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The first application of Selectfluor™ in electrophilic fluorination of amines: a new route to $-NF_2$, –NHF, and >NF compounds

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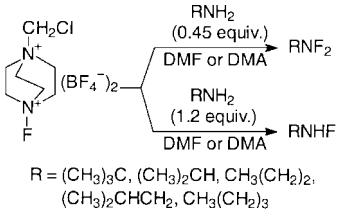
Reactions of primary amines, RNH_2 [R = $(CH_3)_3C$–, $(CH_3)_2CH$–, $CH_3(CH_2)_2$–, $(CH_3)_2CHCH_2$–, $CH_3(CH_2)_3$–] and secondary amines, R_2NH [(R = CH_3CH_2–, $CH_3(CH_2)_2$–, $(CH_3)_2CHCH_2$–], with Selectfluor™ in acetonitrile or DMF or DMA result in formation of the corresponding RNF_2, RNHF, and R_2NF in high yields.

The synthesis and reactivity of compounds that contain the nitrogen–fluorine bond have been studied extensively.[1–7] Many methods have been developed to prepare *N*-fluoroamines and *N*,*N*-difluoroamines by using either elemental fluorine or other fluorine-transfer reagents which often gave poor yields of the final products and required extreme precautions. In 1960, Frazer reported the formation of RNF_2 (R = CH_3, C_2H_5) in moderate yields from photolysis of RI + N_2F_4 through Pyrex.[8] Thermolysis of mixtures of alkanes and N_2F_4 at 300 °C resulted in mono and disubstituted difluoroamino compounds.[9] However, with the advent of modern day electrophilic fluorinating reagents, such as CF_3OF, XeF_2, ClO_3F and $CsSO_4F$, as well as fluorine itself, it has been possible to prepare a variety of >NF or −NHF compounds.[9–11] A decade ago we reported the effective synthesis of acyclic secondary and cyclic fluoroamines, in addition to *N*-nitrosoamines, by using trifluoroamine oxide (NF_3O) as the fluorinating agent at < 0 °C.[12]

The application of Selectfluor™ for the electrophilic fluorination of primary and secondary amines provides a powerful straightforward one step route to $-NF_2$ and >NF compounds and, for the first time, the opportunity to prepare –NHF compounds *via* control of reaction stoichiometry. Since the discovery of this reagent, considerable success in the electrophilic fluorination of organic molecules, especially in the formation of C–F bonds, has been realized but the mechanism of the fluorine-transfer step has remained minimally understood.[13-15]

Initially, *tert*-butylamine (3 mmol) was reacted with Selectfluor™ (6.2 mmol) at 0 °C in acetonitrile for 6 h. Analysis of the reaction mixture with GCMS showed complete consumption of the *tert*-butylamine. Separation of *tert*-butyldifluoroamine from acetonitrile was not very clean due to the small difference between the boiling points of the solvent and the product. *tert*-Butyldifluoroamine was characterized spectroscopically in acetonitrile solution. The above reaction was also found to be equally successful when DMF or DMA was used as solvent and was completed within an hour. These solvents were found to be suitable due to their high boiling points which made the separation of the products from the solvent relatively straightforward. In some cases, the formation of $(CH_3)_2NCOF$[16] (≤ 5%) was observed as a byproduct when DMF was used as a solvent. By using similar reaction conditions,† the other primary amines, RNH_2 [R = $(CH_3)_2CH$–, $CH_3(CH_2)_2$–, $(CH_3)_2CHCH_2$–, $CH_3(CH_2)_3$–], were converted in DMA solution into the corresponding difluoroamines in good yields (Scheme 1, Table 1). An attempt to prepare *tert*-butyl fluoroamine [$(CH_3)_3CNHF$] by the slow addition of a DMF solution of *tert*-butylamine (3 mmol) into a stirred suspension of Selectfluor™ (3 mmol) solution in DMF resulted in the formation of a mixture of difluoro and fluoroamine in a 9:1 ratio. However, when the addition of the reagents was reversed, *tert*-butylfluoroamine was formed as the sole product (Scheme 1, Table 1).

