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Generation and Reaction of Metal Free Trifluoroacetimidoyl Carbanion

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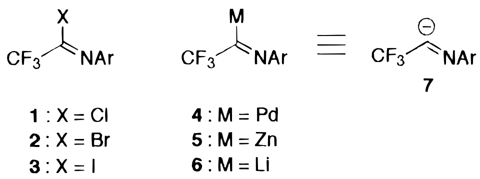
One of the synthetic methods for trifluoromethylated compounds involves the utilization of trifluoromethyl building blocks.[1] *N*-Aryl-2,2,2-trifluoroacetimidoyl halides **1**−**3** are among the promising building blocks for trifluoromethylated heterocycles, which are potentially bioactive.[2] We have already demonstrated a one-pot synthesis[3] of **1** and **2** and their electrophilic,[4] radical,[5] and nucleophilic[6−8] carbon−carbon bond formations at the imino carbon. In particular, metalations of **3** such as palladation,[6] zincation,[7] and lithiation[8] are useful for the generation of the carbanion equivalents **(7)** (Scheme 1).

Among them, lithium species **(6)** behave as the most typical carbanions, but they are unstable at room temperature and must be handled below −60 °C in the case of the *N*-2,6-dimethylphenyl compound and −100 °C for the *N*-4-methoxyphenyl compound.[8] Lithium preferably attaches on the nitrogen atom of the imine moiety; thus the lithium species **(6)** behave as carbene type intermediates **(8)** and predominantly dimerize at temperatures higher than −60 °C[8,9] (Scheme 2).

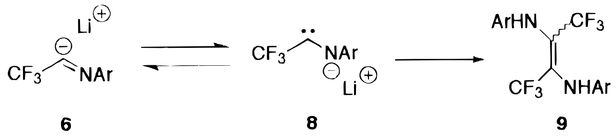
The imine moiety (C═NR) of **1**−**3** is equivalent to an acyl moiety so that the trifluoroacetimidoyl carbanion **(7)**[10] is a synthetic equivalent of a trifluoroacetyl carbanion.

Therefore, it is challenging to generate the metal free trifluoroacetimidoyl carbanion **(12)** as the corresponding tetraalkylammonium species, which should be more stable than **6**. It has been reported that the quaternary ammonium species was more useful as a counter cation than lithium for the α-carbanion of 2,2,2-trifluoroethyl phenyl sulfone generated by the action of LDA in THF−HMPA. The carbanion could be trapped with CH_3I and I_2.[11,12] Replacement of lithium with tetraalkylammonium cation would stabilize the carbanion **(7)** and promote preferential carbon−carbon bond formation at the imine carbon. Here, we describe a synthesis of (trifluoroacetimidoyl)trimethylsilanes **(10)**, fluoride ion catalyzed generation of carbanion **(12)**, and its reaction with various electrophiles.

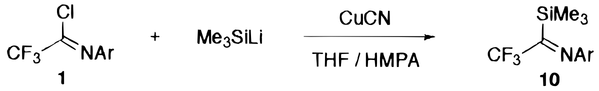
Scheme 1



Scheme 2



Scheme 3



Results and Discussion

Preparation of (Trifluoroacetimidoyl)trimethylsilanes (10). (Trifluoroacetimidoyl)trimethylsilane (**10a**, Ar = $2,6\text{-}Me_2C_6H_3$) was prepared in 84% yield by the reaction of (trifluoroacetimidoyl)lithium **(6)** with TMSCl. But, this method was usable only for the *N*-2,6-dimethylphenyl compound and useless for other substituted phenyl compounds because of the instability of **6** under the reaction conditions.[8] Then, preparation of **10** by the action of trimethylsilyl metals on chlorides **(1)** was examined. The various types of silyl metals such as silyllithium, silylsodium, and silylpotassium were unsuccessful in this reaction. A successful reagent was silyl cuprate which was prepared by the metal exchange reaction of (trimethylsilyl)lithium with copper(I)[13] (Scheme 3).

