

Reactivity of Stable Trifluoroacetaldehyde Hemiaminals. 1. An Unexpected Reaction with Enolizable Carbonyl Compounds.

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Supporting information

General Remarks : Solvents were distilled prior to use. Other reagents were used as received. ^1H , ^{13}C and ^{19}F NMR spectra were recorded in CDCl_3 at 300, 75 and 188 MHz, respectively. Chemical shifts are given in ppm relative to TMS (^1H , ^{13}C) or CFCl_3 (^{19}F) as internal references. Coupling constants are given in Hertz. Flash chromatography was performed on silica gel 60M (0.04-0.063 mm). Mass spectrometry was performed under electronic impact at 70eV. Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus. Elemental analyses were carried out by the “Centre de Microanalyse” of the CNRS at Solaize.

Reagents **1**, **2** and **3** were prepared according to our previous work.^{3a-c} Pentafluoroethyl (**6**) and chlorodifluoro analogues (**7**) were prepared by the same techniques.

1-(4-benzylpiperazino)-2,2,3,3,3-pentafluoropropyl trimethylsilyl ether (6) : (Yellow oil). ^1H NMR : $\delta = 7.30\text{-}7.38$ (massif, 5H), 4.59 (t, 1H, $J = 11.6$), 3.55 (AB system, 2H, $J = 13$), 2.92 (dt, 2H, $J = 11.0$, $J = 5.0$), 2.79 (dt, 2H, $J = 11.0$, $J = 5.0$), 2.49 (t, 4H, $J = 5.0$), 0.25 (s, 9H). ^{13}C NMR : $\delta = 138.54$, 129.58, 128.65, 127.48, 119.41 (qt, $J = 286.2$, $J = 35.3$), 114.06 (qt, $J = 261.3$, $J = 34.5$), 84.97 (dd, $J = 26.7$, $J = 22.7$), 63.51, 53.68, 48.18, 0.3. ^{19}F NMR : $\delta = -82.75$ (s,

3F), -120.75 (dd, 1F, $J = 274.1$, $J = 11.6$), -127.70 (dd, 1F, $J = 274.1$, $J = 11.6$). $m/z = 396$ ($M^{+\bullet}$), 307, 277, 91, 73. $C_{17}H_{25}F_5N_2OSi$: calcd : C (51.50), H (6.36), N (7.07). Found : C (51.72), H (6.30), N (7.39).

1-(4-benzylpiperazino)-2-chloro-2,2-difluoroethyl trimethylsilyl ether (7) : (Yellow oil). 1H NMR : δ 7.25-7.5 (massif, 5H), 4.5 (dd, 1H, $J = 8.5$, $J = 7.3$), 3.55 (AB system, 2H, $J = 13$), 2.88 (broad t, 4H, $J = 4.6$), 2.50 (t, 4H, $J = 4.6$), 0.26 (s, 9H). ^{13}C NMR : $\delta = 138.53$, 129.59, 129.00 (t, $J = 302.6$), 128.66, 127.50, 89.86 (t, $J = 27.3$), 63.55, 53.88, 47.88, 0.47. ^{19}F NMR : $\delta = -63.42$ (d, 1F, $J = 7.3$), -63.51 (d, 1F, $J = 7.3$). $C_{16}H_{25}ClF_2N_2OSi$: calcd : C (52.95), H (6.94), N (7.72). Found : C (52.79), H (7.13), N (7.34).

Typical procedure for the synthesis of 4 under catalysis with *t*-BuOK. A 1M solution of *t*-BuOK in THF (1 mL) was added, at room temperature, to a solution of **1** (2 mmol) and enolizable carbonyl substrate (1 mmol) in THF (1mL). Then, the reaction mixture was heated to 80°C for 24h. After cooling, the crude mixture was evaporated and purified by flash chromatography. Eluents are indicated for each compounds. Because of their rather limited stability, compounds **4** were rapidly engaged in the elimination step after NMR control.

Typical procedure for the synthesis of 4 under catalysis with BF_3/Et_2O . BF_3 , Et_2O (1.2 mmol) was added, at room temperature, to a solution of **2**, **6** or **7** (1 mmol) and enolizable carbonyl substrate (1 mmol) in CH_2Cl_2 (1 mL). Then, the mixture was heated to 50°C for 5h. After cooling and evaporation, the crude mixture was deposited at the top of a column filled with silica gel and eluted.

