

Supporting information

Facile Radical Trifluoromethylation of Lithium Enolates

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General:

¹H NMR and ¹³C NMR were measured on Varian Gemini 2000 (300 MHz) spectrometers and ¹⁹F NMR was measured on Varian UNITY INOVA (400 MHz) spectrometers. Chemical shift of ¹H NMR was expressed in parts per million downfield from tetramethylsilane as an internal standard ($\delta=0$) in CDCl₃. Chemical shifts of ¹³C NMR were expressed in parts per million downfield from CDCl₃ as an internal standard ($\delta=77.0$) in CDCl₃. Chemical shifts of ¹⁹F NMR were expressed in parts per million downfield from BTF as an internal standard ($\delta=-63.24$) in CDCl₃. IR spectrum was measured on JASCO FT/IR-5000 spectrometer. EI Mass spectra were measured on Shimadzu QP-5000 spectrometer. Analytical thin layer chromatographies (TLC) were performed on a glass plates and /or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F₂₅₄, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, KMnO₄ and phosphomolybdic acid. Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane and dichloromethane mixture as an eluent unless otherwise noted. THF was distilled from benzophenone-kethyl under Ar prior to use. All experiments were carried out under argon atmosphere unless otherwise noted.

Typical experimental procedure of radical trifluoromethylation of lithium enolate

A: Reaction of ketone

To a solution of ⁱPr₂NH (28.0 μ l, 0.20 mmol) in THF (2.0 mL) was added ⁿBuLi (126.3 μ l of 1.58 M solution in hexane, 0.20 mmol) at -78 °C. The reaction mixture was stirred at 0 °C for 30 minutes and then cooled to -78 °C. To the solution was added cyclohexanone (20.7 μ l, 0.2 mmol) and stirred for 60 minutes at the temperature. Then, gaseous CF₃I (ca. 200 mg, ca. 1.0 mmol) was added with a cannula. Next, a syringe, which was filled with 0.12 mL of 5M solution of acetic acid in THF, was set to the reaction vessel and kept untouch till quenching the reaction. Then Et₃B (0.2 mL of 1.0 M solution in hexane, 0.2 mmol) was added in flat 15 s to start the radical addition reaction. The reaction mixture was immediately quenched (in ~1 s) by acetic acid solution, which was set beforehand, at -78 °C. After warming to room temperature, BTF (10 μ l, 0.082 mmol) was added as an internal standard. The yield was determined by ¹⁹F NMR of the crude mixture (81%).

B: Reaction of silyl enol ether

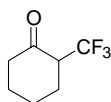
To a solution of 1-(trimethylsilyloxy)cyclohexene (38.9 μ l, 0.2 mmol) in THF was added ⁿBuLi (128.2 μ l of 1.56 M solution in hexane, 0.20 mmol) at 0 °C and stirred for 30 minutes at the temperature. Then, the reaction mixture was cooled to -78 °C. To the mixture was added gaseous CF₃I (ca. 200 mg, ca. 1.0 mmol) with a cannula followed by Et₃B (0.2 mL of 1.0 M solution in hexane, 0.2 mmol). The reaction mixture was stirred for 2 hours at -78 °C and then quenched by acetic acid (0.12 mL of 5

M solution in THF) at $-78\text{ }^{\circ}\text{C}$. After warming to room temperature, BTF (10 μl , 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR of the crude mixture (77%).

Product purification

Most of the product presented in this paper is volatile. Therefore, for accuracy, the yield was determined by ^{19}F NMR using BTF as an internal standard without purification. Some of the non-volatile product (**2b**, **2e**, **2f**) could be isolated by silica gel column chromatography (using hexane/dichloromethane or hexane/ethylacetate as an eluant) after filtration over celite and concentration under vacuum. The NMR yield and isolated yield were in comparable value.

2-Trifluoromethyl-cyclohexanone (**2a**)



^1H NMR (CDCl_3 , 400 MHz)

1.62~1.88 (m, 3H), 1.92~2.14 (m, 2H), 2.24~2.39 (m, 2H), 2.42~2.53 (m, 1H), 2.98~3.13 (m, 1H) (ppm)

^{13}C NMR (CDCl_3 , 75 Hz)

23.7, 27.1, 27.5 (q, $J=2.4$ Hz), 42.2, 53.6 (q, $J=25.7$ Hz), 124.6 (q, $J=279.5$ Hz), 203.0 (ppm)

^{19}F NMR (CDCl_3 , 376 Hz)

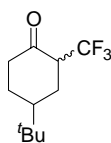
-69.3 (d, 7.9 Hz) (ppm)

IR (neat)

2954, 2876, 2364, 1729, 1272, 1170, 1125, 1060 (cm^{-1})

EI-MS $m/z=166$ [M^{+}]