Several secondary amines, R_2NH [(R = CH_3CH_2–, $CH_3(CH)_2$–, $(CH_3)_2CHCH_2$–], were reacted at 0 °C to 25 °C with 1.2 equiv. of Selectfluor™ in DMA‡ for 2 h. Separation of



Scheme 1

Table 1 Electrophilic fluorination of amines with Selectfluor™[a]

Entry	Substrates	Products[b]	Conversion (%)	Yield (%)[c] (pure)	^{19}F NMR (δ in ppm)
1	$(CH_3)_3CNH_2$	$(CH_3)_3CNF_2$	100	80	28.6
2	$(CH_3)_3CNH_2$	$(CH_3)_3CNHF$[d]	100	85	−120.3
3	$(CH_3)_2CHNH_2$	$(CH_3)_2CNF_2$	100	78	39.0
4	$(CH_3)_2CHNH_2$	$(CH_3)_2CHNHF$[d]	100	82	−131.7
5	$CH_3(CH_2)_2NH_2$	$CH_3(CH_2)_2NF_2$	100	75	55.0
6	$CH_3(CH_2)_2NH_2$	$CH_3(CH_2)_2NHF$[d]	100	63	−117.3
7	$(CH_3)_2CHCH_2NH_2$	$(CH_3)_2CHCH_2NF_2$	100	74	33.0
8	$(CH_3)_2CHCH_2NH_2$	$(CH_3)_2CHCH_2NHF$[d]	100	66	−140.9
9	$CH_3(CH_2)_3NH_2$	$CH_3(CH_2)_3NF_2$	100	72	54.8
10	$CH_3(CH_2)_3NH_2$	$CH_3(CH_2)_3NHF$[d]	100	80	−116.6
11	$(CH_3CH_2)_2NH$	$(CH_3CH_2)_2NF$	100	65	−53.0
12	$(CH_3CH_2CH_2)_2NH$	$(CH_3CH_2CH_2)_2NF$	100	76	−50.3
13	$[(CH_3)_2CHCH_2]_2NH$	$[(CH_3)_2CHCH_2]_2NF$	100	73	−46.5

[a] All the reactions were carried out in *N*,*N*-dimethylacetamide (DMA). [b] All the products were characterized by spectroscopic analysis and known compounds were identified by comparing with the spectroscopic data reported in the literature. [c] The yields in entries No. 1–4 were identical when either DMF or DMA was used as solvent. [d] New compounds.

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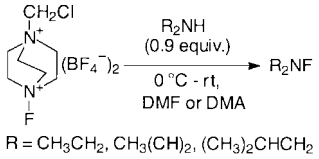

Scheme 2

the product by low temperature trap-to-trap distillation gave the corresponding *N*-fluoroamines, R_2NF [(R = CH_3CH_2–, $CH_3(CH)_2$–, $(CH_3)_2CHCH_2$–] in good isolated yields (Scheme 2).

The present report describes a powerful and simple method for the preparation of *N*-difluoro and *N*-fluoro compounds (high energy molecules) with some advantages in comparision with some other routes. The stability of these volatile liquids is variable. While all are stable in solution in Pyrex glass containers for several days at 25 °C, various degrees of decomposition occur over time. For example, $(CH_3)_3CNF_2$ was found to be stable in a sealed tube for at least three months under refrigeration, while $CH_3CH_2CH_2CH_2NHF$ decomposed fully after an equal time in Pyrex at 25 °C. A sample of $(CH_3)_3CNHF$ refrigerated in a vial for several months showed no decomposition based on NMR spectral measurements. However, R_2NF compounds are reported to be unstable in Pyrex glass for extended periods.[12]

