Letters to the Editor

Trifluoromethylation of the amide group*

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Amines containing an α-trifluoromethyl substituent constitute an important class of biologically active compounds.[1—4] In particular, such a fragment is similar in biological properties to an amide fragment.

Replacement of the oxo fragment in a peptide drug by a trifluoromethyl group and a hydrogen atom can substantially enhance its therapeutic effect.[1,2]

Known general routes to CF_3-substituted amines involve nucleophilic addition to imines[5—7] and fluorination of amino acids.[8,9] Below we describe a first example of the straightforward transformation of amides into CF_3-containing amines.

Earlier,[5,10—13] in a search for efficient ways of trifluoromethylation of the C=N bond, we have shown that *N*,*N*-dialkyliminium cations react with Me_3SiCF_3 in the presence of a fluoride or acetate anion.[13] Here we propose to use a cation generated in the *O*-alkylation of a carbamoyl group as an electrophile.[14,15]

Methylation of *N*-benzylpyrrolidone (**1**) with methyl triflate in hot 1,2-dichloroethane produces cation **A**, which can be transformed into α-methoxy-α-trifluoromethyl amine **2** by a reaction with Me_3SiCF_3 and KF in DMF (Scheme 1).** Compound **2** should be stored at −25 °C because of its low stability at room temperature.

Reduction of α-methoxy amine **2** with $NaBH_4$—$BF_3 \cdot OEt_2$ gives 2-trifluoromethylpyrrolidine **3** in 87% yield (Scheme 2). The methoxy group in amine **2** can also be replaced by an aliphatic residue or a cyano group in reactions with various C-nucleophiles or trimethylsilyl cyanide to give the corresponding products **4a—d** in good yields. It should be emphasized that compound **4c** contains adjacent quaternary C atoms,

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** With dimethyl sulfate used to generate iminium salt **A**, the reaction gives α-methoxy amine **2** in 58% yield and a by-product (supposedly, 1-benzyl-5-trifluoromethyl-2,3-dihydro-1*H*-pyrrole) in 15% yield.

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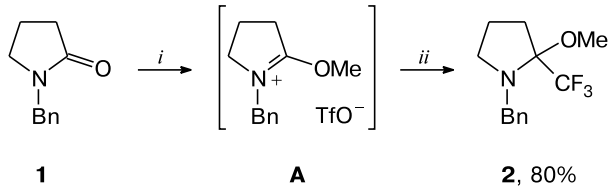
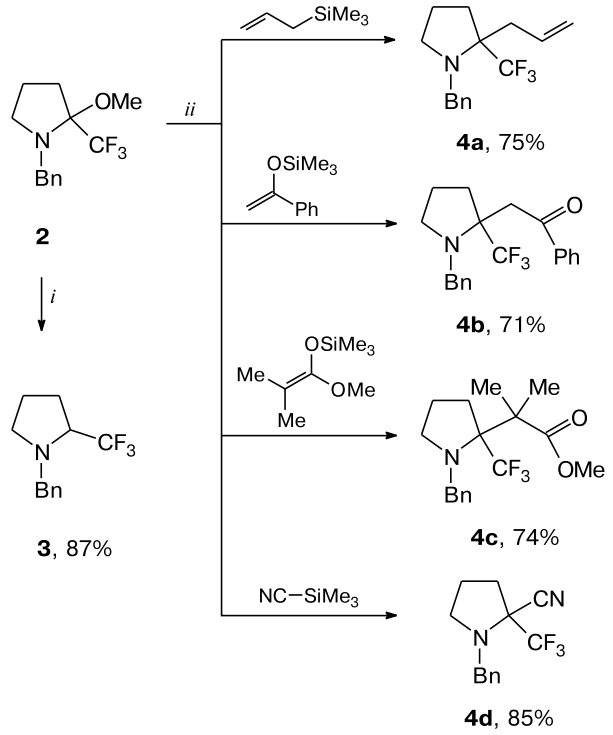
Scheme 1



1 **A** **2**, 80%

i. MeOTf, 1,2-dichloroethane, 80 °C, 15 min;
ii. Me_3SiCF_3, KF, DMF, 50 °C, 1 h

Scheme 2



4a, 75% **4b**, 71% **2** **4c**, 74% **3**, 87% **4d**, 85%

i. $NaBH_4$, $BF_3 \cdot OEt_2$, dioxane, 50 °C, 2 h;
ii. $BF_3 \cdot OEt_2$, CH_2Cl_2, −25→20 °C, 1 h.

which is evidence for the efficiency of this method of C—C bond formation.

