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N-Acyl-1-chloro-2,2,2-trifluoroethylamine as a 2,2,2-Trifluoroethylamine-Building Block

Kiyoshi Tanaka,* Yoshiharu Ishiguro, and Keiryo Mitsuhashi
Faculty of Engineering, Seikei University, Musashino, Tokyo 180

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Synopsis. The reactions of *N*-benzoyl- and *N*-acetyl-1-chloro-2,2,2-trifluoroethylamines with various carbon-nucleophiles gave the corresponding 1-substituted *N*-acyl-2,2,2-trifluoroethylamines in good yields and the efficient reactivity was applied on the synthesis of 2-acylamino-2-trifluoromethylethanol derivative.

Chlorine atom of benzyl or *t*-butyl *N*-(1-chloro-2,2,2-trifluoroethyl)carbamate is easily substituted with the nucleophiles such as alcohols, thiols, and amines to give the corresponding substituted products, which generate the original nucleophiles on acid hydrolysis. For these properties alkyl *N*-(1-chloro-2,2,2-trifluoroethyl)carbamates were utilized as the precursors of protected amino acids by Weygand and his co-workers (Scheme 1).[1—3] High reactivities of *N*-acyl-1-chloro-2,2,2-trifluoroethylamine derivatives against nucleophiles suggest the facile carbon–carbon bond formation may be possible, if the carbon-nucleophiles are applied instead of the oxygen-, sulfur-, and nitrogen-nucleophiles. As a part of continuing investigation of the trifluoromethyl-containing building blocks,[4,5] we now wish to demonstrate the versatile synthetic method of *N*-acyl-2,2,2-trifluoroethylamines by the reactions of *N*-benzoyl- and *N*-acetyl-1-chloro-2,2,2-trifluoroethylamines (**1** and **2**) with various carbon-nucleophiles.

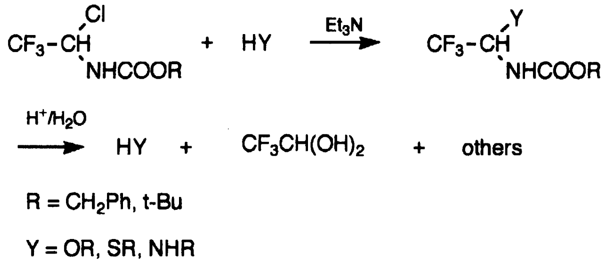
The reaction of **1** with benzylmagnesium chloride afforded 1-benzyl substituted *N*-benzoyl-2,2,2-trifluoroethylamine (**3a**) in a moderate yield. The reactions with an excess of nitromethane, malononitrile, and diethyl malonate in the presence of excess sodium hydride produced the corresponding 1-substituted products **3b**, **3c**, and **3d**, respectively, in good yields (Scheme 2). The reaction with acetylacetone under similar conditions produced 1-acetonyl substituted *N*-benzoyl-2,2,2-trifluoroethylamine (**3e′**), derived by elimination of acetyl group from the initially formed substituted product **3e**. However, on using an equimolar ratio of sodium hydride the expected product **3e** was obtained in a good yield. *N*-Acetylchlorotrifluoroethylamine (**2**) has a similar efficient reactivity and, for example, the reaction with malononitrile afforded 1-substituted *N*-acetyltrifluoroethylamine (**4c**) in 77% yield.

As an application of the efficient reactivities of **1** and **2** with the carbon-nucleophiles, we examined the synthesis of 2-acylamino-2-trifluoromethylethanol derivative. The reaction of **2** with lithium salt of 2-phenyl-1,3-dithiane yielded 1-substituted *N*-acetyltrifluoroethylamine (**5**) in 61% yield, and desulfurization of **5** was carried out by treatment with *N*-chlorosuccinimide (NCS) and silver nitrate to give 85% of *N*-acetyl-1-benzoyl-2,2,2-trifluoroethylamine (**6**) together with 14% of 2-methyl-5-phenyl-4-trifluoromethyloxazole (**7**). By reduction of **6** with sodium borohydride, one diastereoisomeric 2-acetamido-1-phenyl-2-trifluoromethylethanol (**8**) was isolated in 49% yield. Stereochemistry of **8** was determined to be the *erythro* configuration by the chemical conversion of **8** into *trans*-2-methyl-5-phenyl-4-trifluoromethyl-2-oxazoline (**9**)(Scheme 3, Fig. 1).[6]