3-(4-benzylpiperazino)-4,4,4-trifluoro-1-phenyl-1-butanone (4a) : (Petroleum Ether / Ether 19/1 + 1% Et₃N - Yellow oil). ¹H NMR : δ 7.96-8.02 (massif, 2H), 7.59-7.65 (massif, 1H), 7.48-7.57 (massif, 2H), 7.23-7.38 (massif, 5H), 4.05 (ddq, 1H, *J* = 8.7, *J* = 4.3, *J* = 8.1), 3.47 (s, 2H), 3.43 (dd, 1H, *J* = 16.7, *J* = 8.7), 3.11 (dd, 1H, *J* = 16.7, *J* = 4.3), 2.87-3.14 (massif, 2H), 2.72-2.79 (massif, 2H), 2.37-2.44 (massif, 4H). ¹³C NMR : δ 196.56, 138.46, 137.16, 133.81, 129.58, 129.17, 128.62, 128.52, 127.47, 127.33 (q, *J* = 288.9), 63.38, 61.55 (q, *J* = 26.6), 54.06, 49.82, 35.34. ¹⁹F NMR : δ -70.00 (d, *J* = 8.1).

3-(4-benzylpiperazino)-4,4,4-trifluoro-2-methyl-1-phenyl-1-butanone (4c – mixture of 2 diast.) : (Petroleum Ether / Ether 9/1 + 1% Et₃N - Yellow oil). ¹H NMR : δ 7.85-7.10 (massif, 2H), 7.40-7.70 (massif, 3H), 7.10-7.40 (massif, 5H), 3.95 (m, 1H), 3.75 and 3.60 (m, 1H), 3.55 and 3.29 (s, 2H), 2.75-3.10 (massif, 3H), 2.3-2.4 (massif, 3H), 1.7-2.25 (massif, 2H), 1.25 (m, 3H). ¹³C NMR : δ 202.24, 201.84, 138.43, 138.26, 137.62, 136.66, 133.75, 133.42, 129.60, 129.49, 129.16, 128.66, 128.55, 128.43, 127.85 and 127.78 (q, *J* = 327.2 and 303.3), 68.23 and 66.05 (q, *J* = 25.1 and 24.1), 63.56, 54.32, 53.70, 49.96 (broad s), 39.44, 38.67, 16.54, 14.76 (q, *J* = 2.7). ¹⁹F NMR : δ -64.16 (d, *J* = 8.0), -66.58 (d, *J* = 6.0).

2-[1-(4-benzylpiperazino)-2,2,2-trifluoroethyl]-3,4-dihydro-1(2H)-naphthalenone (4d – mixture of 2 diast.) : (Petroleum Ether / Ether 9/1 + 1% Et₃N - Yellow oil). ¹H NMR : δ 7.18-7.30 (massif, 9H), 4.14 and 4.10 (dq, 1H, *J* = 4.36 and 6.1, *J* = 10.1 and 9.1), 3.47 (s, 2H), 2.2-3.2 (massif, 13H). ¹³C NMR : δ 196.92, 143.79, 142.96, 138.44, 138.39, 132.90, 132.61, 133.93, 133.64, 129.64, 129.59, 129.11, 128.60, 128.26, 128.23, 127.47, 127.45, 127.19, 124.30 (q, *J* =

236.0), 63.44, , 62.47 and 62.39 (q, $J = 25.8$ and 25.48), 54.30, 53.95, 50.31, 49.65, 49.09, 46.26, 28.40, 27.59, 25.74, 25.43. ^{19}F NMR : δ -65.34 (d, $J = 10.5$), -66.39 (d, $J = 10.0$).

