Supporting information

Mannich-type Reaction with Trifluoromethylated *N,O*-Hemiacetal: Facile Preparation of β-Amino-β-Trifluoromethyl Carbonyl Compounds

Jun Takaya, Hirotaka Kagoshima, and Takahiko Akiyama*
Department of Chemistry, Faculty of Science, Gakushuin University,
1-5-1, Mejiro, Toshima-ku, Tokyo 171-8588, Japan
takahiko.akiyama@gakushuin.ac.jp

General Information

NMR spectra were observed with a Varian Unity-INOVA 400 spectrometer in $CDCl_3$. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^1H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. Chemical shift values of ^{19}F NMR were given in ppm relative to internal C_6F_6. IR spectra were recorded on a Shimadzu FT-IR 8600PC spectrometer. Mass spectra were recorded on a Shimadzu QP-5000 mass spectrometer. Purification of products was performed by column chromatography on silica gel (Fuji-sylisia D60L) or preparative TLC on silica gel (Wako gel B-5F). Trifluoroacetaldehyde ethyl hemiacetal was purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). All solvents were purified according to the standard procedures. Molecular Sieves 4A was used as powder and was pre-dried prior to use.

Preparation of 2,2,2-trifluoro-1-(4-methoxyphenylamino)ethanol (**1**). A suspension of trifluoroacetaldehyde ethylhemiacetal (90% solution in EtOH, 0.24 mL, 1.86 mmol), *p*-anisidine (222 mg, 1.80 mmol), and MS 4A (600 mg) in Et_2O (1.0 mL) was stirred under N_2 atmosphere for 1.5 h. The reaction mixture was filtrated over Celite pad and the filtrate was concentrated in vacuo to afford **1** (388 mg, 1.75 mmol) in 97% yield. This compound was dissolved in propionitrile and used as a 1.0 mol/L solution. Mp 47.0-48.0 ˚C (hexane-Et_2O); IR ($CHCl_3$) 3587, 3422, 1514, 1244, and 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=2.82 (1H, br), 3.76 (3H, s), 4.16 (1H, brs), 5.20 (1H, brs), 6.77 (2H, d, *J*=8.9 Hz), 6.82 (2H, d, *J*=8.9 Hz), ^{13}C NMR(100 MHz, $CDCl_3$) δ= 55.64, 78.08 (q, *J*=34.1 Hz), 114.97, 117.02, 122.83 (q, *J*=282.3 Hz), 136.98, 154.41, ^{19}F NMR (376 MHz, $CDCl_3$) δ= 79.23 (d, *J*=4.5 Hz) ; MS (EI) : m/z 203 (M^+-18, 75), 134 (100), 107 (34), 92 (46). Found: C, 49.16; H, 4.59, N, 6.66%. Calcd for $C_9H_{10}F_3NO_2$: C, 48.87; H, 4.56; N, 6.33%.

A typical experimental procedure for the Mannich-type reaction by means of $GaCl_3$. (Table 2, Entry 1) To a solution of **1** (0.16 mmol) and **3a** (66 μl, 0.322 mmol) in propionitrile (1.0 mL) was added a solution of $GaCl_3$ in cyclohexane (1.0 mol/L solution, 1.6 mL, 0.16 mmol) at room temperature. After being stirred at the temperature for 1.5 h, the reaction mixture was quenched by addition of sat. $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether and

the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to leave crude material, which was purified by thin layer chromatography (SiO_2, ethyl acetate : hexane = 1 : 5 / v:v) to afford **4a** (51.9 mg, 0.151 mmol) quantitatively.