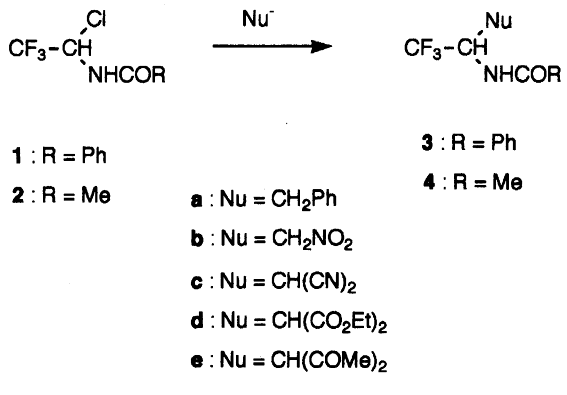
In summary, the present method using **1** and **2** is useful for the synthesis of *N*-acyl-2,2,2-trifluoroethylamines bearing polyfunctional groups.[7]

Experimental

The IR spectra were recorded on a JASCO A-100 spectrometer and samples were run as potassium bromide pellets unless otherwise noted. The ^{1}H NMR spectra were measured with a JEOL JNM-GX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard, the chemical shifts being given in δ scale downfield. Samples were



Scheme 1.



Product	3a	3b	3c	3d	3e	4c
Yield(%)	36	76	85	80	62	77

Scheme 2.

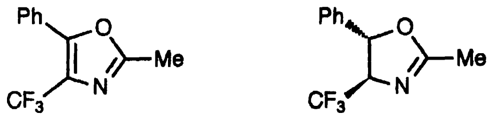


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Fig. 1.

prepared by dissolving in deuteriochloroform.

Preparations of *N*-Benzoyl- and *N*-Acetyl-1-chloro-2,2,2-trifluoroethylamines (1 and 2).[2] A mixture of 1-ethoxy-2,2,2-trifluoroethanol (6.34 g, 44.0 mmol) and benzamide (4.84 g, 40.0 mmol) in 60 cm^3 of dioxane was refluxed for 2 d. After removal of the solvent, the residue was chromatographed (silica gel, hexane–ethyl acetate=2/1) to give 6.02 g (69%) of 1-benzamido-2,2,2-trifluoroethanol; mp 129—130°C (recrystallized from hexane–ethyl acetate) (lit,[3] mp 127°C).

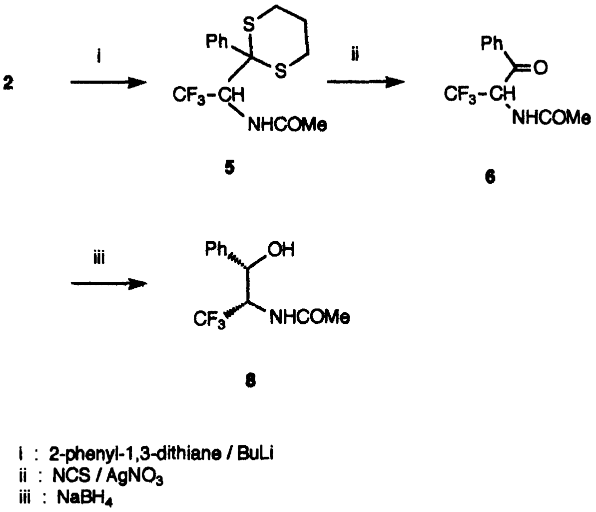
A mixture of thus obtained 1-benzamido-2,2,2-trifluoroethanol (7.28 g, 33.2 mmol) and phosphorus pentachloride (7.86 g, 37.7 mmol) was stirred at room temperature for 30 min and heated at 70°C for 15 min. After evaporation under reduced pressure, the residue was recrystallized from petroleum ether to give 6.91 g (88%) of **1**; mp 95—96°C (lit,[2] mp 96°C); ^{1}H NMR δ=6.6 (1H, dq, J=11.6, 5.8 Hz), 6.8 (1H, d, J=11.6 Hz), 7.4—7.9 (5H, m); IR 3260 (NH), 1665 (C=O), 1190, 1140 cm^{-1} (CF_3).