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Notes and references

† To a solution of 3 mmol (1.06 g) of Selectfluor™ in 3.5 mL of DMF or DMA, 1.35 mmol of primary amine or 2.7 mmol of secondary amine in 1.5 mL of DMF or DMA was added dropwise at 0 °C. After 0.5 h stirring, the reaction mixture was stirred for an additional 1.5 h at 25 °C. In general, trap-to-trap distillation under vacuum allowed the separation of the solvent (trap at −20 °C) from the product which may be stopped in a trap at −78 °C or may pass through a trap at −78 °C and stop in a trap at −100 °C. **$(CH_3)_3CNF_2$**:[9] IR (gas phase): 2991 vs, 2944 s, 1485 s, 1375 vs, 1253 m, 1222 m, 980 vs, 880 vs, 587 m cm^{-1}; δ_H (200 MHz, CD_3CN): 1.24 (t, 9H, $J_{H\text{-}F}$ = 1.6 Hz); δ_F (188 MHz, CD_3CN): 28.7 broad singlet; δ_C (50 MHz, CD_3CN): 22.8, 70.6 (t, J = 6.8 Hz); MS (EI) *m/e* (species intensity): 110 (M + H, 1), 94 ($M^+ - CH_3$, 5), 57 ($(CH_3)_3C^+$, 85), 41 (CH_3CN^+, 100). **$(CH_3)_2CHCH_2]_2NF$**:[12] (trapped at −78 °C, passing −40 °C) IR (gas phase): 2986 vs, 2897 vs, 2808 s, 1472 s, 1390 s, 1371 s, 1290 w, 1243 w, 1142 s, 1111 m, 930 w, 833 m cm^{-1}; δ_F (188 MHz, CD_3CN): 0.98 (d, 12H, J = 21 Hz), 2.1 (m, 2H), 2.88 (dd, 4H, $J_{H\text{-}F}$ = 40.8 Hz); δ_F (200 MHz, CD_3CN): −46.5 q ($J_{F\text{-}H}$ = 40.0 Hz); MS (EI) *m/e* (species intensity): 147 (M^+, 6), 127 ($M^+ - HF$, 1), 104 ($M^+ - (CH_3)_2CH$, 63), 57 ($(CH_3)_2CHCH_2^+$, 100).

‡ To a stirred solution of primary amine (3.2 mmol in 2 mL of DMF or DMA), a Selectfluor™ solution (3 mmol in 3 mL of DMF or DMA) was added dropwise at 0 °C. After 0.5 h stirring, the reaction mixture was stirred at 25 °C for an additional 0.5 h. Solvent was retained in a trap at −20 °C and the product was isolated from a trap maintained at −78 °C. **$(CH_3)_3CNHF$**: δ_H (200 MHz, CD_3CN): 1.06 (d, 9H, $J_{H\text{-}F}$ = 2.2 Hz), 8.70 (br d, $J_{H\text{-}F}$ = 45 Hz); δ_F (188 MHz, CD_3CN): −131.7 (broad doublet, $J_{H\text{-}F}$ = 45 Hz); δ_C (50 MHz, CD_3CN): 25.2, 59.0 (d, J = 10.7 Hz); MS (EI) *m/e* (species intensity): 92 (M + H, 1), 76 ($M^+ - CH_3$, 100), 57 ($(CH_3)_3C^+$, 40), 41 (CH_3CN^+, 92). **$(CH_3)_2CHNHF$**: 2977 vs, 2895 s, 1466 s, 1379 s, 1006s, 937m, 868 vs; δ_H (200 MHz, CD_3CN): 1.20 (br dd, 6H), 3.41 (d sept, $J_{CH3\text{-}H}$ = 6.2 Hz, $J_{CH\text{-}F}$ = 37.5 Hz), 8.44 (br d, $J_{H\text{-}F}$ = 46.5 Hz); δ_F (188 MHz, CD_3CN): −120.3 (dd sept, $J_{NH\text{-}F}$ = 46.0 Hz, $J_{CH3\text{-}F}$ = 1.3 Hz); δ_C (50 MHz, CD_3CN): 23.0, 24.18, 41.28; MS (EI) *m/e* (species intensity): 77 (M^+, 3), 63 ($M^+ - CH_3$, 71), 62 ($M^+ - (CH_3 + H)$, 100), 42 ($(CH_3)_2C^+$, 81).

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16 Characterization data: IR (gas phase): 2975 vs, 2877 vs, 1738 s $\nu_{C=O}$, 1475 s, 1440 s, 1205 s, 927 s, 927 s, 786 vs cm^{-1}; NMR: δ_H (200 MHz, CD_3CN): 2.92 (d, 6H, $J_{H\text{-}F}$ = 36.5 Hz); δ_F (188 MHz, CD_3CN): −24.49 (sept, 1F, $J_{H\text{-}F}$ = 36.5 Hz); δ_C (50 MHz, CD_3CN): 55.7, 112.7. MS (EI) *m/e* (species intensity): 91 (M^+, 1), 76 ($M^+ - CH_3$, 2), 48 (COF^+ + 1, 100), 44 (CH_3CN^+, 3).