Trifluoromethylation and pentafluorophenylation of enamines

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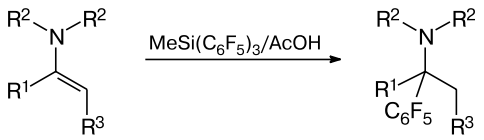
A reaction of enamines with Me_3SiCF_3 and $Me_3SiC_6F_5$ in the presence of carboxylic acids leading to α-CF_3- and α-C_6F_5-substituted amines has been studied. 3-Cyanobenzoic acid was found to be the optimal promoter of these reactions.

Key words: silanes, iminium cations, pentacoordinate silicon, amines, enamines, organosilicon compounds, organofluorine compounds.

Amines with fluorinated substituent at α-carbon atom are widely used in pharmaceutical industry and agrochemistry.[1,2] Recently, we started a systematic research on the synthesis of these compounds, based on the reaction of fluorinated silanes with the *in situ* generated iminium cations.[3—7] As a particular example, a reaction of pentafluorophenylation of enamines upon treatment with $MeSi(C_6F_5)_3$ and acetic acid was proposed[4] (Scheme 1).

Scheme 1



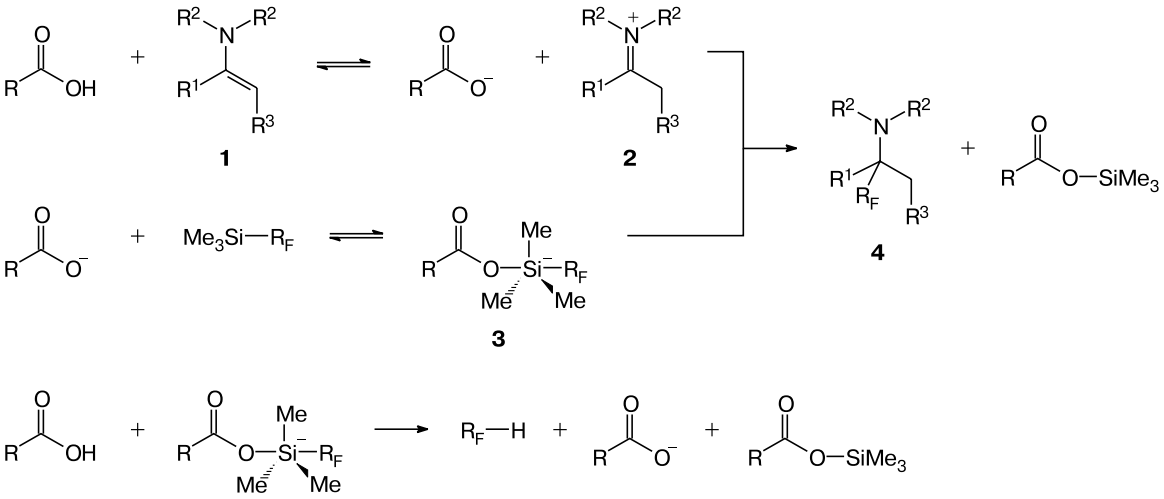
R^1 = Ph, R^2_2 = $(CH_2)_4$, $(CH_2)_5$, R^3 = H, Me
R^1R^3 = $(CH_2)_4$, $(CH_2)_5$

This method has a disadvantage of high cost of this silyl reagent. The present study is aimed at a quest of conditions for utilization of the less expensive fluorinated organosilanes Me_3SiCF_3 and $Me_3SiC_6F_5$.

The general mechanism of the process is given in Scheme 2. In the first step, an equilibrium protonation of enamine **1** by a carboxylic acid takes place to form iminium cation **2** and a carboxylate anion. By interaction of the carboxylate anion with silane, an anionic pentacoordinate silicon intermediate **3** is generated (see Refs 8-10), from which the fluorinated group is transferred to iminium cation **2**. The reaction between cation **2** and complex **3**, accompanied by the formation of a new C—C bond, can proceed either through the intermediate formation of carbanion species R_F^- or as a concerted process.[11]

It should be noted that concentrations of electrophile and nucleophile are defined by the opposite factors. Thus an increase of RCO_2H acid strength causes an increase of

Scheme 2



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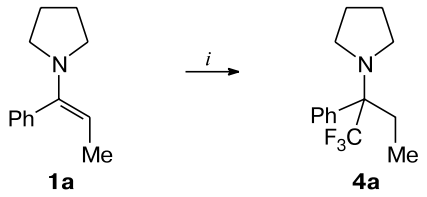
iminium cation **2** concentration and, at the same time, decreases basicity of the carboxylate anion necessary for the formation of pentacoordinate silicon intermediate **3**. Moreover, the protonation of complex **3** by the carboxylic acid with the formation of R_F—H can become a significant side process, resulting in unproductive consumption of the fluorinated organosilane.