3-(4-benzylpiperazino)-4,4,4-trifluoro-1-(3-pyridinyl)-1-butanone (4e) : (Petroleum Ether / Acetone 9/1 - Yellow oil). ^1H NMR : δ 9.13 (m, 1H), 8.67 (m, 1H), 8.21 (m, 1H), 7.44 (m, 1H), 7.18-7.30 (massif, 5H), 3.96 (ddq, 1H, $J = 8.7$, $J = 4.4$, $J = 9.0$), 3.48 (s, 2H), 3.39 (dd, 1H, $J = 16.7$, $J = 8.7$), 3.07 (dd, 1H, $J = 16.7$, $J = 4.4$), 2.8-2.9 (massif, 2H), 2.6-2.8 (massif, 2H), 2.2-2.5 (massif, 4H). ^{13}C NMR : δ 195.45, 153.77, 149.51, 137.88, 136.14, 132.58, 129.67, 128.60, 127.55, 124.31, 127.40 (q, $J = 289.1$), 63.22, 61.46 (q, $J = 26.8$), 53.85, 49.58, 35.72. ^{19}F NMR : δ -69.77 (d, $J = 9.0$).

3-(4-benzylpiperazino)-4,4,4-trifluoro-1-(2-pyridinyl)-1-butanone (4f) : (Petroleum Ether / Acetone 19/1 -Yellow oil). ^1H NMR : δ 8.67 (m, 1H), 8.06 (m, 1H), 7.84 (m, 1H), 7.48 (m, 1H) 7.2-7.32 (massif, 5H) 4.08 (qdd, 1H, $J = 8.8$, $J = 9.0$, $J = 4.8$), 3.78 (dd, 1H, $J = 16.0$, $J = 9.0$), 3.41 (s, 2H), 3.29 (dd, 1H, $J = 16.0$, $J = 4.8$), 2.93 (m, 2H), 2.67 (m, 2H), 2.10-2.40 (massif, 4H). ^{13}C NMR : δ 198.37, 153.41, 149.31, 138.48, 137.37, 129.52, 128.56, 127.70, 128.56, 127.30 (q, $J = 289.5$), 122.41, 63.37, 61.93 (q, $J = 26.6$), 54.04, 49.62, 34.83. ^{19}F NMR : δ -69.74 (d, $J = 8.8$).

2,6-bis[1-(4-benzylpiperazino)-2,2,2-trifluoroethyl]cyclohexanone (4g) : (Petroleum ether / acetone 19/1 – Yellow oil). ^1H NMR : untractable spectrum (complex mixture of 5 diast.). ^{19}F NMR : δ -64.19 (m), -6558 (broad d, $J = 9.3$), -66.48 (d, $J = 6.7$), -66.69 (d, $J = 6.6$), -67.11 (d, $J = 6.7$). .

Diethyl 2-[1-(4-benzylpiperazino)-2,2,2-trifluoroethyl]malonate (4h) : (Petroleum Ether / Ether 5/1 - Colorless oil). ^1H NMR : δ 7.1-7.4 (massif, 5H), 4.10-4.28 (massif, 4H), 3.95 (dq, 1H, $J = 11.0$, $J = 7.0$), 3.81 (d, 1H, $J = 11.0$), 3.48 (s, 2H), 2.9-3.1 (massif, 2H), 2.6-2.8 (massif, 2H), 2.2-2.5 (massif, 4H), 1.26 (q, 6H, $J = 7.2$). ^{13}C NMR : δ 166.23, 166.09, 137.66, 129.67, 128.31, 127.57, 126.38 (q, $J = 292.1$), 64.82 (q, $J = 26.4$), 63.24, 62.46, 62.33, 54.01, 52.86 (q, $J = 1.2$), 49.80 (broad s), 14.52, 14.19. ^{19}F NMR : δ -66.99 (d, $J = 7.0$).

Typical procedure for the synthesis of 5 from 4. Trifluoroacetic acid (0.5 mL) was added, at 0 °C, to a solution of **4** (1 mmol) in CH_2Cl_2 (1 mL). The mixture was heated in a closed vessel at 80°C for 5h. After cooling, it was washed twice with a 6% aqueous solution of NaHCO_3 , dried over Na_2SO_4 and evaporated *in vacuo* at room temperature. Then, the crude residue was purified by flash chromatography. Eluents are indicated for each compounds.

