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Tetrabutylammonium Salt Induced Denitration of Nitropyridines: Synthesis of Fluoro-, Hydroxy-, and Methoxypyridines

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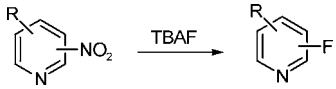
ABSTRACT



An efficient method for the synthesis of fluoropyridines via the fluorodenitration reaction is reported. The reaction is mediated by tetrabutylammonium fluoride (TBAF) under mild conditions without undue regard to the presence of water. The fluorodenitration is general for 2- or 4-nitro-substituted pyridines, while 3-nitropyridines require attendant electron-withdrawing groups for the reaction to proceed efficiently. Nitropyridines also undergo hydroxy- and methoxydenitration under mild conditions in the presence of the corresponding tetrabutylammonium species.

Research efforts concerning the use of fluorinated organic compounds are of considerable interest as there are numerous examples wherein fluorine dramatically alters the chemical and biological properties of a molecule.[1] The fluorine atom exerts minimal conformation effects and is generally accepted to be an isosteric substitution for hydrogen. However, fluorine has dramatic electronic effects on neighboring atoms due to its electronegativity, thereby altering the physicochemical properties of a molecule.[2] Accordingly, new and efficient methods for the synthesis of fluorine-containing organic compounds warrant attention.

The classically employed method for introducing fluorine into an aromatic ring is the Balz−Schiemann reaction (Figure 1).[3] In this two-step process, an aromatic amine is initially diazotized in the presence of tetrafluoroboric acid. Subsequent decomposition of the resultant tetrafluoroborate is generally achieved thermally, producing products in fair yields. When functionalized pyridines are employed in the Balz−Schiemann reaction, chemoselectivity issues arise. In these instances, complex reaction mixtures can be formed, resulting in inferior yields of the desired product.

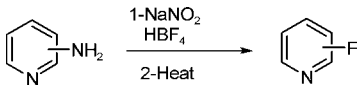


Figure 1. The classical Balz−Schiemann reaction.

The treatment of aromatic compounds with electrophilic sources of fluorine has become more widespread in recent years as a substitute for the Balz−Schiemann reaction.[4] Alternatively, the use of nucleophilic fluorine to displace a leaving group on an aromatic ring has also found application in the synthesis of fluoroaromatic compounds.[5] An intriguing yet under-utilized version of the latter approach is the fluorodenitration reaction.[6] In this case, a nitro group is displaced, typically with an inorganic fluoride salt in DMSO

(1) (a) Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (b) Edwards, P. N. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Publishing Corp.: New York, 1994; pp 501−541. (c) Welch, J. T.; Eswarakrishanan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991.

(2) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.

(3) Suschitzky, H. *Adv. Fluorine Chem.* **1965**, *1*, 4.

(4) Sankar-Lal, G.; Pez. G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.

(5) (a) Hewitt, C. D.; Silvester, M. J. *Aldrichimica Acta* **1988**, *21*, 3. (b) Gertensberger, M. R. C.; Haas, A. *Angew. Chem., Intl. Ed. Engl.* **1981**, *20*, 647.

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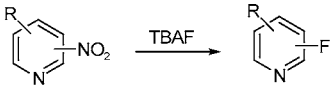
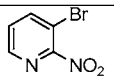
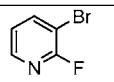
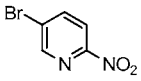
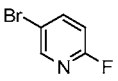
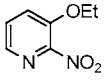
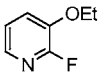
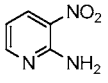
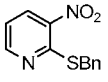
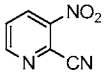
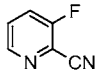
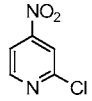
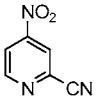
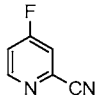
at high temperatures.[7] Anhydrous tetrabutylammonium fluoride (TBAF) has also previously been shown to promote fluorodenitration for a limited number of nitrobenzenes.[8] In this communication, we disclose our own efforts in this area and expand the scope of the tetrabutylammonium salt promoted denitration to include nitropyridines as substrates.

Several substituted 2-,3-, and 4- nitropyridines were subjected to fluorodenitration with commercially available TBAF (1 M in THF) in DMF[9] to yield fluoropyridines in good yield.[10] In some instances, decreased yields were observed and these results are attributable to the volatility of the corresponding fluoropyridine products. As the data in Table 1 indicate, pyridines with nitro groups at the 2- or 4-position (entries 1−3, 7, and 8) underwent smooth denitration to afford the corresponding fluoropyridines after a few hours either at room temperature or at 70 °C.[11] While pyridines with electron-donating groups required both heating and prolonged reaction times to go to completion (entry 3), the observation that they participate under these conditions is unique since the fluorodenitration of nitrobenzenes is limited to electron-deficient substrates.[12] It is also notable that the fluorodenitration reaction is highly chemoselective since the nitro is displaced in preference to the ortho bromide in entry 1. Fluorodenitration of 3-nitropyridines appears limited to substrates containing electron-withdrawing groups (entry 6), since no reaction was seen with electron-rich examples (entries 4 and 5).[13]