A similar treatment using acetamide gave 69% of 1-acetamido-2,2,2-trifluoroethanol; mp 111—114°C (recrystallized from hexane–ethyl acetate) (lit,[2] 116°C). Thus obtained 1-acetamido-2,2,2-trifluoroethanol was also reacted with phosphorus pentachloride to give 78% of **2**; mp 79—82°C (recrystallized from hexane–ethyl acetate) (lit,[2] 85°C); ^{1}H NMR δ=2.0 (3H, s), 5.7 (1H, dq, J=10.0, 6.0 Hz), 8.5 (1H, d, J=10.0 Hz); IR 3260 (NH), 1660 (C=O), 1190, 1140, 1110 cm^{-1} (CF_3).

Preparation of 1-Benzyl Substituted *N*-Benzoyl-2,2,2-trifluoroethylamine 3a. A solution of **1** (5.00 g, 21.0 mmol) in 20 cm^3 of diethyl ether was added dropwise to a diethyl ether solution of benzylmagnesium chloride, which was prepared from 1.72 g (70.8 mmol) of magnesium and 8.88 g (70.1 mmol) of benzyl chloride in 80 cm^3 of diethyl ether. After stirring at room temperature for 20 h, the mixture was acidified to pH 2 with dilute hydrochloric acid and extracted with diethyl ether. The extracts were washed with water and brine and dried over magnesium sulfate. After removal of the solvent, the residue was recrystallized from hexane–ethyl acetate to give 2.23 g (36%) of **3a**; mp 166—169°C; ^{1}H NMR δ=3.0 (1H, dd, J=13.9, 10.1 Hz), 3.3 (1H, dd, J=13.9, 4.3 Hz), 5.2 (1H, m), 6.6 (1H, bs), 7.2—7.7 (10H, m); IR 3270 (NH), 1640 (C=O), 1195, 1150, 1115 cm^{-1} (CF_3).

Found: C, 65.62; H, 4.84; N, 4.62%. Calcd for $C_{16}H_{14}NF_3O$: C, 65.52; H, 4.81; N, 4.78%.

Preparations of the 1-Substituted *N*-Acyl-2,2,2-trifluoroethylamines 3b, 3c, 3d, 3e′, and 4c. General Procedures. A solution of 34.0 mmol of nitromethane, malononitrile, diethyl malonate, or acetylacetone in 10 cm^3 of tetrahydrofuran (THF) was added dropwise to a suspension of sodium hydride (33.0 mmol) in 50 cm^3 of THF and the mixture was stirred at room temperature for 2 h. To the mixture was added dropwise a solution of 8.4 mmol of **1** or **2** in 15 cm^3 of THF. After the mixture was stirred at room temperature for 25 h, 3 cm^3 of ethanol was added. The mixture was evaporated under reduced pressure and the residue was extracted with diethyl ether. The extracts were washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel to give the substituted *N*-acyltrifluoroethylamine which was purified by recrystallization from hexane–ethyl acetate.



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Scheme 3.

3b: Mp 158—159°C; ^{1}H NMR δ=4.8 (1H, dd, J=14.2, 4.3 Hz), 5.0 (1H, dd, J=14.2, 8.5 Hz), 5.7 (1H, dddq, J=8.7, 8.5, 4.3, 7.5), 7.4—8.0 (5H, m), 8.4 (1H, d, J=8.7 Hz); IR 3260 (NH), 1645 (C=O), 1550 (NO_2), 1175, 1150, 1115 cm^{-1} (CF_3).

Found: C, 45.81; H, 3.33; N, 10.64%. Calcd for $C_{10}H_9N_2F_3O_3$: C, 45.81; H, 3.46; N, 10.68%.

3c: Mp 143—145°C; ^{1}H NMR δ=4.8 (1H, d, J=7.8 Hz), 5.5 (1H, ddq, J=9.4, 7.8, 8.0 Hz), 7.4—8.0 (5H, m), 8.7 (1H, d, J=9.4 Hz); IR 3260 (NH), 2260 (C≡N), 1650 (C=O), 1175, 1145 cm^{-1} (CF_3).

Found: C, 53.98; H, 2.97; N, 15.87%. Calcd for $C_{12}H_8N_3F_3O$: C, 53.94; H, 3.02; N, 15.73%.

