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Novel and Effective Synthesis of Trifluoromethylated Amines by Use of an $Et_3GeNa/C_6H_5SCF_3$ Combination

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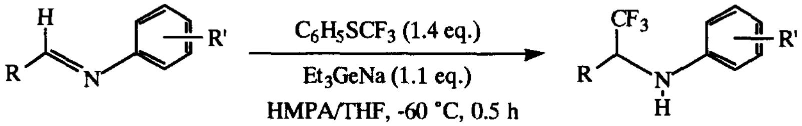
***Abstract*:** Efficient synthesis of trifluoromethylated amine derivatives by use of an $Et_3GeNa/C_6H_5SCF_3$ combination is described. This reaction proceeded smoothly to give the desired compound in excellent yield. © 1997 Elsevier Science Ltd.

The development of a preparative reaction of perfluoroalkylated amines is a very important objective in organic synthesis, because these compounds have unique biological, chemical and physical properties.[1] Several synthetic methods of these compounds were reported.[2,3] Among them, the most useful and straightforward synthesis is nucleophilic perfluoroalkylation of imines. For example, Suzuki and his co-workers reported that various imines reacted with perfluoroalkyl lithium which was generated from $C_nF_{2n+1}I$ in the presence of $BF_3 \cdot OEt_2$.[3] This reaction gave the desired compound in moderate to good yield, but trifluoromethylated amine derivatives (n=1) could not be synthesized at all.[3b] Moreover, there are no reports of preparation of these compounds by nucleophilic trifluoromethylation of imines. Accordingly, the study of an efficient synthetic method of trifluoromethylated amines by nucleophilic trifluoromethylation is significant. In this regard, we applied the novel trifluoromethylation method ($Et_3GeNa/C_6H_5SCF_3$) which was reported in our previous paper[4] for the formation of the foregoing compound (Scheme).

Scheme. Trifluoromethylation of Various Imines



This reaction proceeded smoothly under mild conditions to give the corresponding compounds in excellent yields. In this paper, we describe the syntheses of various types of trifluoromethylated amines using this method.

At first, we investigated trifluoromethylation of various imines which were synthesized from benzaldehyde and the substituted aniline derivatives. Some results are summarized in Table 1 with ^1H-, ^{13}C-, and ^{19}F-NMR data of the target products.

Table 1. Trifluoromethylation of Various Benzaldehyde Derivatives (R=Ph)

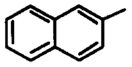
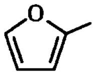
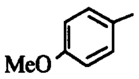
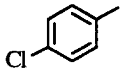
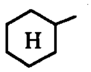
Entry	R'	Yield$^{a)}$ /%	^{1}H-NMR$^{b)}$ $PhC\underline{H}(CF_3)NH$-	^{13}C-NMR$^{c)}$ $Ph\underline{C}H(CF_3)NH$-	^{19}F-NMR$^{d)}$
1	H	96	4.93 (qd, 1H, *J* = 8.0, 6.6 Hz)	60.5 (q, *J* = 30 Hz)	-76.9 (d, *J* = 8.0 Hz)
2	*o*-Me	96	4.96 (qd, 1H, *J* = 8.0, 6.4 Hz)	60.5 (q, *J* = 30 Hz)	-77.1 (d, *J* = 8.0 Hz)
3	*m*-Me	96	4.91 (qd, 1H, *J* = 8.0, 7.3 Hz)	60.8 (q, *J* = 30 Hz)	-76.9 (d, *J* = 8.0 Hz)
4	*p*-Me	96	4.87 (qd, 1H, *J* = 7.0, 6.9 Hz)	62.2 (q, *J* = 30 Hz)	-76.9 (d, *J* = 6.9 Hz)
5	*o*-OMe	96	4.91 (qd, 1H, *J* = 7.3, 6.9 Hz)	60.3 (q, *J* = 30 Hz)	-77.0 (d, *J* = 6.9 Hz)
6	*m*-OMe	96	4.90 (qd, 1H, *J* = 7.3, 6.9 Hz)	60.5 (q, *J* = 30 Hz)	-76.9 (d, *J* = 6.9 Hz)
7	*p*-OMe	97	4.80 (m, 1H)	61.7 (q, *J* = 29 Hz)	-77.0 (d, *J* = 6.9 Hz)
8	*o*-Cl	96	4.95 (qd, 1H, *J* = 8.0, 7.3 Hz)	60.2 (q, *J* = 30 Hz)	-77.1 (d, *J* = 8.0 Hz)
9	*p*-Cl	97	4.87 (qd, 1H, *J* = 7.3, 6.9 Hz)	60.7 (q, *J* = 30 Hz)	-76.9 (d, *J* = 6.9 Hz)

a) Isolated yield. b) δ in ppm. c) δ in ppm. d) δ in ppm, referenced from $CFCl_3$.

