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Convenient fluorination of nitro and nitrile compounds with Selectfluor

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Abstract—A variety of nitro and nitrile compounds were fluorinated in good yields by Selectfluor under mild conditions. For these transformations to be successful, it is crucial to select proper amounts of an appropriate base as a function of the properties of the substrate and also to use Selectfluor only as required.

The remarkable synthetic importance of nitro compounds is based on two facts: (1) nitro compounds, especially aromatic nitro compounds, are valuable precursors for azo dyes and explosives; and (2) their easy availability and transformation into a variety of other diverse functionalities makes them important reagents for syntheses of complex target molecules.[1] The widespread interest in halogenated nitro compounds also stems from their pronounced antimicrobial and insecticidal activity.[2] Although halogenation of nitroalkanes is especially well known and simple,[3] there are few satisfactory methods for introducing fluorine or fluorine-containing groups into nitro compounds.[4] The usual method is reaction of nitronate salts with fluorine[5] or perchloryl fluoride.[6] However, these reagents are not as readily used as off-the-shelf reagents, and their high reactivities while offering little or no selectivity has curtailed their use. In a rather novel process, fluorination of nitro compounds with acetyl hypofluorite was reported.[7] However, this requires the preparation of a rather unstable fluorinating reagent, which must be utilized immediately.

More convenient, more efficient, and more straightforward methods for introduction of fluorine into nitro compounds are highly desired. The use of a variety of N–F-containing electrophilic fluorinating reagents including perfluoropiperidine,[8] *N*-fluoro-*N*-alkyl-sulfonamides,[9] and *N*-fluoroquinuclidinium fluoride[10] for fluorination of nitro compounds was studied, but each of these methods was examined with only a small number of nitro compounds. Currently, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™, F-TEDA-BF_4) is a commercially available, powerful electrophilic fluorinating agent, which is effective for site-selective fluorination of a variety of organic molecules.[11] In order to develop a convenient method for introducing fluorine into nitro compounds with the potential for modifying the properties of some traditional high energy nitro compounds, the base mediated reactions of nitro compounds with Selectfluor were investigated.

The reaction of phenyl nitromethane **1a** with Selectfluor did not proceed under neutral conditions even when subjected to heat or microwave radiation. It was clear that in order to carry out this transformation an anionic center would have to be formed initially. Potassium hydroxide was an adequate base to cause the reaction to occur. A mixture of acetonitrile and water (1:1) was the best choice of solvent in which Selectfluor, KOH, and **1a** were dissolved. This reaction was carried out in a stepwise process. After stirring the base and **1a** for 2–3 hours in order to form the corresponding potassium nitronate salt, Selectfluor was added in one portion, and stirring was continued for 12 h to complete the reaction. In most cases, a mixture of monofluorinated **2a**, difluorinated **3a**, and starting material **1a** was found. The nature of the base and amounts of base and Selectfluor were controlled to guide the outcome of the reaction. After a series of runs (Table 1), undertaken by balancing the

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Table 1. Optimization of the reaction conditions between **1a** and Selectfluor

1	1	None	CH_3CN[a]	No reaction				
1	1	KOH (1)	CH_3CN/H_2O	10 (72%)[b]	:	0	:	1
1	2	KOH (1)	CH_3CN/H_2O	10	:	0	:	1.1
1	1	KOH (2)	CH_3CN/H_2O	10	:	2	:	1.6
1	2	KOH (2)	CH_3CN/H_2O	10 (70%)[b]	:	2.5	:	0
1	**1.5**	**KOH (1.5)**	**CH_3CN/H_2O**	**13 (81%)[b]**	**:**	**1**	**:**	**0.1**
1	1	TBAH (2)	CH_3CN	0	:	1	:	0[c]
1	2	TBAH (2)	CH_3CN	1	:	2	:	0

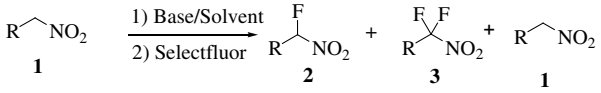
[a] Reflux or irradiation by microwave.
[b] Isolated yield.
[c] Complicated reaction.

yield of the intended product **2a**, the chemoselectivity (ratio of **2a** to **3a**) and conversion of **1a**, the optimized reaction conditions (highlighted in Table 1) using 1.5 equiv of KOH and Selectfluor was found, which led to the monofluorinated product **2a** in high yield, although minor amounts of the difluorinated species **3a** and a trace amount of starting material **1a** was observed in the crude product mixture prior to column separation.