General Procedure for the Mannich-type reaction under the influence of $GaCl_3$-PhCOCl. (Table 3, Entry 1) To a solution of **1** (0.16 mmol) in propionitrile (1.0 mL) were successively added benzoyl chloride (4.0 μL, 0.0345 mmol), **3a** (66 μl, 0.322 mmol), a solution of $GaCl_3$ in cyclohexane (1.0 mol/L solution, 32 μL, 0.032 mmol) at room temperature. After being stirred at the temperature for 1.5 h, the reaction mixture was quenched by addition of sat. $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to leave crude material, which was purified by thin layer chromatography (SiO_2, ethyl acetate : hexane = 1 : 5 / v:v) to afford **4a** (50.5 mg, 0.128 mmol) in 80%.

4,4,4-Trifluoro-3-(4-methoxyphenylamino)-1-phenyl-1-butanone (**4a**). IR ($CHCl_3$) 3400, 3011, 1690, 1514, 1236, 1180, 1121, and 822 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ= 3.32 (1H, dd, *J*= 17.0, 7.2 Hz), 3.34 (1H, dd, *J*=17.0, 4.8 Hz), 3.54 (1H, brs), 3.72 (3H, s), 4.66-4.71 (1H, m), 6.72 (2H, d, *J*=8.9 Hz), 6.76 (2H, d, *J*=8.9 Hz), 7.46 (2H, dd, *J*=8.5, 8.5 Hz), 7.56 (2H, dd, *J*=8.5, 8.5 Hz), 7.92 (1H, d, *J*= 8.5 Hz), ^{13}C NMR(100 MHz, $CDCl_3$) δ= 38.26, 53.69 (q, *J*= 29.9 Hz), 55.56, 114.76, 115.88, 126.18 (q, *J*=283.5 Hz), 128.10, 128.73, 133.68, 136.25, 139.77, 153.34, 195.32, ^{19}F NMR (376 MHz, $CDCl_3$) δ= 86.27 (d, *J*=6.8 Hz). MS (EI): m/z 323 (M^+, 48), 105 (100), 77 (69).

4,4,4-Trifluoro-3-(4-methoxyphenylamino)-2-methyl-1-phenyl-1-butanone (**4b**) (major : minor= 70:30). IR ($CHCl_3$) 3412, 3017, 1684, 1514, 1244, 1178, 1138, and 908 cm^{-1}; ^1H NMR(400 MHz, C_6D_6) δ=1.01 (3H, d, *J*=7.1 Hz), 3.13 (1H, d, *J*=7.1 Hz, major), 3.35 (1H, s, major), 3.36 (1H, s, minor), 3.54 (1H, dq, *J*= 7.1, 7.1 Hz, major), 3.71 (1H, dq, *J*=6.4, 6.4 Hz, syn), 3.89-4.01 (1H, m, minor), 4.70 (1H, ddq, *J*= 7.1, 7.1, 3.6 Hz, major), 4.98 (1H, d, *J*= 9.3 Hz, minor), 6.45 (2H, d, *J*=8.9 Hz, major), 6.55 (2H, *J*=8.7 Hz, minor), 6.67 (2H, d, *J*=8.9 Hz, major), 6.73 (2H, *J*=8.7 Hz, minor), 7.06 (2H, dd, *J*= 7.1, 7.1 Hz), 7.12 (1H, d, *J*=7.1 Hz), 7.81 (2H, d, *J*=7.1 Hz), ^{13}C NMR(100 MHz, $CDCl_3$) δ= 13.77, 16.28, 38.28, 40.87, 55.63, 57.98 (q, *J*= 27.2 Hz), 60.81 (q, *J*= 28.8 Hz), 114.88, 115.28, 125.99 (q, *J*= 284.2 Hz), 128.20, 128.26, 128.86, 133.44, 133.73, 136.65, 140.31, 141.23, 152.84, 153.12, 200.40, 202.48, ^{19}F NMR (376 MHz, $CDCl_3$) δ= 87.87 (d, *J*=6.8 Hz, minor), 88.98 (d, *J*=7.9 Hz, major); MS (EI): m/z 337(M^+, 34), 204 (55), 134 (63), 105 (100), 77 (78).