3d: Mp 70—71°C; ^{1}H NMR δ=1.1 (3H, t, J=7.1 Hz), 1.3 (3H, t, J=7.1 Hz), 3.9 (1H, d, J=2.9 Hz), 4.2 (2H, m), 4.3 (2H, q, J=7.1 Hz), 5.6 (1H, ddq, J=10.1, 2.9, 7.0 Hz), 7.4—7.9 (5H, m), 8.1 (1H, d, J=10.1 Hz); IR 3280 (NH), 1740, 1735, 1640 (C=O), 1175, 1125 cm^{-1} (CF_3).

Found: C, 53.46; H, 4.61; N, 4.00%. Calcd for $C_{16}H_{18}NF_3O_5$: C, 53.19; H, 5.02; N, 3.88%.

3e′: Mp 152—153°C; ^{1}H NMR δ=2.3 (3H, s), 2.85 (1H, dd, J=17.4, 5.8 Hz), 3.05 (1H, dd, J=17.4, 5.8 Hz), 5.2 (1H, m), 7.3—7.9 (6H, m, Ph and NH); IR 3260 (NH), 1715, 1645 (C=O), 1170, 1155, 1120 cm^{-1} (CF_3).

Found: C, 55.35; H, 4.93; N, 5.39%. Calcd for $C_{12}H_{12}NF_3O_2$: C, 55.60; H, 4.67; N, 5.40%.

4c: Mp 94—96°C; ^{1}H NMR δ=2.1 (3H, s), 4.3 (1H, bd), 5.4 (1H, m), 8.5 (1H, bs); IR 3195 (NH), 2250 (C≡N), 1660 (C=O), 1180, 1140 cm^{-1} (CF_3).

Found: C, 41.32; H, 2.70; N, 20.59%. Calcd for $C_7H_6N_3F_3O$: C, 40.99; H, 2.95; N, 20.48%.

Preparation of 3e. A solution of acetylacetone (1.05 g, 10.5 mmol) in 5 cm^3 of THF was added dropwise to a suspension of sodium hydride (0.10 g, 4.2 mmol) in 30 cm^3 of THF and the mixture was stirred at room temperature for 2 h. To the mixture was added dropwise a solution of **1** (1.00 g, 4.2 mmol) in 10 cm^3 of THF. After the mixture was stirred at room temperature for 21 h, the solvent was evaporated under reduced pressure and the residue was extracted with diethyl ether. The extracts were washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was recrystallized from hexane–ethyl acetate to give 0.79 g (62%) of **3e**: Mp 157—158°C; ^{1}H NMR δ=2.33 (3H, s), 2.35 (3H, s), 4.2 (1H, d, J=3.6 Hz), 5.6 (1H, ddq, J=9.8, 3.6, 7.5 Hz), 7.4—7.9 (5H, m), 8.0 (1H, d, J=9.8 Hz); IR 3290 (NH), 1730, 1705, 1645 (C=O), 1170, 1155, 1115 cm^{-1} (CF_3).

Found: C, 55.66; H, 4.73; N, 4.64%. Calcd for $C_{14}H_{14}NF_3O_3$: C, 55.82; H, 4.68; N, 4.65%.

Preparation of 2-Acetamido-1-phenyl-2-trifluoromethylethanol (8). A hexane solution of butyllithium (1.6 M, 19 cm^3, 30.4 mmol, 1 M=1 mol dm^{-3}) was added dropwise to a solution of 2-phenyl-1,3-dithiane (5.60 g, 28.5 mmol) in 30 cm^3 of THF at −78°C under an atmosphere of nitrogen and the mixture was stirred for 2 h. To the mixture was added dropwise a solution of **2** (2.50 g, 14.2 mmol) in 15 cm^3 of THF at −60°C. Stirring the mixture, the temperature was raised to room temperature for 40 h and 3 cm^3 of methanol was added. After the solvent was removed, the mixture was extracted with diethyl ether. The extracts were washed with water and brine, dried over magnesium sulfate, and evaporated to leave a residue. The residue was chromatographed (silica gel, hexane–chloroform) to give 2.90 g (61%) of **5**: Mp 118—120°C (recrystallized from hexane–ethyl acetate); ^{1}H NMR δ=1.9 (2H, m), 2.1 (3H, s), 2.5—3.0 (4H, m), 5.1 (1H, dq, J=9.0, 7.5 Hz), 6.2 (1H, d, J=9.0 Hz), 7.2—8.2 (5H, m); IR 3320 (NH), 1665 (C=O), 1170, 1155, 1130 cm^{-1} (CF_3).