Further experiments led to the conclusion that there were no general reaction conditions that would work well for all substrates.[12] Depending on the substrate, a different base, solvent system, and quantity of base and Selectfluor were required for the intended transformation to occur. The optimized reaction results for each substrate are given in Table 2.[13]

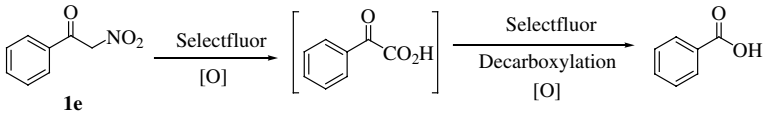
For most of the aryl substituted nitromethane compounds (**1a**–**c**), 1.5 equiv of KOH and Selectfluor were required for complete conversion of the starting material resulting in the monofluorinated compound as the major product. However, when the same amounts of KOH and Selectfluor were used in the reaction with 4-nitrophenyl nitromethane **1d**, the reaction exhibited poor chemoselectivity for both monofluorinated and difluorinated products in a ratio of 2:1. Under similar conditions with benzoyl nitromethane **1e**, the monofluorinated product **2e** was obtained in very low yield although most of the starting material had been consumed. This reaction did not give the difluorinated product but rather benzoic acid was found as a low yield by-product. If 1 equiv of each KOH and Selectfluor were used (Table 2), **2e** was obtained in 40% yield accompanied by a 20% yield of benzoic acid. Since difluoronitromethane, which would be the expected hydrolyzed product of the difluorinated compound, was not detected by ^{19}F NMR spectra in the reaction mixture, the following decarboxylation[14] and oxidation process is proposed (Scheme 1) in order to rationalize the forma-

Table 2. Monofluorination of nitro compound **1** with Selectfluor



R	Base[a]	S–F[b]	Solvent	**2**:**3**:**1**	**2**[c]	^{19}F NMR[d]
1a Ph	KOH (1.5)	1.5	CH_3CN/H_2O[e]	13:1:0.1	81	−139.9
1b 4-$MeOC_6H_4$–	KOH (1.5)	1.5	CH_3CN/H_2O[e]	12.4:1:0	79	−137.3
1c 4-BrC_6H_4–	KOH (1.5)	1.5	CH_3CN/H_2O[e]	5.2:1:0	64	−140.9
1d 4-$O_2NC_6H_4$–	KOH (1.0)	1	CH_3CN/H_2O[e]	7:1:0	83	−142.9
1e PhCO–	KOH (1.0)	1	CH_3CN/H_2O[e]	1:0:0	40	−144.8
1f $PhCH_2$–	TBAH[f] (1.5)	1.5	CH_3CN/H_2O[g]	33:1:1	89	−145.8
1g $C_{11}H_{23}$–	TBAH (1.5)	1.5	CH_3CN/H_2O[g]	1:0:0	98	−146.7
1h $CH_3CO(CH_2)_2$–	TBAH (1.5)	1.5	CH_3CN/H_2O[g]	37:1:0.5	88	−147.5
1i *n*-$BuO_2C(CH_2)_2$–	NaH (1.1)	1.1	DMF	6:0:1	70	−148.0
1j PhC(OH)–	KOH (1.5)	1.5	CH_3CN/H_2O[g]	20:0:1	30	−153.9[h] −163.1[h]

[a] Equivalents.
[b] Selectfluor, equivalents.
[c] Yield, %. All compounds were confirmed by NMR.
[d] δ (ppm).
[e] 1:1 ratio.
[f] Tetrabutylammonium hydroxide.
[g] 2:1 ratio.
[h] Two diastereomers were produced in a ratio of 10:8.



Scheme 1.

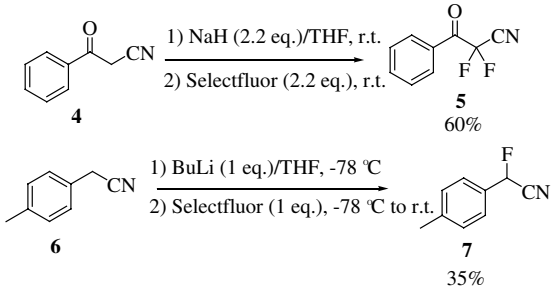
tion of benzoic acid. Selectfluor can also behave as an oxidizing agent, and nitro compounds are labile to oxidation to aldehydes or acids by some moderately strong oxidizers.[1] It has been reported that some secondary and primary nitro compounds could be oxidized to ketones and aldehydes, respectively, by using $FClO_3$.[6d] The proposed ketoacid intermediate was not detected.

