaindole **20b** could also be isolated in 18% yield.

From a mechanistic standpoint, a plausible rationalization for the apparent erratic behavior of these various substrates may be proposed. It hinges on the competition between oxidation of cyclized radical (e.g., **4** and **14a,b**) and β-scission of the strong carbon−fluorine bond (a more detailed discussion of this step is given below). Both steps are relatively slow. In the presence of an electron-releasing amine, as in substrates **1**, **11a**, **11b**, and **18a**, the oxidation of the intermediate cyclized radical is slightly faster than elimination of a fluorine atom. This gives rise, via the resulting iminium species, to demethylation in the case of **1**, to aromatization to pyrrole in the case of **11a**, or to decomposition products in the case of **11b** and **18a**.

Acetylation of the cyclopropylamine in **18b** slows down the electron transfer to the peroxide allowing the fragmentation of the carbon−fluorine bond to overtake the oxidation step. As a consequence, the yield of azaindoline **19b** increases nearly 4-fold over **19a** and becomes synthetically useful, especially when combined with that of indole **20b**. The formation of the latter is apparently due to further oxidation of indoline **19b** by the peroxide. Blank experiments indicated that this is indeed possible, even if complete conversion to the indole could not be accomplished cleanly. Furthermore, re-examination of the crude NMR spectra indicated that indoles were formed in small amounts in all previous cyclization reactions but were missed because of the relative complexity of the mixtures.

The beneficial effect of an electron-withdrawing group on the nitrogen on limiting the formation of side products was next exploited to access variously substituted difluoroazaindolines. The starting materials **18** are shown in Scheme 4, along with the corresponding indolines and indoles **19** and **20** (Xa = −SC(=S)OEt and −NPhth = phthalimido, throughout; the yield of adducts **18** is also given throughout, even though the precursors, xanthates **10** and alkenes **17**, are not shown). A mesyl group may be present on the nitrogen in the 4-position of the pyridine ring with no significant effect on the outcome (**18d**). In the case of xanthate **18f**, we observed, in addition to indoline **19f** and indole **20f**, a small amount of the tetralone (not shown) derived by the competing addition of the intermediate radical to the fluorobenzene ring.[9]

We also found that aniline substituents (**18h,i**) gave comparable yields of cyclization products without the need for acetylation or mesylation and, curiously, the amount of the accompanying indoles was much lower than in the case with aliphatic amide substituents. With a phenoxy (**18j**) and heteroaromatic substituents, such as a pyrrole, an imidazole, a triazole, and even an indole, on the 4-position (**18k,n**), the formation of the corresponding 7-azaindole was again significant.

The tetrazole adduct **18o** did not behave as expected. We were surprised to find a major side product, where the benzyl tetrazole motif had completely disappeared and which proved to be nitrile **21** (Scheme 5). This compound results most probably from a rare 1,6-hydrogen atom shift to give benzylic radical **23** followed by rupture of the tetrazole ring and expulsion of molecular nitrogen and iminyl radical **24**. This radical fragmentation appears to be unprecedented. In any case, the translocation of radical **22** reflects the inherent sluggishness of the cyclization step and is a testimony to the rather unique nature of the radical chemistry of xanthates that indeed allows such a difficult process to take place.

Mechanistically, the ring-forming step deserves some additional comments. Prior to our work, radical *ipso*-substitutions of an aromatic or heteroaromatic fluorine atom were extremely rare, and the possibility of homolysis of a strong C−F bond was almost never invoked.[10] We have argued for its occurrence in our initial disclosures,[7] and while incontrovertible proof is still