(E)-4,4,4-trifluoro-1-phenyl-2-buten-1-one (5a)⁷ : (Petroleum Ether / Ether 50/1 - White solid). Mp = 28 °C. ^1H NMR : δ 7.93-8.04 (massif, 2H), 7.62-7.70 (massif, 1H), 7.50-7.60 (massif, 2H), 7.55 (dq, 1H, $J = 15.5$, $J = 2.2$), 6.83 (dq, 1H, $J = 15.5$, $J = 6.5$). ^{13}C NMR : δ 188.39, 136.56, 134.54, 131.44 (q, $J = 5.4$), 130.64 (q, $J = 35.1$), 129.39, 129.21, 127.33 (q, $J = 270.3$). ^{19}F NMR : δ -65.59 (d, $J = 6.5$). $m/z = 200$ (M^+), 105, 77, 51, 28. $\text{C}_{10}\text{H}_7\text{F}_3\text{O}$: calcd : C (60.01), H (3.53). Found : C (60.15), H (3.42).

(E)-4,4,4-trifluoro-2-methyl-1-phenyl-2-buten-1-one (5c) : (Petroleum Ether / Ether 50/1 - Yellow oil). ^1H NMR : δ 7.75-7.85 (massif, 2H), 7.60-7.70 (massif, 1H), 7.45-7.60 (massif, 2H),

6.05 (qq, 1H, $J = 7.0$, $J = 1.5$), 2.24 (dq, 3H, $J = 1.5$, $J = 2.4$). ^{13}C NMR : δ 196.94, 147.33 (q, $J = 4.8$), 135.88, 133.84, 130.10, 129.10, 125.14 (q, $J = 34.9$), 123.36 (q, $J = 272.2$), 15.06. ^{19}F NMR : δ -59.48 (d, $J = 7.0$). $m/z = 214$ ($\text{M}^{+\bullet}$), 105, 77, 51, 39, 28. $\text{C}_{11}\text{H}_9\text{F}_3\text{O}$: calcd : C (61.68), H (4.24). Found : C (61.45), H (4.29).

(E)-2-[2,2,2-trifluoroethylidene]-3,4-dihydro-1(2H)-naphthalenone (5d) : (Petroleum Ether / Ether 50/1 - White solid). Mp = 72 °C. ^1H NMR : δ 8.08 (m, 1H), 7.54 (m, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 6.75 (q, 1H, $J = 8.1$), 3.05 (broad s, 4H). ^{13}C NMR : 186.02, 145.86 (q, $J = 5.0$), 144.14 , 134.64, 132.49, 128.94, 128.87, 127.78, 123.80 (q, $J = 271.5$), 122.84 (q, $J = 34.9$), 28.65, 27.37 (q, $J = 1.2$). ^{19}F NMR : δ -58.70 (d, $J = 8.1$). $m/z = 226$ ($\text{M}^{+\bullet}$), 198, 129, 118, 90, 77, 63, 51, 39, 28. $\text{C}_{12}\text{H}_9\text{F}_3\text{O}$: calcd : C (63.72), H (4.01). Found : C (63.81), H (3.98).

(E)-4,4,4-trifluoro-1-(3-pyridinyl)-2-buten-1-one (5e) : (Petroleum Ether / Acetone 40/1 - White Solid). Mp = 54 °C. ^1H NMR : δ 9.17 (broad s, 1H), 8.83 (m, 1H), 8.24 (m, 1H), 7.50 (dq, 1H, $J = 15.6$, $J = 2.0$), 7.46-7.51 (massif, 1H), 6.85 (dq, 1H, $J = 15.6$, $J = 6.7$). ^{13}C NMR : δ 187.28, 154.73, 150.38, 136.40 , 131.96, 131.62 (q, $J = 35.4$), 130.61(q, $J = 5.6$), 124.30, 122.66 (q, $J = 270.3$). ^{19}F NMR : δ -65.79 (d, $J = 7.0$). $m/z = 201$ ($\text{M}^{+\bullet}$), 132, 106, 78, 51, 28. $\text{C}_9\text{H}_6\text{F}_3\text{NO}$: calcd : C (53.74), H (3.01), N (6.96). Found : C (53.97), H (3.21), N (6.62).