4-Tertiarybutyl-2-trifluoromethyl-cyclohexanone (**2b**)



Major isomer

^1H NMR (CDCl_3 , 300 MHz)

0.94 (s, 9H), 1.42~1.68 (m, 3H), 2.18~2.20 (m, 1H), 2.26~2.42 (m, 2H), 2.44~2.56 (m, 1H), 3.00~3.16 (m, 1H) (ppm)

^{13}C NMR (CDCl_3 , 75 Hz)

27.5, 28.1, 28.6, 32.5, 41.7, 46.1, 53.0 (q, $J=25.7$ Hz), 124.6 (q, $J=279.6$ Hz), 203.2 (ppm)

^{19}F NMR (CDCl_3 , 376 Hz)

-69.7 (d, $J=7.9$ Hz) (ppm)

IR (KBr)

2970, 2878, 1734, 1392, 1369, 1274, 1170, 1120, 1067 (cm^{-1})

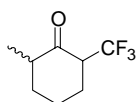
EI-MS $m/z=222$ [M^{+}]

Minor isomer (Isonerization was observed during isolation. Therefore, only ^{19}F NMR data could be shown)

^{19}F NMR (CDCl_3 , 376 Hz)

-66.1 (d, $J=10.5$ Hz)(ppm)

2-Methyl-6-trifluoromethyl-cyclohexanone (2c)



Major isomer

^1H NMR (CDCl_3 , 300 MHz)

1.03 (d, $J=6.3$ Hz, 3H), 1.34~1.49 (m, 1H), 1.63~1.87 (m, 2H), 1.88~2.03 (m, 1H), 2.08~2.19 (m, 1H), 2.30~2.49 (m, 2H), 2.98~3.16 (m, 1H) (ppm)

^{13}C NMR (CDCl_3 , 75 Hz)

13.8, 24.0, 28.3, 36.3, 45.9, 53.7 (q, $J=25.7$ Hz), 124.8 (q, $J=279.5$ Hz), 204.6 (ppm)

^{19}F NMR (CDCl_3 , 376 Hz)

-69.8 (d, $J=8.3$ Hz) (ppm)

IR (neat)

2942, 2874, 2366, 1731, 1456, 1392, 1332, 1272, 1170, 1137, 1123, 1038, 832, 688 (cm^{-1})

EI-MS $m/z=180$ [M^+]

Minor isomer

^1H NMR (CDCl_3 , 300 MHz)

1.11 (d, $J=6.6$ Hz, 3H), 1.46~2.21 (m, 6H), 2.57~2.71 (m, 1H), 3.07~3.22 (m, 1H) (ppm)

^{13}C NMR (CDCl_3 , 75 Hz)

15.0, 20.2, 26.9, 29.6, 34.2, 44.5, 52.3 (q, $J=25.7$), 125.2 (q, $J=280.7$ Hz), 206.3 (ppm)

^{19}F NMR (CDCl_3 , 376 Hz)

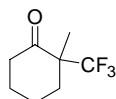
-66.7 (d, $J=10.2$ Hz) (ppm)

IR (neat)

2928, 2858, 2364, 2344, 1725, 1458, 1265, 1143, 801 (cm^{-1})

EI-MS $m/z=180$ [M^+]

2-Methyl-2-trifluoromethyl-cyclohexanone (2d)



^1H NMR (CDCl_3 , 300 MHz)

1.36 (s, 3H), 1.70~2.00 (m, 5H), 2.06~2.20 (m, 1H), 2.35~2.58 (m, 2H) (ppm)

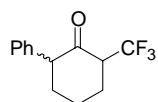
^{13}C NMR (CDCl_3 , 75 Hz)

17.7 (q, $J=2.4$ Hz), 20.5, 26.4, 33.5, 39.4, 53.7 (q, $J=23.2$ Hz), 126.5 (q, $J=283.2$ Hz), 206.2 (ppm)

^{19}F NMR (CDCl_3 , 376 Hz)

-73.6 (s) (ppm)
IR (neat)
2936, 2874, 1725, 1274, 1170, 1137 (cm⁻¹)
EI-MS m/z=180 [M⁺]

2-Phenyl-6-trifluoromethyl-cyclohexanone (2e)



Major isomer

¹H NMR (CDCl₃, 300 MHz)

1.83~2.21 (m, 4H), 2.28~2.40 (m, 1H), 2.40~2.56 (m, 1H), 3.16~3.35 (m, 1H), 3.56~3.68 (dd, *J*=5.4, 12.6 Hz, 1H), 7.11~7.17 (m, 2H), 7.25~7.40 (m, 3H) (ppm)

¹³C NMR (CDCl₃, 75 Hz)