(Trifluoroacetimidoyl)trimethylsilane **(10a)** was thus prepared in 55% by the reaction of trifluoroacetimidoyl chloride **(1a)** and trimethylsilyl cuprate in HMPA−THF at −55 °C for 10 min. However, in the cases of **10b** (Ar = $4\text{-}MeOC_6H_4$) and **10c** (Ar = $4\text{-}ClC_6H_4$), products were a mixture of the desired **10** and the corresponding disilyl

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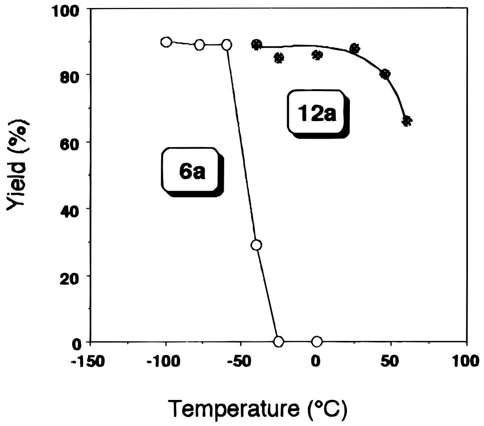
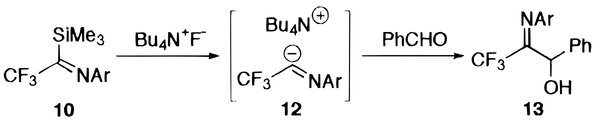


Figure 1. Effect of the reaction temperature.

Scheme 4



compound **11**.[14] The best results were obtained in ratios of **10b**:**11b** (89:11) and **10c**:**11c** (92:8).[15] Separation of the mixture by medium pressure column chromatography afforded pure **10b** and **10c** (Table 1).

Reactions of Trifluoroacetimidoyl Carbanion (12) with Electrophiles. The reaction of **10a** with benzaldehyde by the action of tetrabutylammonium fluoride (TBAF) was conducted in the presence of 4 Å molecular sieves in THF at room temperature. It was completed within 3 min. The desired aldol type adduct **13a** was obtained in 88% yield (Scheme 4). This result was in sharp contrast to the complete failure in the same reaction of the lithium species **(6)** at room temperature.[8] In this reaction, trifluoroacetimidoyl carbanion **(12)** must be generated as an intermediate. We envisaged that the carbanion **(12)** with the tetrabutylammonium counter ion was more stable at the higher temperature than the lithiated **(6)**. Therefore, the stabilities of the two species **6** and **12** were compared by analyzing the yield of **13a** at each reaction temperature.

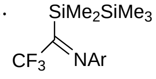
The stability of the imidoyl carbanions was dramatically increased when the counter cation was changed from lithium to tetrabutylammonium as shown in Figure 1. The reaction of the lithium species was markedly affected by the reaction temperature, and the desired products could not be obtained above −40 °C (circle point). At higher temperature, the dimers **9** from **6** were the major products. On the other hand, the metal free carbanion **12** was stable even at 40 °C to react with benzaldehyde without decomposition (filled circle), affording **13**.

The effect of solvents revealed that THF and diethyl ether were favorable, but toluene, DMF, and acetonitrile were less useful. Therefore, THF was employed as the solvent for the reaction of **10** with various electrophiles. At first, reactions of **10a**−**c** with benzaldehyde were carried out (Table 2). The products **13b** and **13c** were so unstable toward the column chromatography that they were transformed into the corresponding acetates (entries 2 and 3). As shown in Table 2, the lithium species **6** gave no **13** at 0 °C and formed the carbon−carbon bond with benzaldehyde only at −100 °C for **6a** and **6b**. 4-Chlorophenyl species **(6c)** failed even at −100 °C. In contrast to these, the carbanions **12b** and **12c** were stable at 0 °C to react with benzaldehyde, affording the adduct **13**.

Table 1. Reaction of 1 with Trimethylsilyl Cuprate[a]

entry	Ar	product (yield,[b] %)
1	$2,6\text{-Me}_2\text{C}_6\text{H}_3$	**10a** (55)
2	$4\text{-MeOC}_6\text{H}_4$	**10b** (65)[c]
3	$4\text{-ClC}_6\text{H}_4$	**10c** (75)[c]

[a] **1** (0.4 mmol), CuCN (0.4 mmol), and TMSLi (0.8 mmol) in dry THF (1.5 mL), −55 °C. [b] Isolated yield based on **1**. [c] Yield of a mixture of **10** and **11**.



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10b: **11b** = 89:11
10c: **11c** = 92:8

Table 2. Reaction of 6 and 12 with Benzaldehyde

		yield of **13** (%)[c]		
entry	Ar	Bu_4N (0 °C)[a]	Li (0 °C)[b]	Li (−100 °C)[b]
1	$2,6\text{-Me}_2\text{C}_6\text{H}_3$	86	0	90
2	$4\text{-MeOC}_6\text{H}_4$	70[d]	0	60[d]
3	$4\text{-ClC}_6\text{H}_4$	65[d]	0	trace

[a] **10** (0.18 mmol), TBAF (0.18 mmol), and benzaldehyde (0.36 mmol) in dry THF (0.2 mL), 0 °C. [b] **3** (0.31 mmol), *n*-BuLi (0.37 mmol), and benzaldehyde (0.47 mmol) in dry ether (1.5 mL), 0 or −100 °C. [c] Isolated yield based on **10** and **3**. [d] Yields of the corresponding acetates.