When *N*-benzylideneaniline was treated with $C_6H_5SCF_3$ and Et_3GeNa in THF/hexamethylphosphoric triamide (HMPA) at -60 °C, the corresponding trifluoromethylated amine was produced quantitatively (entry 1).[5] Toluidine derivatives (*o*-, *m*-, and *p*-substituted) could be used as substrates and the desired compounds were obtained in excellent yields (entries 2-4). Furthermore, anisidine derivatives which had less reactive reaction centers for the nucleophilic reaction could be transformed to the corresponding products perfectly (entries 5-7). When *o*- and *p*-chlorinated aniline compounds were used as the starting materials, trifluoromethylated amines were obtained without decomposition of their structures (entries 8 and 9). All obtained products were identified by ^{1}H-, ^{13}C-, and ^{19}F-NMR. These compounds gave satisfactory spectral data.

Several results of trifluoromethylation of anils are shown in Table 2. Some arylated imines, such as naphthyl-, 2-furfuryl-, *p*-methoxyphenyl-, and *p*-chlorophenylimine, were transformed to the desired amines in excellent yields under the reaction conditions (entries 1-4). Furthermore, less reactive alkyl imines could be used as the substrate in this type of trifluoromethylation. Thus, *n*-hexyl-, *n*-heptyl-, and *n*-undecylimine reacted with a reactive species (trifluoromethyl anion) to give the corresponding compounds quantitatively (entries 5-7). Particularly, it is worth noting that a sterically hindered cyclohexyl derivative was easily prepared by this reaction (entry 8). These results suggested that this trifluoromethylation is useful for the synthesis of various trifluoromethylated amines.

Table 2. Transformation of Various Anils (R'=H) to the Corresponding Amine Derivatives

Entry	R	Yield[a] /%	^{1}H-NMR[b]	^{13}C-NMR[c]	^{19}F-NMR[d]
			$\mathrm{PhC\underline{H}(CF_3)NH}$-	$\mathrm{Ph\underline{C}H(CF_3)NH}$-	
1		95	5.08 (qd, 1H, J = 7.1, 6.9 Hz)	60.8 (q, J = 30 Hz)	-76.6 (d, J = 6.9 Hz)
2		98	5.07 (qd, 1H, J = 9.2, 6.9 Hz)	54.9 (q, J = 33 Hz)	-77.4 (d, J = 6.9 Hz)
3		95	4.85 (qd, 1H, J = 7.1, 6.9 Hz)	60.0 (q, J = 30 Hz)	-77.2 (d, J = 6.9 Hz)
4		97	4.89 (qd, 1H, J = 6.9, 6.8 Hz)	60.0 (q, J = 30 Hz)	-79.0 (d, J = 6.9 Hz)
5	C_6H_{13}	94	3.83 (m, 1H)	55.7 (q, J = 29 Hz)	-79.0 (d, J = 6.9 Hz)
6	C_7H_{15}	95	3.83 (m, 1H)	55.6 (q, J = 30 Hz)	-79.0 (d, J = 6.9 Hz)
7	$C_{11}H_{23}$	94	3.83 (m, 1H)	55.6 (q, J = 30 Hz)	-79.0 (d, J = 6.9 Hz)
8		95	3.74 (m, 1H)	60.0 (q, J = 28 Hz)	-74.7 (d, J = 6.9 Hz)

a) Isolated yield. b) δ in ppm. c) δ in ppm. d) δ in ppm, referenced from $CFCl_3$.

A typical procedure is as follows. To a THF (5 mL) solution of $C_6H_5SCF_3$ (386 mg, 2.17 mmol) and *N*-benzylideneaniline (281 mg, 1.55 mmol) was added Et_3GeNa in 4 mL of HMPA solution[6] (0.428 mol/dm^3, 1.71 mmol) slowly at -60 °C. After stirring for 0.5 h at -60 °C, the resulting mixture was passed through a short column of silica gel and eluted with ether. Concentration of this eluate followed by column chromatographic purification afforded 374 mg (96%) of the corresponding amine (table 1, entry 1).

In conclusion, we have reported a novel and effective synthesis of the trifluoromethylated amine derivative using an $Et_3GeNa/C_6H_5SCF_3$ combination. This reaction proceeded smoothly under mild conditions to give the desired compounds in excellent yield. It is thought that this reaction is very important as a first example of the nucleophilic trifluoromethylation of imines using germanium compounds in not only organic synthesis or fluorine chemistry but also group 14 element chemistry.

References and Notes.

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4. Yokoyama, Y.; Mochida, K. *Synlett* **1996**, 1991.
5. When *N*-benzylidenebenzylamine or *N*-benzylideneallylamine was used as the substrate, the corresponding trifluoromethylated amines were not obtained; nevertheless, the starting materials were consumed. Many products which could not be identified were formed. Further investigation is now in progress.
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