24.2, 28.3, 35.6, 54.1 (q, *J*=25.6 Hz), 57.8, 124.6 (q, *J*=280.8 Hz), 127.4, 128.4, 128.8, 137.0, 201.6 (ppm)

¹⁹F NMR (CDCl₃, 376 Hz)

-69.6 (d, *J*=7.9 Hz) (ppm)

IR (KBr)

3036, 2946, 2872, 1722, 1605, 1452, 1385, 1270, 1168, 1133, 1045, 761, 704, 592 (cm⁻¹)

EI-MS m/z=242 [M⁺]

Minor isomer

¹H NMR (CDCl₃, 300 MHz)

1.86~2.28 (m, 5H), 2.37~2.52 (m, 1H), 3.12~3.30 (dq, *J*=6.0, 9.3 Hz, 1H), 3.82~3.92 (distorted t, *J*=6.3 Hz, 1H), 7.17~7.43 (m, 5H) (ppm)

¹³C NMR (CDCl₃, 75 Hz)

20.4, 27.4, 31.3, 52.0 (q, *J*=26.9 Hz), 55.1, 125.1 (q, *J*=280.8 Hz), 127.4, 127.6, 129.0, 136.7, 203.5 (ppm)

¹⁹F NMR (CDCl₃, 376 Hz)

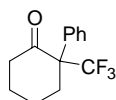
-67.9 (d, *J*=9.0 Hz) (ppm)

IR (neat)

3066, 3032, 2954, 2878, 2364, 1725, 1603, 1584, 1499, 1454, 1390, 1332, 1274, 1183, 1141, 698 (cm⁻¹)

EI-MS m/z=242 [M⁺]

2-Phenyl-2-trifluoromethyl-cyclohexanone (2f)



¹H NMR (CDCl₃, 300 MHz)

1.63~1.86 (m, 3H), 1.89~2.00 (m, 1H), 2.12~2.25 (m, 1H), 2.31~2.40 (m, 2H), 2.91 (qd, *J*=3.0, 14.4 Hz, 1H), 7.29~7.35 (m, 2H), 7.35~7.47 (m, 3H) (ppm)

^{13}C NMR (CDCl_3 , 75 Hz)

20.2, 27.4, 29.9 (q, $J=2.4$ Hz), 39.8, 62.2 (q, $J=22.0$ Hz), 125.1 (q, $J=283.2$ Hz), 128.7, 128.8, 129.0, 131.8, 204.7 (ppm)

^{19}F NMR (CDCl_3 , 376 Hz)

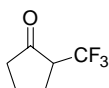
-72.9 (s) (ppm)

IR (neat)

3066, 2954, 2874, 1725, 1282, 1255, 1176, 1152 (cm^{-1})

EI-MS $m/z=242$ [$\text{M}^{+\bullet}$]

2-Trifluoromethyl-cyclopentanone (2g)



^1H NMR (CDCl_3 , 300 MHz)

1.77~2.00 (m, 1H), 2.01~2.21 (m, 2H), 2.22~2.48 (m, 3H), 2.78~2.97 (qm, $J=9.6$ Hz, 1H) (ppm)

^{13}C NMR (CDCl_3 , 75 Hz)

20.0, 24.4, 38.5, 51.1 (q, $J=26.9$ Hz), 124.6 (q, $J=278.3$ Hz), 209.4 (ppm)

^{19}F NMR (CDCl_3 , 376 Hz)

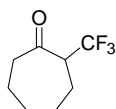
-67.9 (d, $J=10.5$) (ppm)

IR (neat)

2986, 2896, 2366, 2344, 1758, 1638, 1367, 1313, 1257, 1187, 1151, 1096, 1046 (cm^{-1})

EI-MS $m/z=152$ [$\text{M}^{+\bullet}$]

2-Trifluoromethyl-cycloheptanone (2h)



^1H NMR (CDCl_3 , 300 MHz)

1.22~1.48 (m, 2H), 1.48~1.75 (m, 2H), 1.86~2.05 (m, 3H), 2.09~2.20 (m, 1H), 2.54~2.61 (m, 2H), 3.16~3.31 (qdd, $J=4.1, 8.9, 11.1$ Hz, 1H) (ppm)

^{13}C NMR (CDCl_3 , 75 Hz)

24.4, 24.7 (q, $J=2.4$ Hz), 27.5, 29.1, 43.1, 55.5 (q, $J=24.5$ Hz), 124.9 (q, $J=280.8$ Hz), 205.9 (ppm)

^{19}F NMR (CDCl_3 , 376 Hz)

-69.0 (d, 9.0 Hz) (ppm)

IR (neat)

2940, 2866, 1721, 1178, 1151, 1096 (cm^{-1})

EI-MS $m/z=180$ [$\text{M}^{+\bullet}$]