Table 3. Reaction of 10a (*N* = 2,6-Dimethylphenyl) with Electrophiles[a]

			yield (%)[b]	
entry	electrophiles	product	Bu_4N (rt)	Li (−78 °C)
1	PhCHO	**13**	88	89
2	$4\text{-ClC}_6\text{H}_4\text{CHO}$	**14**	80	81
3	$4\text{-MeOC}_6\text{H}_4\text{CHO}$	**15**	81	81
4	$n\text{-C}_5\text{H}_{11}\text{CHO}$	**16**	67	74
5	PhCH=CHCHO	**17**	56	48
6	PhCOCH_3	**18**	71	39
7	cyclohexanone	**19**	40	40
8	ClCO_2Et	**20**	46[c]	69

[a] **10a** (0.18 mmol), TBAF (0.18 mmol), and electrophile (0.36 mmol) in dry THF (0.2 mL), room temperature. [b] Isolated yield based on **10a**. [c] TBAF (2.5 equiv) and ClCO_2Et (1.5 equiv) were employed.

Next, the reaction of **12a** with various electrophiles was examined and the yields of the adducts were compared with those obtained from **6a** (Table 3). Reactions of **10a** with aromatic aldehydes proceeded readily, affording the imino alcohols in reasonable yields (entries 1, 2, and 3) regardless of the electronic nature of the substituent on the benzene ring. The carbanion **12a** also reacted with hexanal to give the desired product in 67% (entry 4) and smoothly with the less reactive α,*β*-unsaturated aldehyde (entry 5) which, in contrast, gave a lower yield of **17** on reacting with the lithium imidoyl **6** at −78 °C.[8] In particular, reaction of **12a** with a less reactive ketone gave the corresponding adduct in much higher yield (entry 6). When ethyl chloroformate was used as an electrophile, almost all of the starting material **10a** was recovered under the usual conditions. But, the treatment with 2.5 molar equiv of TBAF yielded ethyl 3,3,3-trifluoro-2-(*N*-arylimino)propanoate **(20)** up to 46% (entry 8). This suggests that the reaction proceeds *via* the

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(14) The cleavage of the carbon−silicon bond in the reaction of $\text{Me}_3\text{SiSiMe}_3$ with MeLi has been proposed. Hudrlik, P. F.; Waugh, M. A.; Hudrlik, A. M. *J. Organomet. Chem.* **1984**, *271*, 69.

(15) Determined by GC analysis.

replacement of chlorine atom of ethyl chloroformate with fluorine atom followed by the reaction of the fluoroformate with **12a** to give the product **20**.[16]

Experimental Section

General Methods. THF was freshly distilled from Na and benzophenone, and HMPA was distilled from CaH_2 and stored under nitrogen over molecular sieves. A commercially available THF solution of TBAF was also dried with 4 Å molecular sieves prior to use. Column chromatography was carried out with E. Merck silica gel (kieselgel 60, 230−400 mesh). The ^{19}F NMR were recorded using C_6F_6 as an internal standard. The IR, ^{1}H NMR, and ^{19}F NMR spectral data of compounds **14**−**20** were consistent with those reported.[8]

Silylation of Trifluoroacetimidoyl Chloride (1). MeLi (0.6 mL, 0.8 mmol, 1.4 M solution in hexane) was added dropwise into a solution of hexamethyldisilane (0.2 mL, 1.2 mmol) in 0.5 mL of anhydrous HMPA under an argon atmosphere. After 15 min, 1.5 mL of THF was added to the mixture which was cooled at 0 °C. Then, the solution of Me_3SiLi was added to 38 mg (0.4 mmol) of CuCN in one portion. After being stirred for 30 min, the mixture was added to an equimolar amount of trifluoroacetimidoyl chloride **(1a)** (0.1 g, 0.4 mmol) in 1.5 mL of anhydrous THF cooled at −55 °C. The mixture was stirred for 10 min and then quenched with aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and condensed. Column chromatography of the residue gave **10a** in 55% yield. The spectral data of **10a** were compared with those reported.[8]

10b: IR (neat) 1506, 1282, 1246, 1124, 850 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 9 H), 3.81 (s, 3 H), 6.71 (d, 2 H, $J = 8.8$ Hz), 6.87 (d, 2 H, $J = 8.8$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ 93.06 (CF_3); EI MS m/z (relative intensity) 275 (M^+, 23), 206 (98), 73 (100). Anal. Calcd for $C_{12}H_{16}F_3NOSi$ (275.35): C, 52.35; H, 5.86; N, 5.09. Found: C, 52.38; H, 5.83; N, 4.85.