Found: C, 49.86; H, 4.88; N, 4.27%. Calcd for $C_{14}H_{16}NF_3OS_2$: C, 50.14; H, 4.81; N, 4.18%.

A solution of **5** (0.87 g, 2.6 mmol) in 10 cm^3 of acetonitrile was added dropwise to a solution of NCS (1.39 g, 10.4 mmol) and silver nitrate (1.99 g, 11.7 mmol) in 50 cm^3 of acetonitrile–water (4/1). After stirring for 30 min at room temperataure, saturated aqueous solutions of sodium sulfite (3 cm^3), sodium carbonate (3 cm^3), and sodium chloride (3 cm^3) were added. After 60 cm^3 of hexane–dichloromethane (1/1) was added, the soild was filtered off. The filtrates were extracted with hexane–dichloromethane (1/1) and the extracts were dried over magnesium sulfate. After removal of the solvent, the residue was chromatographed (silica gel, hexane–ethyl acetate–chlorofrom =2/1/1) to give 0.54 g (85%) of **6** and 0.08 g (14%) of **7**.

6: Mp 93—95°C (recrystallized from hexane–ethyl acetate); ^{1}H NMR δ=2.1 (3H, s), 6.4 (1H, dq, J=9.0, 7.5 Hz), 7.0 (1H, d, J=9.0 Hz), 7.3—8.1 (5H, m); IR 3280 (NH), 1660 (C=O), 1160, 1120 cm^{-1} (CF_3).

Found: C, 53.58; H, 4.23; N, 5.59%. Calcd for $C_{11}H_{10}NF_3O_2$: C, 53.88; H, 4.11; N, 5.71%.

7: Pale yellow oil; ^{1}H NMR δ=2.5 (3H, s), 7.2—7.7 (5H, m); IR (neat) 1195, 1155, 1125 cm^{-1} (CF_3).

Found: C, 58.27; H, 3.61; N, 6.12%. Calcd for $C_{11}H_8NF_3O$: C, 58.16; H, 3.55; N, 6.17%.

A solution of **6** (0.36 g, 1.5 mmol) in 10 cm^3 of 2-propanol was added dropwise to a mixture of sodium borohydride (0.12 g, 3.2 mmol) in 20 cm^3 of 2-propanol at 0°C and the mixture was stirred for 2 h. Diethyl ether (80 cm^3) was added and the solid was filtered off. The filtrates were evaporated under reduced pressure to leave a residue, which was extracted with diethyl ether. The extracts were washed with brine, dried over magnesium sulfate, and evaporated. The resulting residue was recrystallized from hexane–ethyl acetate to give 0.18 g (49%) of **8**: Mp 133—134°C; ^{1}H NMR δ=2.0 (3H, s), 2.6 (1H, d, J=3.8 Hz), 5.0—5.2 (2H, m), 5.6 (1H, bd), 7.3—7.4 (5H, m); IR 3370 (OH), 3330 (NH), 1665 (C=O), 1165, 1115 cm^{-1} (CF_3).

Found: C, 53.24; H, 4.75; N, 5.53%. Calcd for $C_{11}H_{12}NF_3O_2$: C, 53.44; H, 4.89; N, 5.67%.

Preparation of *trans*-2-Methyl-5-phenyl-4-trifluoromethyl-2-oxazoline (9). A mixture of **8** (0.12 g, 0.5 mmol) and phosphorus pentaoxide (2.30 g, 16.2 mmol) in 20 cm^3 of toluene was refluxed for 3 h. After water was added, the mixture was extracted with diethyl ether. The extracts were washed with water and brine, dried over magnesium sulfate, and evaporated to leave a residue. The residue was chromatographed (silica gel, hexane–ethyl acetate =3/1) to give 0.04 g (35%) of **9**, which was purified by gas chromatography: Colorless oil; ^{1}H NMR δ=2.2 (3H, d, J=1.3 Hz), 4.45 (1H, dqq, J=6.7, 6.7, 1.3 Hz), 5.5 (1H, d, J=6.7 Hz), 7.2—7.5 (5H, m); IR (neat) 1665 (C=N), 1160, 1125 cm^{-1} (CF_3).

Found: C, 57.53; H, 4.44; N, 6.10%. Calcd for $C_{11}H_{10}NF_3O$: C, 57.64; H, 4.40; N, 6.11%.

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