2-[2,2,2-Trifluoro-1-(4-methoxyphenylamino)ethyl]cyclohexanone (**4c**). (major : minor= 68:32). IR ($CHCl_3$) 3425, 2947, 1712, 1514, 1234, 1038, and 821 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ= 1.60-2.58 (8H, m), 2.70-2.78 (1H, m, major), 2.81-2.88 (1H, m, minor), 3.40, (1H, brs, major), 3.74 (3H, s), 4.05 (1H, qd, *J*=2.7, 8.2 Hz, minor), 4.46 (1H, brs, minor), 4.81 (1H, qd, *J*=3.1, 8.4 Hz, major), 6.63 (2H, d, *J*=9.0 Hz, minor), 6.78 (2H, d, *J*=9.0 Hz, major), 6.79-6.80 (4H, m), ^{13}C

NMR(100 MHz, $CDCl_3$) δ= 24.55, 24.92, 26.51, 27.52, 31.79, 41.68, 42.58, 49.77, 50.32, 54.06 (q, *J*=28.0 Hz), 55.60, 55.63, 57.90 (q, *J*=29.2 Hz), 114.81, 115.74, 125.75 (q, *J*=285.4 Hz), 126.56 (q, *J*=285.0 Hz), 140.43, 140
47, 152.80, 153.16, 207.91, 209.92, ^{19}F NMR (376 MHz, $CDCl_3$) δ= 90.44 (d, *J*=9.4 Hz, minor), 88.39 (d, *J*=8.3 Hz, major); MS (EI): m/z 301(M^+, 45), 204 (100), 134 (59).

Methyl 4,4,4-trifluoro-3-(4-methoxyphenylamino)-2,2-dimethylbutanoate (**4d**). IR ($CHCl_3$) 3422, 3031, 2955, 1734, 1516, 1217, 1163, and 821 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ= 1.31 (3H, s), 1.32 (3H, s), 3.68 (3H, s), 3.75 (3H, s), 3.77 (1H, d, *J*= 11.1 Hz), 4.27 (1H, dq, *J*=7.9, 11.1 Hz), 6.68 (2H, d, *J*=9.0 Hz), 6.78 (2H, d, *J*=9.0 Hz), ^{13}C NMR(100 MHz, $CDCl_3$) δ= 21.10, 23.07, 45.24, 52.33, 55.67, 62.26 (q, *J*= 27.7 Hz), 114.86, 115.13, 128.72 (q, *J*= 285.8 Hz), 140.64, 153.07, 175.60; ^{19}F NMR (376 MHz, $CDCl_3$) δ= 92.29 (d, *J*=7.9 Hz); MS (EI): m/z 305 (M^+, 145), 204 (100).

Methyl 4,4,4-trifluoro-3-(4-methoxyphenylamino)-2-phenylbutanoate (**4e**). (major : minor= 54:46). IR ($CHCl_3$) 3416, 3011, 1736, 1514, 1271, 1240, 1124, 1038, and 822 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ= 3.04 (1H, brs, major), 3.68 (3H, s, major), 3.71 (3H, s, minor), 4.00 (1H, d, *J*=8.1 Hz, major), 4.04 (1H, *J*= 6.2 Hz, minor), 4.30 (1H, brs, major), 4.55 (1H, brs, minor), 4.69 (1H, brs, minor), 6.43 (2H, d, *J*=9.0 Hz, major), 6.61 (2H, d, *J*=9.0 Hz, minor), 6.67 (2H, d, *J*=9.0 Hz, minor), 6.73 (2H, d, *J*=9.0 Hz, major), 7.20-7.42 (5H, m), ^{13}C NMR(100 MHz, $CDCl_3$) δ= 50.61, 51.54, 52.47, 52.67, 55.52, 55.55, 58.69 (q, *J*=28.4 Hz), 60.40 (q, *J*=28.4 Hz), 114.55, 114.70, 115.27, 115.58, 125.49 (q, *J*=285.8 Hz), 125.79 (q, *J*=283.5 Hz), 128.34, 128.41, 128.71, 128.81, 129.23, 129.39, 140.13, 140.29, 153.01, 153.18, 171.42, 171.54; ^{19}F NMR (376 MHz, $CDCl_3$) δ= 88.84 (d, *J*=6.8 Hz, minor), 87.38 (d, *J*=7.2 Hz, major); MS (EI): m/z 351 (M^+, 13), 204 (100).