10c: yellow crystal, mp 48−49 °C; IR (CH_2Cl_2) 1482, 1192, 1130, 846 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 9 H), 6.70 (d, 2 H, $J = 8.7$ Hz), 7.31 (d, 2 H, $J = 8.7$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ 92.59 (CF_3); EI MS m/z (relative intensity) 279 (M^+, 8), 210 (66), 73 (100). Anal. Calcd for $C_{11}H_{31}ClF_3NSi$ (279.76): C, 47.23; H, 4.68; N, 5.01. Found: C, 47.36; H, 4.82; N, 4.98.

11b: IR (neat) 1504, 1278, 1246, 1130, 834 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.03 (s, 6 H), δ 0.13 (s, 9 H), 3.81 (s, 3 H), 6.70 (d, 2 H, $J = 8.9$ Hz), 6.86 (d, 2 H, $J = 8.9$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ 93.58 (CF_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ −3.45, −1.91, 55.44, 114.00, 119.07, 121.01 (q, $J_{C-F} = 284$ Hz, CF_3), 144.12, 157.52, 175.69 (q, $J_{C-C-F} = 41$ Hz, $C-CF_3$); EI MS m/z (relative intensity) 333 (M^+, 1), 264 (10), 131 (63), 73 (100); HRMS calcd for $C_{14}H_{22}F_3NOSi_2$ (M^+) 333.1190, found 333.1141 and calcd for $C_{13}H_{22}NOSi_2$ ($M^+ - CF_3$) 264.1239, found 264.1240.

11c: IR (neat) 1484, 1280, 1276, 1132, 834 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.03 (s, 6 H), δ 0.13 (s, 9 H), 6.69 (d, 2 H, $J = 8.7$ Hz), 7.29 (d, 2 H, $J = 8.7$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ 93.17 (CF_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ −3.44, −1.95, 118.90, 120.80 (q, $J_{C-F} = 280$ Hz, CF_3), 128.89, 130.51, 149.03, 176.98 (q, $J_{C-C-F} = 34$ Hz, C-CF_3); EI MS m/z (relative intensity) 337 (M^+, 1), 268 (7), 131 (60), 73 (100); HRMS calcd for $C_{13}H_{19}F_3NClSi_2$ (M^+) 337.0695, found 337.0677 and calcd for $C_{12}H_{19}NClSi_2$ ($M^+ - CF_3$) 268.0743, found 268.0744.

Reaction of (Trifluoroacetimidoyl)trimethylsilane 10a with Benzaldehyde. To a mixture of (*N*-(2,6-dimethylphenyl)-2,2,2-trifluoroacetimidoyl)trimethylsilane **(10a)** (0.05 g, 0.18 mmol), benzaldehyde (0.04 mL, 0.36 mmol), and 4 Å molecular sieves in dry THF (0.2 mL) was added dropwise tetrabutylammonium fluoride (0.18 mL, 0.18 mmol, 1.0 M solution in THF) under nitrogen at room temperature. The mixture was stirred for 3 min, and the usual workup gave **13a** in 88% yield. The spectral data of **13a** were also compared with those reported.[8]

13b: IR (neat) 1758, 1506, 1292, 1248, 1216, 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3 H), 3.80 (s, 3 H), 6.77 (s, 1 H), 6.88 (s, 4 H), 7.16−7.36 (m, 5 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 94.67 (CF_3); EI MS m/z (relative intensity) 351 (M^+, 2), 202 (8), 107 (34), 43 (100). Anal. Calcd for $C_{18}H_{16}F_3O_3N$ (351.33): C, 61.54; H, 4.59; N, 3.99. Found: C, 61.42; H, 4.45; N, 3.76.

13c: IR (neat) 1756, 1486, 1216, 1186, 1148, 840 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.14 (s, 3 H), 6.62 (s, 1 H), 6.81 (d, 2 H, $J = 8.6$ Hz), 7.13−7.36 (m, 7 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 94.25 (CF_3); EI MS m/z (relative intensity) 355 (M^+, 8), 206 (12), 107 (100), 43 (76). Anal. Calcd for $C_{17}H_{13}ClF_3O_2N$ (355.74): C, 57.40; H, 3.68; N, 3.94. Found: C, 57.21; H, 3.75; N, 4.18.

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(16) ^{19}F NMR analysis of crude reaction mixture after 5 min showed a peak of 145.2 ppm which was also detected in the absence of imidoyltrimethylsilane **10a** and almost consistent with that (145.5 ppm) of 2-ethylhexyl fluoroformate.