(E, E)-2,6-bis[2,2,2-trifluoroethylidene]cyclohexanone (5g)⁷ : (Pentane - Yellow oil). ^1H NMR : δ 6.68 (qt, 2H, $J = 8.7$, $J = 2.2$), 2.85-2.95 (massif, 4H), 1.88 (q, 2H, $J = 6.4$). ^{13}C NMR : δ 187.20, 144.45 (q, $J = 4.8$), 125.16 (q, $J = 35.1$), 123.33 (q, $J = 271.5$), 27.01 (q, $J = 1.3$),

20.75. ^{19}F NMR : $\delta = -59.59$ (d, $J = 8.4$). $m/z = 258$ (M^+), 230, 161, 141, 108, 69, 53, 39, 28.
 $\text{C}_{10}\text{H}_8\text{F}_6\text{O}$: calcd : C (46.52), H (3.12). Found : C (46.41), H (3.34).

Diethyl 2-(2,2,2-trifluoroethylidene)malonate (5h)⁷ : (Petroleum Ether / Acetone 10/1 - Yellow oil). ^1H NMR : δ 6.75 (q, 1H, $J = 7.6$), 4.34 and 4.31 (q, 4H, $J = 7.2$), 1.32 and 1.39 (t, 6H, $J = 7.2$). ^{13}C NMR : δ 162.99, 161.85, 135.94 (q, $J = 5.2$), 128.11 (q, $J = 36.8$), 121.58 (q, $J = 271.5$), 63.27, 62.87, 14.20, 14.11. ^{19}F NMR : δ -62.78 (d, $J = 7.6$). $m/z = 195$ ($\text{M}^+ - \text{OEt}$), 167, 53, 29, 28. $\text{C}_9\text{H}_{11}\text{F}_3\text{O}_4$: calcd : C (45.01), H (4.62). Found : C (45.39), H (4.87).

Typical procedure for the one-pot synthesis of 5 from 2, 6 or 7. BF_3 , Et_2O (1.2 mmol) was added, at room temperature, to a solution of **2**, **6** or **7** (1 mmol) and enolizable carbonyl substrate (1 mmol) in CH_2Cl_2 (1 mL). Then, the mixture was heated to 50°C for 5h. After cooling at 0°C , trifluoroacetic acid (0.5 mL) was added and the mixture was heated again to 50°C for 5h. After cooling and evaporation, the crude mixture was deposited at the top of a column filled with silica gel and eluted.

(E)-2-(2,2,2-trifluoroethylidene)-cholest-4-en-3-one (5i) : (Petroleum Ether / Ether 19/1 - Yellow oil) ^1H NMR : δ 6.51 (qd, 1H, $J = 8.6$, $J = 2.3$), 5.94 (s, 1H), 3.23 (d, 1H, $J = 14.3$), 2.25-2.51 (massif, 3H), 2.09 (m, 1H), 1.78-1.90 (massif, 2H), 0.78-1.7 (massif, 31H), 0.72 (s, 3H). ^{13}C NMR : δ 187.33, 175.67, 144.45 (q, $J = 5.0$), 123.95, 123.80 (q, $J = 271.5$), 122.09 (q, $J = 34.5$), 56.46, 56.20, 53.49, 42.73, 41.64, 40.10, 39.88, 39.85, 36.49, 36.12, 35.96, 33.42, 32.19, 28.54, 28.39, 24.52, 24.19, 23.19, 22.93, 21.63, 19.47, 18.99, 12.27. ^{19}F NMR : δ -58.95 (d, $J = 8.6$).
 $\text{C}_{29}\text{H}_{43}\text{F}_3\text{O}$: calcd : C (74.96), H (9.33). Found : C (75.12), H (9.35).