For alkyl substituted nitromethanes **1f–h**, tetrabutylammonium hydroxide (TBAH), was used. When the ratio of acetonitrile and water was changed to 2:1, the reactions gave the monofluorinated products **2f–h** in high yields and only traces of unreacted starting material and difluorinated products were observed. In the case of the nitro ester **1i**, since the ester moiety, whether in the starting material or in the product, underwent vigorous hydrolysis when either KOH or TBAH was used as base, this reaction was carried out using anhydrous DMF as solvent with NaH as base. Perhaps due to the hydroxyl functionality, the reaction of nitro alcohol **1j** was very complicated and gave the desired product only in low yield.

Under the same conditions using KOH as base, we found that the monofluorinated compound **2a** could undergo further fluorination to give the difluorinated product **3a** in 73% yield. Thus, if another portion of base and Selectfluor was added to the same reaction mixture after the first monofluorination step of **1a** was completed, the difluorinated product **3a** could be directly obtained in one pot through two stages. This two-stage process[15] gave the difluorinated products of **1a–d** as expected in a straightforward manner although in a moderate yield (Table 3).

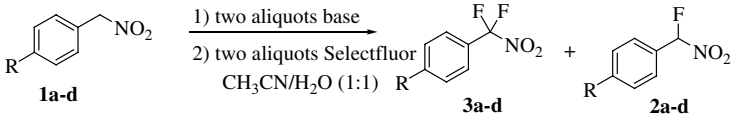
Given the success of fluorinating nitro compounds, we attempted, by using the same method, to introduce fluorine into some nitrile compounds since these materials also play a very important role in synthetic organic chemistry. Some direct fluorination methods by treatment of the corresponding carbanion species of nitrile compounds with electrophilic fluorinating agents such as $FClO_3$,[16] *N*-fluorobenzene disulfonimide,[17] and fluorine[18] have been investigated. However, we looked for a general method to fluorinate a variety of nitrile compounds with Selectfluor.

Since protons alpha to the nitrile group have lower acidity than those in nitro compounds, bases such as KOH and TBAH did not promote the reaction of a nitrile compound with Selectfluor. Although sodium hydride did work in the reaction of α-benzoyl acetonitrile (**4**),[19] it was a surprise to find that the reaction gave a mixture of difluorinated (^{19}F δ −92.04 ppm), and monofluorinated products (^{19}F δ −191.70 ppm) and starting material in a ratio of 10:4:7 with difluorinated product (**5**) as the major product even when 1 equiv each of NaH and Selectfluor were used in the reaction (Scheme 2). The second fluorination step from monofluorinated product to difluorinated product occurs more readily than the first step fluorination of the starting material. Thus, the monofluorinated product was not obtained. Finally, **4** reacted with 2.2 equiv each of NaH and Selectfluor to furnish the difluorinated product **5** exclusively in 60% yield (Scheme 2). Only a very strong base such as BuLi



Scheme 2.

Table 3. Two-stage difluorination of nitro compound **1** with Selectfluor



Entry	1	Base[a]	S–F[b]	3:2	3[c]	^{19}F NMR[d]
1	**1a** H	1.5	1.5	1:0	47	−86.8
2	**1b** MeO–	1.5	1.5	5:1	41	−85.9
3	**1c** Br	1.5	1.5	1:0	28	−86.8
4	**1d** NO_2	1	1	10:1	66	−86.8

[a] KOH, equivalents.
[b] Selectfluor, equivalents.
[c] Isolated yield, %.
[d] δ (ppm).

promoted the fluorination of 4-methylbenzyl cyanide (**6**). When 1 equiv of BuLi was used, the reaction gave only the corresponding monofluorinated product **7** (^{19}F δ −164.38 ppm) in 30% yield (Scheme 2) along with other by-products. About 50% of the starting material was recovered. Increasing the quantity of BuLi resulted in lower starting material conversion and more by-product formation. Efforts to find the conditions to fully convert the starting material and improve the reaction yield are still in progress.

In conclusion, the reactions of a variety of nitro compounds with Selectfluor were investigated. By choosing an appropriate base as a function of the properties of the substrate and using proper quantities of the base and Selectfluor, these compounds could be monofluorinated or difluorinated in good to high yield with nearly complete conversion. The study for efficient fluorination of nitrile compounds is continuing.