A model reaction of enamine **1a** with Me_3SiCF_3 was investigated in the presence of various carboxylic acids. The reaction was carried out in DMF at 20 °C for 4 h (Scheme 3).*

Scheme 3



1a **4a**

i. 1.5 equiv. Me_3SiCF_3, 1 equiv. RCO_2H, DMF, 20 °C, 4 h

R	pK_a (RCO_2H)	Yield **4a** (%)
Me	4.76	37
Ph	4.20	50
3-NCC_6H_4	3.64	72
3,5-$(O_2N)_2C_6H_3$	2.82	37

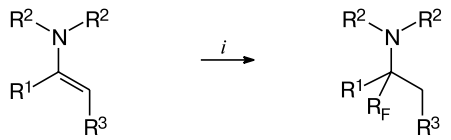
Both acetic and benzoic acids gave product **4a** in 37 and 50% yield, respectively. The yield was considerably higher in the presence of the stronger 3-cyanobenzoic acid (72%). However, the further increase in acidity by the use of 3,5-dinitrobenzoic acid led to a decrease in the yield of amine **4a** to 37%. Further optimization of the reaction conditions with participation of 3-cyanobenzoic acid showed that by the prolongation of the reaction time to 18 h, the yield of **4a** can be raised up to 77%.

The observed influence of the carboxylic acid strength on the effectivity of the reaction can be explained by the assumption that, for the weaker acids, the formation of iminium cation **2** is not complete, which results in the protonation of pentacoordinate complex **3** by the remainder of the acid. At the same time, for the stronger acids, capable of exhausting themselves in protonation of enamine, the Lewis basicity of carboxylate anion is not sufficient for the generation of the pentacoordinate silicon intermediate.[11]

* The literature data[12,13] point to the fact that during nucleophilic trifluoromethylation, carried out in strongly basic conditions or in the presence of fluoride anion, DMF can play the role of mediator due to the formation of the anionic intermediate during the interaction with trifluoromethyl carbanion. However, it was also shown that, when the activation of Me_3SiCF_3 by carboxylic acid salts (RCO_2M) occurs, the main function of the solvent is reduced to the solvation of the metal ion.[8,10]

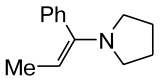
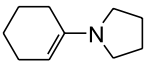
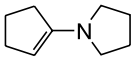
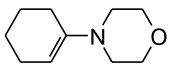
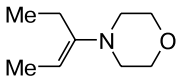
As it follows from the foregoing material, 3-cyanobenzoic acid is the most efficient promoter of the addition of Me_3SiCF_3 to enamines. Under the optimal conditions, a series of enamines has been involved into reaction of trifluoromethylation with the use of Me_3SiCF_3 and pentafluorophenylation with the use of $Me_3SiC_6F_5$ (Scheme 4).

Scheme 4



1a—c **4a—j**

i. 1.5 equiv. Me_3SiR_F, 1 equiv. 3-$NCC_6H_4CO_2H$, DMF, 20 °C, 18 h

Enamine		R_F	**4**	Yield of **4** (%)
	(**1a**)	CF_3	**4a**	77
		C_6F_5	**4b**	60
	(**1b**)	CF_3	**4c**	66
		C_6F_5	**4d**	78
	(**1c**)	CF_3	**4e**	60
		C_6F_5	**4f**	72
	(**1d**)	CF_3	**4g**	50
		C_6F_5	**4h**	31
	(**1e**)	CF_3	**4i**	51
		C_6F_5	**4j**	49

Enamines with pyrrolidine and piperidine moieties led to the corresponding products in good yields. However, substrates with morpholine fragment afforded amines **4g—j** in only 31—51% yield. The lower effectivity in the reactions with morpholine enamines can be attributed to the electron-withdrawing effect of oxygen atom, which destabilizes the iminium cation thus decreasing its equilibrium concentration. The influence of oxygen atom is confirmed both by pK_a values for the conjugate acids of the cyclic amines (morpholine, 8.36; piperidine, 11.22; pyrrolidine, 11.27) and by the kinetic data on nucleophilicity of enamines derived from the cyclic amines.[14]

In conclusion, the reactions of trifluoromethylation and pentafluorophenylation of enamines were studied and it was shown that 3-cyanobenzoic acid was the optimal promoter of the reaction. The use of Me_3SiCF_3 allows one to obtain α-CF_3-substituted amines in 51—77% yield, which are difficult to access by other methods. At the same time, the product yields vary from 31 to 78% in the reaction with $Me_3SiC_6F_5$, which demonstrates the lower

effectivity of this reagent in comparison with tris(pentafluorophenyl)silyl derivatives.[4]

Experimental

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AM-300, Bruker WM-250, or Bruker AC-200 spectrometers in $CDCl_3$. Dimethylformamide was distilled *in vacuo* over P_2O_5 and kept over molecular sieves 4 Å. Enamines **1a—d** [15] and **1e** [16] and $Me_3SiC_6F_5$ [17,18] were obtained according to the known procedures, Me_3SiCF_3 was purchased from PiM Invest.