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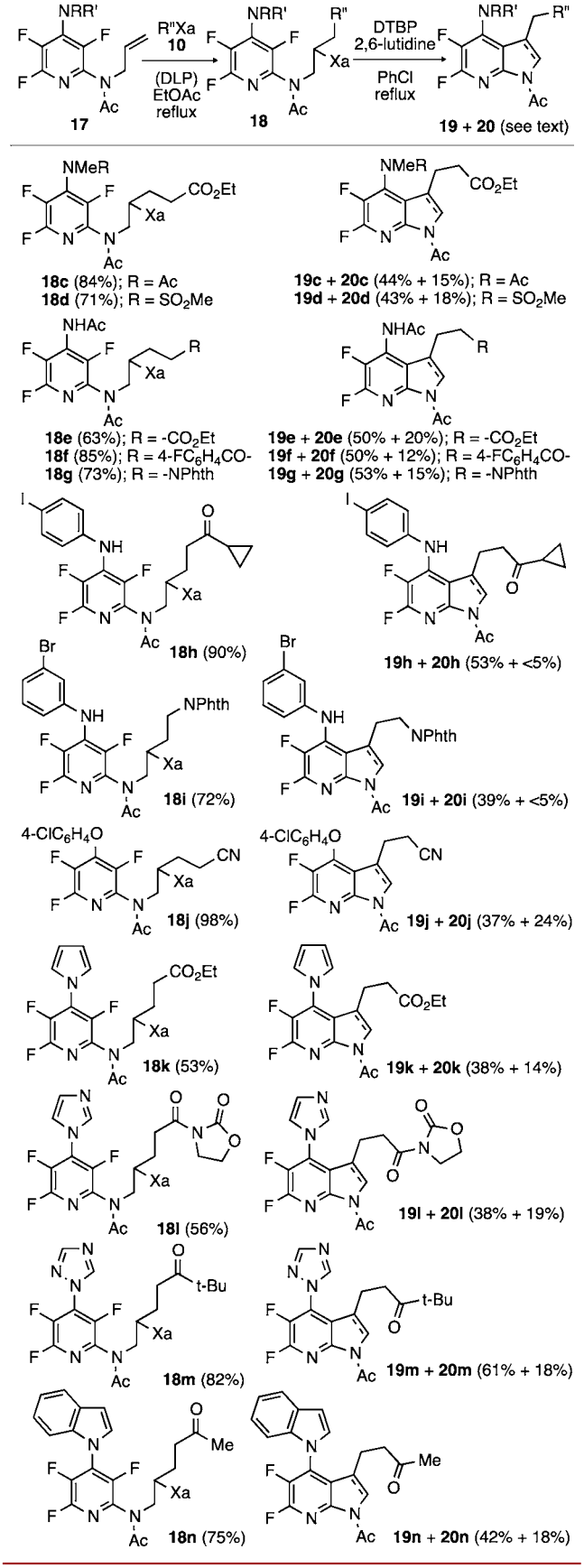
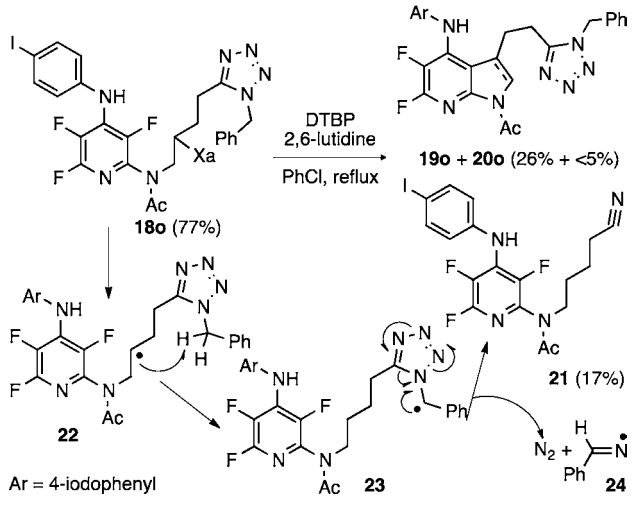
Scheme 4. Synthesis of Substituted 7-Azaindolines



unavailable, all our observations point to it. In particular, the strong effect of temperature (data not shown) is in tune with a