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AM-300 and Bruker AC-200 instruments in $CDCl_3$. Dichloroethane and dichloromethane were distilled over CaH_2 immediately before use; DMF was distilled *in vacuo* over P_2O_5 and kept over molecular sieves (4 Å). *N*-Benzylpyrrolidone was prepared according to a known procedure.[16] Boron trifluoride etherate was purified by distillation *in vacuo*. The other commercial reagents were used as purchased.

1-Benzyl-2-methoxy-2-trifluoromethylpyrrolidine (2). Methyl triflate (176 μL, 1.8 mmol) was added to a solution of *N*-benzylpyrrolidone (263 mg, 1.5 mmol) in 1,2-dichloroethane (1.5 mL). The mixture was stirred at 80 °C for 15 min and concentrated *in vacuo*. The residue was dissolved in DMF (2.5 mL) and then Me_3SiCF_3 (332 μL, 2.25 mmol) and KF (109 mg, 1.88 mmol) were added. The resulting suspension was stirred at 50 °C for 1 h, cooled to room temperature, quenched with saturated aqueous Na_2CO_3 (0.5 mL), and stirred for 2 min. The mixture was diluted with water (6 mL) and extracted with hexane—ether (1 : 1, 3×5 mL). The combined extracts were filtered through Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with a hexane—EtOAc system (15 : 1) containing 0.5% NEt_3 as an eluent. The yield of compound **2** was 311 mg (80%), a light yellow oil, R_f 0.20 (hexane—EtOAc, 6 : 1). ^1H NMR (300 MHz), δ: 1.77—1.97 (m, 2 H); 2.18—2.32 (m, 2 H); 2.88—3.06 (m, 2 H) ($(CH_2)_3$); 3.42 (s, 3 H, OMe); 4.02 (d, 1 H, $NC\underline{H}_AH_B$, J = 14.5 Hz); 4.11 (d, 1 H, $PhCH_A\underline{H}_B$, J = 14.5 Hz); 7.27—7.45 (m, 5 H, Ph). ^{13}C NMR (75 MHz), δ: 21.5 ($NCH_2\underline{C}H_2$); 29.6 (CH_2); 49.7 (CH_2); 50.3 (q, CH_2, J = 1.8 Hz); 51.0 (CH_2); 95.2 (q, $\underline{C}CF_3$, J = 28.9 Hz); 125.1 (q, CF_3, J = 289.9 Hz); 126.8 (CH); 127.8 (CH); 128.3 (CH); 139.5 (C_i). ^{19}F NMR (282 MHz), δ: −79.3 (s, 3 F).

1-Benzyl-2-trifluoromethylpyrrolidine (3). Sodium borohydride (29 mg, 0.75 mmol) and $BF_3 \cdot OEt_2$ (71 μL, 0.56 mmol) were successively added to a solution of α-methoxy amine **2** (130 mg, 0.5 mmol) in dioxane (1 mL). The resulting suspension was stirred at 50 °C for 2 h, cooled to room temperature, quenched with saturated aqueous Na_2CO_3 (0.5 mL), and stirred for an additional 2 min. Then the mixture was diluted with water (6 mL) and extracted with hexane—ether (1 : 1, 3×5 mL). The combined extracts were filtered through Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with hexane—EtOAc (20 : 1) as an eluent, R_f 0.36. The yield of compound **3** was 100 mg (87%), a colorless oil. Found (%): C, 62.74; H, 6.09; N, 6.05. $C_{12}H_{14}F_3N$ (229.24). Calculated (%): C, 62.87; H, 6.16; N, 6.11. ^1H NMR (300 MHz), δ: 1.70—2.08 (m, 4 H, $(CH_2)_2$); 2.41 (td, 1 H, $NC\underline{H}_AH_B$, J = 9.5 Hz, J = 6.6 Hz); 3.00 (t, 1 H, $NCH_A\underline{H}_B$, J = 7.5 Hz); 3.30 (qt, 1 H, $CHCF_3$, J = 7.3 Hz); 3.63 (d, 1 H, $PhC\underline{H}_AH_B$, J = 13.3 Hz); 4.22 (d, 1 H, $PhCH_A\underline{H}_B$, J = 13.3 Hz); 7.23—7.42 (m, 5 H, Ph). ^{13}C NMR (75 MHz), δ: 24.3 ($NCH_2\underline{C}H_2$); 26.4 (q, $F_3CCH\underline{C}H_2$, J = 1.8 Hz); 53.8 ($N\underline{C}H_2CH_2$); 59.8 (q, $\underline{C}H_2Ph$, J = 1.1 Hz); 63.4 (q, $\underline{C}HCF_3$, J = 28.3 Hz); 127.0 (CH); 127.1 (q, CF_3, J = 280.3 Hz); 128.3 (CH); 128.6 (CH); 138.9 (C_i). ^{19}F NMR (282 MHz), δ: −76.8 (d, 3 F, J = 7.3 Hz).