Trifluoromethylation and pentafluorophenylation of enamines (general procedure). 3-Cyanobenzoic acid (147 mg, 1.0 mmol) was added to a solution of the corresponding enamine **1** (1.0 mmol) and R_FSiMe_3 (1.5 mmol) in DMF (1 mL) at 20 °C and this was kept for 18 h. Saturated aq. Na_2CO_3 (0.4 mL) was added to the reaction mixture, which was kept for another 5 min and then diluted with Et_2O (10 mL). The resulting mixture was placed into a separatory funnel and washed with water (10 mL). The aqueous phase was extracted with Et_2O (10 mL), the combined extracts were washed with water (10 mL), dried with Na_2SO_4 and concentrated *in vacuo*. Compounds **4a,b,d,f—j** were isolated by column chromatography on SiO_2 using mixtures of light petroleum—EtOAc as the eluent. For compounds **4c,e**, the formed product was dissolved in light petroleum, washed with water (3×10 mL), dried with Na_2SO_4, concentrated, and the residue was distilled *in vacuo*.

1-(1-Phenyl-1-trifluoromethylprop-1-yl)pyrrolidine (4a). Chromatography with light petroleum—EtOAc, 30 : 1, R_f 0.71 (light petroleum—EtOAc, 10 : 1). B.p. 150—155 °C (bath temperature; 25 Torr). Found (%): C, 65.31; H, 7.08; N, 5.26. $C_{14}H_{18}F_3N$ (257.29). Calculated (%): C, 65.35; H, 7.05; N, 5.44. ^{1}H NMR, δ: 0.75 (t, 3 H, CH_3, J = 7.4 Hz); 1.76—1.85 (m, 4 H, CH_2CH_2); 1.93—2.23 (m, 2 H, $C\underline{H}_2CH_3$); 2.84—2.97 (m, 4 H, CH_2NCH_2); 7.28—7.45 (m, 3 H), and 7.58 (d, 2 H, J = 7.9 Hz) (Ph). ^{13}C NMR, δ: 8.5 (CH_3); 23.9 (CH_2CH_2); 28.6 ($\underline{C}H_2CH_3$); 46.3 (CH_2NCH_2); 68.9 (q, $\underline{C}CF_3$, $J_{C,F}$ = 22.1 Hz); 127.3 (CH_{Ph}); 127.5 (q, CH_{Ph}, $J_{C,F}$ = 2.6 Hz); 127.9 (CH_{Ph}); 129.6 (q, CF_3, $J_{C,F}$ = 298.9 Hz); 138.3 (*ipso*-C_{Ph}). ^{19}F NMR, δ: –65.2 (CF_3).

1-(1-Phenyl-1-pentafluorophenylprop-1-yl)pyrrolidine (4b) (see Ref. 4). Chromatography with light petroleum—EtOAc, 40 : 1; R_f 0.45 (light petroleum—EtOAc, 25 : 1).

1-(1-Trifluoromethylcyclohexyl)pyrrolidine (4c). B.p. 125—130 °C (bath temperature; 25 Torr). Found (%): C, 59.63; H, 8.45; N, 6.52. $C_{11}H_{18}F_3N$ (221.26). Calculated (%): C, 59.71; H, 8.20; N, 6.33. ^{1}H NMR, δ: 1.10—1.30 (m, 1 H); 1.37—1.59 (m, 6 H); 1.61—1.80 (m, 5 H); 1.90—2.04 (m, 2 H) ($7CH_2$); 2.81—2.95 (m, 4 H, CH_2NCH_2). ^{13}C NMR, δ: 20.4 (CH_2); 24.4 (CH_2); 25.3 (CH_2); 28.4 (q, CH_2, $J_{C,F}$ = 1.6 Hz); 44.4 (q, CH_2NCH_2, $J_{C,F}$ = 1.6 Hz); 59.7 (q, $\underline{C}CF_3$, $J_{C,F}$ = 21.5 Hz); 129.5 (q, CF_3, $J_{C,F}$ = 298.9 Hz). ^{19}F NMR, δ: –74.3 (CF_3).

1-(1-Pentafluorophenylcyclohexyl)pyrrolidine (4d) (see Ref. 4). Chromatography with light petroleum—EtOAc, 15 : 1; R_f 0.17 (light petroleum—EtOAc, 25 : 1).