Table 1. Fluorodenitration of Pyridines[a]

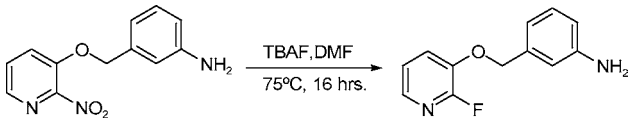


entry	substrate	t (h), *T* (°C)	product	yield
1		2, 23		70%
2		4, 23		80%
3		12, 70		76%
4		24, 90	-	0%
5		24, 90	-	0%
6		1, 23		64%
7		0.5, 23		53%
8		0.25, 23		80%

[a] All reactions were carried out in DMF with 2.0 equiv of TBAF (1 M in THF).

To illustrate the practicality of our protocol, the fluorodenitration of aniline-containing nitropyridine **1** was carried out to afford desired product **2** in one operation (64% yield, unoptimized) (Scheme 1). Our methodology obviates the protection-deprotection of the aniline nitrogen necessitated by the Balz−Schiemann process to access **2**.

Scheme 1



1 **2**, 64%

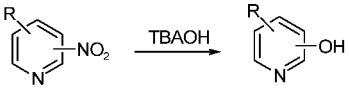
Although there is some precedence for the fluorodenitration of nitropyridines, the reported reaction conditions involve high temperatures and the use of KF as the fluoride source.[14] An important stipulation in these examples is that it is essential for the fluoride salt to be anhydrous, since the presence of water retards the reaction.[15] Similarly, the TBAF-promoted fluorodenitration of nitrobenzenes, required 5 equiv of *anhydrous* TBAF to effect the reaction. [8,16] In the present case, anhydrous conditions are not essential. Indeed, the commercially available solutions of TBAF in THF contain approximately 5% water. In fact, the use of anhydrous TBAF

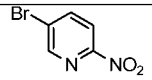
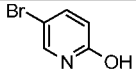
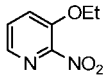
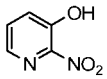
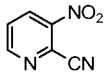
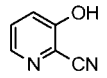
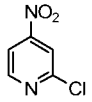
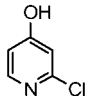
(6) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034.
(7) Attina, M.; Cacace, F.; Wolf, A. P. *J. Chem. Soc., Chem. Comm.* **1983**, 108.
(8) Clark, J. H.; Smith, D. K. *Tetrahedron Lett.* **1985**, *26*, 2233.
(9) The fluorodenitration reaction can be carried out in THF and CH_2Cl_2 with equal facility. DMF is the solvent of choice since the competing hydroxydenitration is suppressed (vide infra).
(10) **General Procedure.** To a solution of 2-cyano-3-nitropyridine (468 mg, 3.14 mmol) in 6 mL of DMF was added 6.3 mL (2 equiv) of a 1 M solution TBAF in THF (Aldrich). After 30 min, the dark red-brown reaction mixture was poured into 50 mL of a 1:1 mixture of water and EtOAc. The organic layer was washed twice with water and brine. The extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel using 5% to 10% ethyl acetate in hexane to afford 244 mg (63%) of volatile 2-cyano-3-fluoropyridine, which exhibited satisfactory ^1H, ^{19}F, and ^{13}C magnetic resonance spectra.
(11) Microwave heating was not beneficial in promoting the reaction. For example, the fluorodenitration of 3-ethoxy-2-nitropyridine (Table 1, entry 3) affords 3-ethoxy-2-fluoropyridine among a mixture of products in low yield (μw conditions: 180 °C, 30 min, <10%; 250 °C, 30 min, ~ 20%).
(12) Adams, D. J.; Clark, J. H.; Nightingale, D. J. *Tetrahedron* **1999**, *55*, 7725.
(13) In the case of entry 4, addition of TBAF produced a bright red reaction mixture. This is indicative of deprotonation of the 2-amino group by the highly basic TBAF.
(14) For example, see: Dolle, F.; Vallette, H.; Bottlander, M.; Hinnen, F.; Vaufre, F.; Guenther, I.; Crouzel. C. *J. Labelled Compd. Radiopharm.* **1998**, *41*, 451.
(15) In our experience, spray-dried KF in dry DMSO or CsF in DMF does promote fluorodenitration, albeit much more slowly than TBAF in DMF. Addition of 1 equiv of water to CsF in DMF inhibits the fluorodenitration.
(16) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216−3219. The authors dried commercial TBAF·$3H_2O$ at 40 °C under high vacuum overnight and reported 0.1−0.3 equiv of water in the anhydrous product.

proved deleterious in our experience.[17] Along these same lines, we determined that the fluorodenitration of 1,2-dinitrobenzene did not require anhydrous TBAF as had been previously reported.[8,18]