Reactions of α-methoxy amine 2 with C-nucleophiles (general procedure). Boron trifluoride etherate (95 μL, 0.75 mmol) was added dropwise at −25 °C to a solution of α-methoxy amine **2** (130 mg, 0.5 mmol) and an appropriate nucleophilic reagent (0.75 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at −25 °C for 10 min and then at room temperature for 1 h. Saturated aqueous Na_2CO_3 (0.5 mL) was added. The mixture was stirred for an additional 2 min, diluted with water (6 mL), and washed with hexane—ether (1 : 1, 3×5 mL). The combined extracts were filtered through Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel.

2-Allyl-1-benzyl-2-trifluoromethylpyrrolidine (4a), an oil, R_f 0.15 (hexane). Found (%): C, 66.87; H, 6.80; N, 5.15. $C_{15}H_{18}F_3N$ (269.31). Calculated (%): C, 66.90; H, 6.74; N, 5.20. ^1H NMR (300 MHz), δ: 1.61—1.88 (m, 2 H), 1.94—2.18 (m, 2 H) ($(CH_2)_2$); 2.45 (dd, 1 H, $=CC\underline{H}_AH_B$, J = 14.5 Hz, J = 8.1 Hz); 2.66 (dd, 1 H, $=CCH_A\underline{H}_B$, J = 14.5 Hz, J = 6.1 Hz); 2.70—2.82 (m, 2 H, NCH_2); 3.87 (d, 1 H, $PhC\underline{H}_AH_B$, J = 13.8 Hz); 4.00 (d, 1 H, $PhCH_A\underline{H}_B$, J = 13.8 Hz); 5.13—5.32 (m, 2 H, CH_2=); 5.85—6.02 (m, 1 H, —CH=); 7.20—7.41 (m, 5 H, Ph).

^{13}C NMR (75 MHz), δ: 22.1 ($NCH_2\underline{C}H_2$); 31.2 (CH_2); 35.7 (CH_2); 51.6 (CH_2); 52.2 (CH_2); 67.2 (q, $\underline{C}CF_3$, J = 23.8 Hz); 119.0 (H_2C=); 126.8 (CH); 128.0 (CH); 128.2 (CH); 128.6 (q, CF_3, J = 291.4 Hz); 132.8 ($\underline{C}H$=CH_2); 140.2 (C_i). ^{19}F NMR (282 MHz), δ: –75.0 (s, 3 F).

1-Benzyl-2-phenacyl-2-trifluoromethylpyrrolidine (4b), an oil, R_f 0.31 (hexane—EtOAc, 25 : 1). Found (%): C, 69.21; H, 5.76; N, 3.99. $C_{20}H_{20}F_3NO$ (347.37). Calculated (%): C, 69.15; H, 5.80; N, 4.03. ^{1}H NMR (300 MHz), δ: 1.78—1.93 (m, 2 H); 2.23 (ddd, 1 H, J = 13.2 Hz, J = 7.0 Hz, J = 4.9 Hz); 2.49 (dtd, 1 H, J = 18.3 Hz, J = 9.1 Hz, J = 0.8 Hz); 2.80—2.90 (m, 1 H); 2.95 (q, 1 H, J = 7.7 Hz) ($(CH_2)_3$); 3.42—3.57 (m, 2 H, CH_2CO); 3.75 (d, 1 H, $PhC\underline{H}_AH_B$, J = 13.6 Hz); 3.99 (d, 1 H, $PhCH_A\underline{H}_B$, J = 13.6 Hz); 7.17—7.32 (m, 5 H, $\underline{Ph}CH_2$); 7.46—7.55 (m, 2 H, PhCO); 7.61 (tt, 1 H, PhCO, J = 7.3 Hz, J = 2.4 Hz); 7.98—8.04 (m, 2 H, PhCO). ^{13}C NMR (75 MHz), δ: 22.7 ($NCH_2\underline{C}H_2$); 32.1 (CH_2); 37.4 (CH_2); 52.1 (CH_2); 53.0 (CH_2); 67.4 (q, $\underline{C}CF_3$, J = 26.0 Hz); 126.7 (CH); 127.9 (CH); 128.0 (CH); 128.0 (q, CF_3, J = 288.6 Hz); 128.2 (CH); 128.7 (CH); 133.3 (CH); 137.7 (C_i); 140.0 (C_i); 196.9 (C=O). ^{19}F NMR (282 MHz), δ: –78.2 (s, 3 F).

