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A Convenient Synthesis of Perfluoroalkylated Amines by Oxidative Desulfurization-Fluorination

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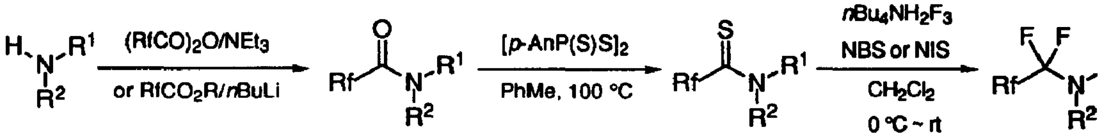
Abstract: *N*-Perfluoroalkylamines were synthesized from perfluoroalkanethioamides, which were easily accessible from perfluoroalkanamides, by the action of *N*-halo imide and $n\text{Bu}_4\text{NH}_2\text{F}_3$.

Perfluoroalkylamines exhibit unique physical and biological properties due to strongly electron-withdrawing character of perfluoroalkyl group. For example, they fairly dissolve molecular oxygen and are applied to artificial blood substitutes.[1] Preparation of perfluoroalkylamines like $(n\text{C}_4\text{F}_9)_3\text{N}$ has been carried out by electrolytic fluorination,[2] but this method can not be applied to synthesis of *mono*(perfluoroalkyl)-amines. We have demonstrated that ***oxidative desulfurization-fluorination*** allows us to readily prepare difluoromethylene compounds,[3] trifluoromethylarenes,[4] trifluoromethyl ethers,[5] and trifluoromethylamines.[6] We have further extended the methodology to the synthesis of perfluoroalkylamines and report herein the experimental results.



1 2 3

Perfluoroalkanamides **1** (Rf = CF_3, $n\text{C}_3\text{F}_7$, and $n\text{C}_8\text{F}_{17}$) were obtained in 82~98% yields from secondary amines by treatment with $(\text{CF}_3\text{CO})_2\text{O}$ or $(n\text{C}_3\text{F}_7\text{CO})_2\text{O}/\text{NEt}_3$/4-(*N,N*-dimethylamino)pyridine in CH_2Cl_2 at room temperature or $n\text{BuLi}/n\text{C}_8\text{F}_{17}\text{CO}_2n\text{Bu}$ in Et_2O at 0 °C, respectively. The amides **1** were converted into the corresponding thioamides **2** in 62~98% yields with the Lawesson's reagent ($[p\text{-AnP(S)S}]_2$, 1.2 equiv.) in toluene at 100 °C for 12 h.[7] *N*-Bromosuccinimide (NBS, 1.1 mmol) was added to a CH_2Cl_2 (1.5 mL) solution of **2** (0.5 mmol) and $n\text{Bu}_4\text{NH}_2\text{F}_3$[8] (1.5 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was poured into an aq. NaHCO_3-NaHSO_3 solution. The resultant was extracted with Et_2O, and the combined ethereal layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel thin layer (or column) chromatography to give the desired *N*-perfluoroalkylamines **3** in yields shown in Table 1.

Table 1. Preparation of Perfluoroalkylamines[a]

Run	Rf	R^1	R^2	**2**	**3**
1	CF_3	Ph	Ph	98	17[b]
2					64[c]
3	CF_3	1-Naph	CH_2Ph	90	57
4	CF_3	4-NC-C_6H_4	CH_2Ph	62	60
5	CF_3	4-Cl-C_6H_4	CH_2Ph	98	80
6	CF_3	4-MeO-C_6H_4	CH_2Ph	98	8[d]
7	nC$_3$F$_7$	Ph	Ph	77	63
8	nC$_3$F$_7$	4-Cl-C_6H_4	CH_2Ph	79	80
9	nC$_8$F$_{17}$	Ph	Ph	84	78
10					72[c]

a) Isolated yields (%) are given. b) Besides the desired product, a regioisomeric mixture of ring halogenated products was obtained. c) Yields using NIS are shown. d) The starting amide was isolated in 62% yield.

Substrates having an electron-deficient aryl substituent R^1 gave the desired perfluoroalkylamines in good yields (runs 4 and 5), whereas *N*-benzyl-*N*-(4-methoxyphenyl)pentafluoroethylamine was isolated in only 8% yield. Thus, **3** with an electron-rich aryl appears to be extremely labile to undergo hydrolysis. This contrasts sharply to the synthesis of trifluoromethylamines: trifluoromethylamines having both electron-deficient and -rich aryls can be obtained in good yields from the corresponding dithiocarbamates.[6] Accordingly, two fluorines and one perfluoroalkyl group or three fluorines on the carbon next to nitrogen appear to be essential to resist hydrolysis. In fact, the reaction of *N*-methyl-*N*-phenylpropanethioamide with NBS/nBu$_4$NH$_2$F$_3$ in CH_2Cl_2 under the same reaction conditions gave only a very complex mixture of products, and the desired α,α-difluoro amine could not be obtained. Ring halogenation was observed in the reaction of *N,N*-diphenyltrifluorothioacetamide and NBS (run 1), but *N*-perfluorobutyl or -nonyl amines were obtained in good yields without ring halogenation (runs 7-9). To avoid the halogenation reaction, NIS is the reagent of choice (run 2).

The method reported herein allows us to prepare hitherto hardly accessible mono(perfluoroalkyl)amines. Studies on physical properties, chemical stabilities and reactivities of these compounds are in progress in our Laboratories.

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