Treatment of 2-cyano-3-nitropyridine with TBAF under the standard reaction conditions (Table 1, entry 6) yielded the expected product, as well as 2-cyano-3-hydroxypyridine (15% yield). The latter byproduct undoubtedly is a consequence of the presence of water in commercial solutions of TBAF. To exploit this observation we explored this potentially useful transformation in the context of tetrabutylammonium salt induced denitration and examined the reactivity of nitropyridines with tetrabutylammonium hydroxide (TBAOH) with selected substrates (Table 2). With

Table 2. Hydroxydenitration of Pyridines[a]



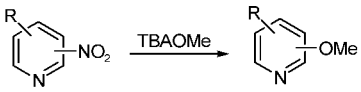
entry	substrate	t (h), *T* (°C)	product	yield
1		12, 23		45%
2		12, 90		69%[b]
3		1, 23		20%
4		4, 23		46%

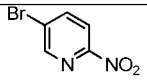
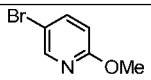
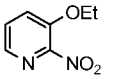
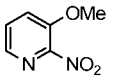
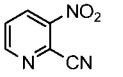
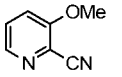
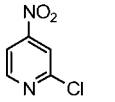
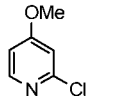
[a] All reactions were carried out in THF with 2.0 equiv of tetrabutylammonium hydroxide (40% in water). [b] The expected product, 3-ethoxy-2-hydroxypyridine, was not observed.

the exception of entry 3, only one major product was formed, as determined by the HPLC profiles of the crude reaction mixtures. However, the hydroxypyridines proved difficult to isolate and only moderate product yields were obtained. Interestingly, 3-ethoxy-2-nitropyridine, which underwent smooth fluorodenitration (Table 1, entry 3), did not afford the anticipated 3-ethoxy-2-hydroxypyridine product (Table 2, entry 2). Instead, the ethoxy group was displaced by hydroxide under the reaction conditions that were employed. The fact that the tetrabutylammonium ion plays an important role in the reaction is evidenced by the observation that the hydroxydenitration could not be efficiently carried out with aqueous NaOH in THF.[19]

In an analogous manner, we also briefly investigated the use of tetrabutylammonium methoxide (TBAOMe) in the formation of methoxypyridines (Table 3). With the exception of electron-rich 3-ethoxy-2-nitropyridine (entry 2), the methoxydenitration reactions were complete within 2 h at room temperature. We have been able to find only one literature

Table 3. Methoxydenitration of Pyridines[a]



entry	substrate	t (h), *T* (°C)	product	yield
1		1, 23		69%
2		4, 65		51%[b]
3		0.5, 23		70%
4		2, 23		95%

[a] All reactions were carried out in THF with 2.0 equiv of TBAOMe (20% in MeOH). [b] Isolated 17% of 1,2-dimethoxypyridine.

report that documents the displacement of a nitro group with alkoxide in the pyridine series.[20] Not surprisingly, this conversion required harsh reaction conditions.[21]

In summary, we have shown that the TBAF-promoted fluorodenitration of nitropyridines is a mild and efficient alternative to the classical two-step Balz−Schiemann procedure for the synthesis of fluoropyridines. The reaction proceeds in good yields and appears to be general for pyridines with nitro substitution at the 2- or 4-positions; 3-nitropyridines require attendant electron-withdrawing groups for efficient conversion to product. We have also shown that hydroxy- and methoxydenitrations of substituted nitropyridines can be carried out with commercially available tetrabutylammonium salts to provide hydroxy- and methoxypyridines in preparatively useful yields.

Acknowledgment. We are grateful to Ms. Joan Murphy for mass spectral analysis and Dr. Steve Pitzenberger for NMR analysis. We would like to thank Mr. Greg Hughes and Dr. Paul O'Shea for useful discussions.

Supporting Information Available: Experimental details and physical characterization data for fluoropyridines. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047688V

(17) Interestingly, when anhydrous TBAF[16] was used with 2-cyano-3-nitropyridine, hydroxydenitration proved to be the predominant reaction pathway over fluorodenitration.

(18) Fluorodenitration of 1,2-dinitrobenzene with 5 equiv of commercial 1 M TBAF in THF was complete in 1 h at room temperature to afford 2-fluoro-nitrobenzene in 72% isolated yield.

(19) Reaction of 2-chloro-4-nitropyridine with 1 N NaOH in THF/water (1:1) required heating to 60 °C for 24 h to effect complete conversion to the 2-chloro-4-hydroxypyridine. Additionally, several uncharacterized byproducts were observed in the hydroxydenitration under these conditions.

(20) Den Hertog, H. J.; Jouwersma, C.; Van Der Wal, A. A.; Willebrands-Schogt, E. C. C. *Rec. Trav. Chim. Bays-Pas* **1949**, *68*, 275.

(21) 5-Bromo-2-nitropyridine was reacted with sodium ethoxide in ethanol at 150 °C for 24 h. No yield was reported.