Methyl 2-(1-benzyl-2-trifluoromethylpyrrolidin-2-yl)-2-methylpropionate (4c), R_f 0.10 (hexane—EtOAc, 30 : 1), m.p. 38—40 °C. Found (%): C, 62.15; H, 6.65; N, 4.07. $C_{17}H_{22}F_3NO_2$ (329.36). Calculated (%): C, 61.99; H, 6.73; N, 4.25. ^{1}H NMR (300 MHz), δ: 1.43 (s, 3 H, $C\underline{Me}_AMe_B$); 1.46 (s, 3 H, $CMe_A\underline{Me}_B$); 1.59—1.81 (m, 2 H); 1.98—2.14 (m, 1 H); 2.45—2.59 (m, 1 H); 2.72 (dd, 1 H, J = 13.9 Hz, J = 7.7 Hz); 2.95—3.06 (m, 1 H) ($(CH_2)_3$); 3.64—3.75 (m, 4 H, $PhC\underline{H}_AH_B$ + CO_2Me); 4.51 (d, 1 H, $PhCH_A\underline{H}_B$, J = 14.7 Hz); 7.21—7.45 (m, 5 H, Ph). ^{13}C NMR (75 MHz), δ: 22.7 (q, $C\underline{Me}_AMe_B$, J = 2.4 Hz); 23.3 ($NCH_2\underline{C}H_2$); 23.5 (q, $CMe_A\underline{Me}_B$, J = 1.5 Hz); 32.5 (q, CH_2, J = 2.2 Hz); 49.3 (CH_2); 52.0 (CH_2); 53.9 (CH_2); 55.0 (q, CH_2, J = 2.4 Hz); 72.4 (q, $\underline{C}CF_3$, J = 22.3 Hz); 126.8 (CH); 127.5 (CH); 128.4 (CH); 129.0 (q, CF_3, J = 294.5 Hz); 140.4 (q, C_i, J = 1.4 Hz); 175.9 (C=O). ^{19}F NMR (282 MHz), δ: –65.3 (s, 3 F).

1-Benzyl-2-trifluoromethylpyrrolidine-2-carbonitrile (4d), an oil, R_f 0.25 (hexane—EtOAc, 15 : 1). Found (%): C, 61.27; H, 5.14; N, 10.87. $C_{13}H_{13}F_3N_2$ (254.25). Calculated (%): C, 61.41; H, 5.15; N, 11.02. ^{1}H NMR (300 MHz), δ: 1.83—2.03 (m, 2 H); 2.43—2.65 (m, 3 H); 3.03—3.16 (m, 1 H) ($(CH_2)_3$); 3.68 (d, 1 H, $PhC\underline{H}_AH_B$, J = 13.2 Hz); 4.35 (d, 1 H, $PhCH_A\underline{H}_B$, J = 13.2 Hz); 7.28—7.44 (m, 5 H, Ph). ^{13}C NMR (75 MHz), δ: 23.4 ($NCH_2\underline{C}H_2$); 34.8 (q, $\underline{C}H_2CCF_3$, J = 1.0 Hz); 52.7 (CH_2); 56.2 (q, CH_2); 66.3 (q, $\underline{C}CF_3$, J = 31.3 Hz); 114.8 (CN); 123.6 (q, J = 283.1 Hz); 127.5 (CH); 128.2 (CH); 128.5 (CH); 137.6 (C_i). ^{19}F NMR (282 MHz), δ: –77.2 (s, 3 F).

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