(E)-4,4,5,5,5-pentafluoro-1-phenyl-2-penten-1-one (5j) : (Petroleum Ether / Ether 50/1 - Yellow oil). ^1H NMR : δ 7.92-8.01 (massif, 2H), 7.49-7.69 (massif, 3H), 7.55 (dt, 1H, $J = 15.5$, $J = 2.2$), 6.87 (dt, 1H, $J = 15.5$, $J = 11.8$). ^{13}C NMR : δ 187.95, 136.51, 134.58, 133.43 (t, $J = 7.5$), 129.74 (t, $J = 23.8$), 129.41, 129.24, 118.99 (qt, $J = 285.7$, $J = 37.00$), 112.51 (tq, $J = 251.65$, $J = 39.21$). ^{19}F NMR : δ -84.99 (s, 3F), -117.34 (d, 2F, $J = 11.8$). $m/z = 250$ ($\text{M}^{+\bullet}$), 133, 105, 77, 51, 28. $\text{C}_{11}\text{H}_7\text{F}_5\text{O}$: calcd : C (52.81), H (2.82). Found : C (52.57), H (2.96).

(E)-2-[2,2,3,3,3-pentafluoropropylidene]-3,4-dihydro-1(2H)-naphthalenone (5k) : (Petroleum Ether / Ether 50/1 - Yellow oil). ^1H NMR : δ 8.11 (m, 1H), 7.55 (m, 1H) 7.38 (m, 1H), 7.30 (m, 1H) 6.72 (t, $J = 15.1$), 2.92-3.20 (massif, 4H). ^{13}C NMR : δ 185.86, 147.99 (t, $J = 4.6$), 144.18, 134.68, 132.37, 129.02, 128.91, 127.81, 120.85 (t, $J = 23.8$), 119.36 (qt, $J = 285.8$, $J = 37.0$), 113.59 (tq, $J = 251.4$, $J = 39.4$), 28.76, 27.60 (t, $J = 2.9$). ^{19}F NMR : δ -85.63 (s, 3F), -11.51 (d, 2F, $J = 15.1$). $m/z = 276$ ($\text{M}^{+\bullet}$), 179, 159, 128, 118, 90, 39, 28. $\text{C}_{13}\text{H}_9\text{F}_5\text{O}$: calcd : C (56.53), H (3.28). Found : C (56.89), H (3.51).

(E)-4-chloro-4,4-difluoro-1-phenyl-2-buten-1-one (5l) : (Petroleum Ether - Yellow oil). ^1H NMR : δ 7.88-8.05 (massif, 2H), 7.47-7.70 (massif, 3H), 7.43 (dt, 1H, $J = 15.3$, $J = 1.7$), 6.98 (dt, 1H, $J = 15.3$, $J = 8.7$). ^{13}C NMR : δ 188.60, 136.75, 136.32 (t, $J = 28.5$), 134.48, 129.37, 129.18, 128.10 (t, $J = 5.5$), 124.57 (t, $J = 287.7$). ^{19}F NMR : δ -53.78 (d, $J = 8.7$). $m/z = 218$ ($\text{M}^{+\bullet} \text{ } ^{37}\text{Cl}$), 216 ($\text{M}^{+\bullet} \text{ } ^{35}\text{Cl}$), 181, 133, 105, 77, 51, 39, 28. $\text{C}_{10}\text{H}_7\text{ClF}_2\text{O}$: calcd : C (55.45), H (3.26). Found : C (55.52), H (3.13).

(E)-2-[2-chloro-2,2-difluoroethylidene]-3,4-dihydro-1(2H)-naphthalenone (5m) :

(Petroleum Ether / Ether 50/1 - Yellow Solid). Mp = 46 °C. ¹H NMR : δ 8.09 (m, 1H), 7.54 (m, 1H), 7.37 (m, 1H), 7.29 (m, 1H), 6.97 (tt, 1H, *J* = 9.6, *J* = 1.7), 3.00-3.16 (massif, 4H). ¹³C NMR : δ 186.27, 144.09, 142.91 (t, *J* = 4.9), 134.60, 132.62, 128.99 (t, *J* = 29.3), 128.93, 128.87, 127.77, 125.30 (t, *J* = 288.5), 28.48, 27.18 (t, *J* = 2.3). ¹⁹F NMR : δ -46.33 (d, *J* = 9.6). *m/z* = 244 (M⁺ ³⁷Cl), 242 (M⁺ ³⁵Cl), 179, 159, 128, 90, 77, 39, 28. C₁₂H₉ClF₂O: calcd : C (59.40), H (3.74), Cl (14.61). Found : C (59.57), H (3.81), Cl (14.23).