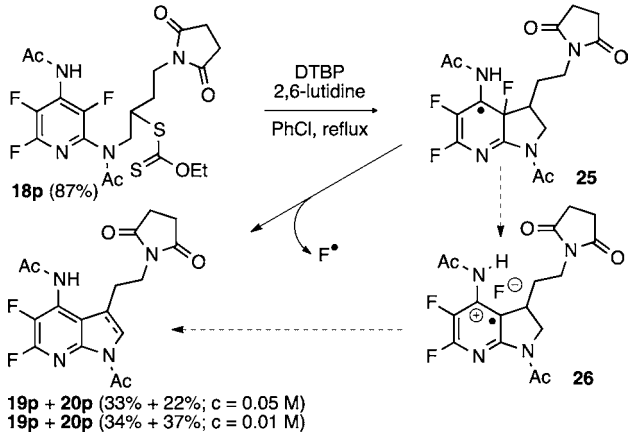
Scheme 5. An Unexpected Fragmentation



slow *unimolecular* fragmentation with a high entropy term (cf. $\Delta G = \Delta H - T\Delta S$).

This is further supported by the experiment shown in Scheme 6, where a 5-fold dilution has essentially no effect on

Scheme 6. Effect of Dilution on the Yield



the yield in the conversion of **18p** into indoline **19p** and indole **20p**. This observation would be incompatible with a slow *bimolecular* oxidation or reduction of intermediate radical **25** and leaves open only two *unimolecular* options: either a simple homolysis with loss of a *fluorine atom* or a solvolysis implying expulsion of a *fluoride anion*.[11] The poor leaving-group ability of a fluoride anion, especially in a nonpolar solvent which cannot stabilize an intermediate such as **26**, militates strongly against the latter possibility.

In summary, this approach offers numerous opportunities for the concise and modular preparation of fluoroindolines and fluoroindoles with potential applications in medicinal and phyto-chemistry.[12] The diversity in the structures may be further increased by postmodification of the products, as illustrated by the conversion of adduct **18q** into ethoxy-substituted indole **27**, without separation of intermediates **19q** and **20q** and by using IBX to complete the oxidative aromatization of the *N*-deacetylated indoline (Scheme 7).[13] It is interesting to note that of the five fluorine atoms in pentafluoropyridine only one fluorine is left in indole **27**. Finally, a preliminary experiment was performed to explore

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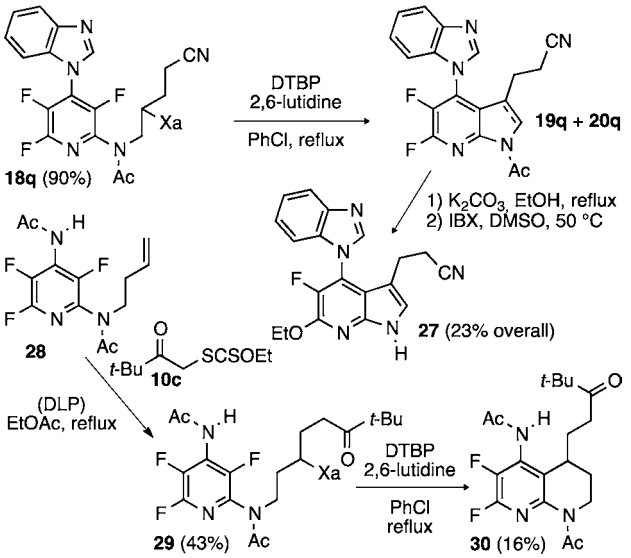
Scheme 7. Further Extensions



access to tetrahydro-azaquinolines such as **30** via the corresponding precursor **29**. This entails the more difficult creation of a six-membered ring. Indeed, the efficiency of the cyclization step proved much lower, as expected, but further work is needed to delineate its scope.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, 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.

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Notes

The authors declare no competing financial interest.

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