Acknowledgments

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13. General procedure for monofluorination of nitro compound **1** (**1d** as an example): 1.1 mL of aqueous 0.5 N KOH solution was added to the mixture of nitrophenylnitromethane **1d** (0.55 mmol, 100 mg) in acetonitrile (5 mL) and water (5 mL). The reaction mixture was stirred at 25 °C for 2 h. Selectfluor (0.55 mmol, 205 mg) was added to the reaction mixture in one portion, and stirring was continued for 12 h. The resulting mixture was poured into 20 mL water and extracted with methylene chloride (3 × 15 mL). The extracts were washed with 20 mL brine, dried (Na_2SO_4), and filtered. The solvent was evaporated and the resulting residue was chromatographed with *n*-hexane/ethyl acetate/CH_2Cl_2 (5:1:1) as eluent to give the monofluorinated nitro compound **2d.**
Compound **2b**: 4-methoxyphenylfluoronitromethane. Pale yellow oil (*n*-hexane/AcOEt (5/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.56 (d, J = 48.4 Hz, 2H), 3.86 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −137.32. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.3, 129.2 (d, J = 5.9 Hz), 123.3 (d, J = 21.8 Hz), 115.4, 111.1 (d, J = 238.4 Hz), 56.3. GC–MS (EI) 154 (M^+−MeO), 140, 139, 124, 109, 96, 91, 70, 63, 50, 39. IR (KBr) 2939, 2843, 1612, 1574, 1516, 1373, 1305, 1257, 1207, 1177, 1095, 1028, 867, 835, 795, 751, 710, 584, 525 cm^{-1}. Anal. Calcd for $C_8H_8FNO_3$: C, 51.90; H, 4.36; N, 7.56. Found: C, 52.00; H, 4.45; N, 7.54.
Compound **2h**: 5-fluoro-5-nitro-2-pentanone. Clear liquid (*n*-hexane/AcOEt (3/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddd, J = 50.5, 6.0, 4.9 Hz, 1H), 2.73–2.36 (m, 4H), 2.22 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −147.46 (dt, J = 50.5, 22.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.1, 110.8 (d, J = 238.8 Hz), 36.8 (d, J = 4.0 Hz), 30.7, 27.9 (d, J = 20.1 Hz). GC–MS (EI) 134 (M^+−O+1), 103, 87, 73, 59, 43, 39. IR (KBr) 2925, 2360, 2341, 1719, 1573, 1427, 1370, 1359, 1170, 1130 cm^{-1}. Anal. Calcd for $C_5H_8FNO_3$: C, 40.27; H, 5.41; N, 9.39. Found: C, 40.62; H, 5.30; N, 9.31.
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15. General procedure for two-stage difluorination of nitro compound **1d** (as a example): 1.1 mL aqueous 0.5 M KOH was added to the mixture of nitrophenylnitromethane **1d** (0.55 mmol, 100 mg) in acetonitrile (5 mL) and water (5 mL). The reaction mixture was stirred at 25 °C for 2 h. Selectfluor (0.55 mmol, 205 mg) was added in one portion, and the mixture was stirred for 3 h. Another quantity of 1.1 mL of aqueous 0.5 M KOH and Selectfluor (0.55 mmol, 205 mg) were added to the reaction mixture again with a 2 h interval. Stirring was continued overnight at 25 °C. The resulting mixture was poured into 20 mL water and extracted with methylene chloride (3 × 15 mL). The

extracts were washed with 20 mL brine, dried (Na_2SO_4), and filtered. The solvent was evaporated to dryness and the resulting residue was chromatographed with *n*-hexane/ethyl acetate/CH_2Cl_2 (10:1:1) as eluent to give the difluorinated nitro compound **3d**.

Compound **3d**: 4-nitrophenyldifluoronitromethane. White solid (mp 81–83 °C, *n*-hexane/AcOEt/CH_2Cl_2 (5:1:1), R_f 0.3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 8.6 Hz, 2H), 8.01 (d, J = 8.6 Hz, 2H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −86.78. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.8, 133.9 (t, J = 25.8 Hz), 128.7 (t, J = 5.3 Hz), 125.2, 121.3 (t, J = 286.1 Hz). GC–MS (EI) 172 (M^+-NO_2), 156, 142, 126, 114, 107, 88, 75, 63, 50, 38. IR (KBr) 3117, 2963, 1948, 1811, 1615, 1599, 1533, 1413, 1352, 1296, 1262, 1217, 1093, 1014, 954, 859, 819, 707, 462, cm^{-1}. Anal. Calcd for $C_7H_4F_2N_2O_4$: C, 38.55; H, 1.85; N, 12.84. Found: C, 38.57; H, 2.07; N, 12.66.

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