Ethyl 4,4,4-trifluoro-3-(4-methoxyphenylamino)-2-methylbutanoate (**4f**). (major : minor= 54:46). IR ($CHCl_3$), 3410, 2986, 1732, 1510, and 822 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ= 0.86 (3H, t, *J*=7.1 Hz, major),.0.90 (3H, t, *J*=7.1 Hz, minor), 1.02 (3H, d, *J*=7.1 Hz, minor), 1.09 (3H, d, *J*=7.1 Hz, major), 2.68 (1H, dq, *J*= 7.1, 7.1 Hz, major), 2.78 (1H, dq, *J*= 7.1, 4.8 Hz, minor), 3.20-3.32 (1H, m, major), 3.35 (3H, s), 3.70-3.80 (1H, m, minor), 3.80-3.95 (2H, m), 4.44 (1H, brq, *J*=7.3 Hz, major), 4.61 (1H, brd, *J*=9.7 Hz, minor), 6.41 (2H, d, *J*=9.0 Hz), 6.68 (2H, d, *J*=9.0 Hz), ^{13}C NMR(100 MHz, $CDCl_3$) δ= 11.46, 13.95, 14.86, 38.98, 39.70, 55.58, 55.62, 58.32 (q, *J*=28.5 Hz), 59.65 (q, *J*=29.5 Hz), 61.14, 61.18, 114.76, 114.85, 114.89, 115.69, 125.61 (q, *J*=284.6 Hz), 125.76 (q, *J*=284.6 Hz), 140.08, 140.68, 152.90, 153.27, 172.70, 173.74; ^{19}F NMR (376 MHz, $CDCl_3$) δ= 89.93 (d, *J*=6.8 Hz, major), 89.58 (d, *J*=6.8 Hz, minor); MS (EI): m/z 305 (M^+, 33), 204 (100).

Removal of the 4-methoxyphenyl group of 4a. To a solution of **4a** (53.7 mg, 0.166 mmol) in acetonitrile (1.0 mL) was added aqueous cerium ammonium nitrate (450 mg, 0.82 mmol) solution (1.0 mL) at 0 ˚C. After being stirred at the temperature for 1 h, the reaction mixture was quenched by addition of sat $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether and the combined organic layers were successively washed with 5% Na_2SO_3 solution, sat.

$NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to leave crude material, which was purified by thin layer chromatography (SiO_2, ethyl acetate : hexane = 1 : 2 / v:v) to afford **5** (28.1 mg, 0.129 mmol) in 78% yield.

3-Amino-4,4,4-trifluoro-1-phenyl-1-butanone (**5**). IR ($CHCl_3$) 3396, 2926, 1688, 1597, 1450, 1171, 1121, and 689 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ= 1.71 (1H, brs), 3.19 (1H, dd, *J*=17.4, 9.7 Hz), 3.33 (1H, dd, *J*=17.4, 2.7 Hz), 4.02 (1H, ddq, *J*=9.7, 9.7, 2.7 Hz), 7.49 (2H, dd, *J*=7.3, 7.3 Hz), 7.61 (1H, dd, *J*=7.3, 7.3 Hz), 7.97 (2H, d, *J*=7.3 Hz), ^{13}C NMR(100 MHz, $CDCl_3$) δ= 39.30, 50.20 (q, *J* =29.4 Hz), 126.41 (q, *J*=275.6 Hz), 128.10, 128.79, 133.73, and 196.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ= 83.46 (d, *J*=7.9 Hz); MS : m/z 197 (M^+, 33), 105 (100), 77 (93), 51 (94).