1-(1-Trifluoromethylcyclopentyl)pyrrolidine (4e). B.p. 88—95 °C (bath temperature; 17 Torr). Found (%): C, 57.91; H, 7.87; N, 6.84. $C_{10}H_{16}F_3N$ (207.24). Calculated (%): C, 57.96; H, 7.78; N, 6.76. ^{1}H NMR, δ: 1.63—2.05 (m, 12 H, 6 CH_2); 2.80—2.91 (m, 4 H, CH_2NCH_2). ^{13}C NMR, δ: 24.0 (CH_2); 24.7 (CH_2); 31.7 (CH_2); 46.6 (q, CH_2NCH_2, $J_{C,F}$ = 1.4 Hz); 69.6 (q, $\underline{C}CF_3$, $J_{C,F}$ = 23.0 Hz); 129.1 (q, CF_3, $J_{C,F}$ = 292.1 Hz). ^{19}F NMR, δ: –72.0 (CF_3).

1-(1-Pentafluorophenylcyclopentyl)pyrrolidine (4f) (see Ref. 4). Chromatography with light petroleum—EtOAc, 25 : 1; R_f 0.32 (light petroleum—EtOAc, 25 : 1). M.p. 89—91 °C (MeOH).

4-(1-Trifluoromethylcyclohexyl)morpholine (4g). Chromatography with light petroleum—EtOAc, 20 : 1, R_f 0.24 (light petroleum—EtOAc, 10 : 1). B.p. 140—145 °C (bath temperature; 30 Torr). Found (%): C, 55.84; H, 7.75; N, 5.91. $C_{11}H_{18}F_3NO$ (237.26). Calculated (%): C, 55.68; H, 7.65; N, 5.90. ^{1}H NMR, δ: 1.17—1.32 (m, 1 H); 1.38—1.62 (m, 6 H); 1.69—1.79 (m, 1 H); 1.94—2.03 (m, 2 H) ($(CH_2)_5$); 2.75—2.91 (m, 4 H, CH_2NCH_2); 3.62—3.68 (m, 4 H, CH_2OCH_2). ^{13}C NMR, δ: 19.5 (CH_2); 25.5 (CH_2); 26.9 (q, CH_2, $J_{C,F}$ = 1.6 Hz); 46.1 (CH_2NCH_2); 60.8 (q, $\underline{C}CF_3$, $J_{C,F}$ = 22.0 Hz); 68.2 (q, CH_2OCH_2, $J_{C,F}$ = 1.4 Hz); 128.5 (q, CF_3, $J_{C,F}$ = 296.3 Hz). ^{19}F NMR, δ: –74.1 (CF_3).

4-(1-Pentafluorophenylcyclohexyl)morpholine (4h) (see Ref. 4). Chromatography with light petroleum—EtOAc, 10 : 1; R_f 0.12 (light petroleum—EtOAc, 15 : 1). M.p. 79—80 °C (MeOH).

4-[3-(Trifluoromethyl)pent-3-yl]morpholine (4i). Chromatography with light petroleum—EtOAc, 20 : 1, R_f 0.30 (light petroleum—EtOAc, 10 : 1). B.p. 130—135 °C (bath temperature; 30 Torr). Found (%): C, 53.58; H, 8.09; N, 6.08. $C_{10}H_{18}F_3NO$ (225.25). Calculated (%): C, 53.32; H, 8.05; N, 6.22. ^{1}H NMR, δ: 0.94 (tq, 6 H, 2 CH_3, J = 0.9 Hz, J = 7.5 Hz); 1.59—1.72 (m, 2 H, 2 $C\underline{H}_AH_B$); 1.73—1.87 (m, 2 H, 2 $CH_A\underline{H}_B$); 2.75—2.80 (m, 4 H, CH_2NCH_2); 3.60—3.65 (m, 4 H, CH_2OCH_2). ^{13}C NMR, δ: 7.4 (q, 2 CH_3, $J_{C,F}$ = 1.6 Hz); 21.9 (q, 2 CH_2, $J_{C,F}$ = 1.6 Hz); 47.1 (q, CH_2NCH_2, $J_{C,F}$ = 1.6 Hz); 64.0 (q, CF_3, $J_{C,F}$ = 20.9 Hz); 68.2 (q, CH_2OCH_2, $J_{C,F}$ = 1.1 Hz); 129.0 (q, CF_3, $J_{C,F}$ = 297.4 Hz). ^{19}F NMR, δ: –69.5 (CF_3).

4-[3-(Pentafluorophenyl)pent-3-yl]morpholine (4j) (see Ref. 4). Chromatography with light petroleum—EtOAc, 15 : 1; R_f 0.24 (light petroleum—EtOAc, 15 : 1).

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