Efficient, Direct α-Methylenation of Carbonyls Mediated by Diisopropylammonium Trifluoroacetate

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General Information

All reactions were carried out open to the atmosphere in oven-dried glassware with magnetic stirring. All commercially obtained reagents were used as received. THF was obtained from a solvent purification system. Heating was accomplished by either a heating mantle or silicone oil bath. Purification of reaction products was carried out by flash column chromatography using silica gel. TLC visualization was accompanied with UV light and/or potassium permanganate staining. ¹H NMR spectra were recorded at 300 MHz, and are reported relative to CDCl₃ (δ 7.27). ¹H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Proton-decoupled ¹³C NMR spectra were recorded at 75 MHz and reported relative to CDCl₃ (δ 77).

Product Product Compound No. Reference Compound No. Reference 1 S1 S16 11 2 S2 12 S8 OH 3 S3 13 S9 4 S4 14 S10 Ot-Bu t-BuO 5 S5 15 S12 °0 0 Me Me TBDPSO S8 6 S2 16 CO₂H S11 18 CO₂Et 7 S6 19 S14 S7 8 Ph Me 9 S7 S8 20 Me Ð ·NH₂Me⊖ S13 I 10 S15 CF₃CO₂

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Procedures and Characterization Data

General Procedure for the Synthesis of Ammonium Salts: To a stirred mixture of secondary amine (100 mmol) in Et_2O (100 mL) at 0 °C is added dropwise the acidic counter-anion (100 mmol). The reaction mixture is stirred at 0 °C for 5 min. The new-formed crystals are filtered and washed with Et_2O (20 mL), dried under vacuum to afford the pure white crystalline salt.

General Procedure for the α -Methylenation: To a mixture of a carbonyl compound (1.0 mmol) and paraformaldehyde (2.0 mmol, 200 mol%) in dry THF (1.0 mL) is added the catalyst (1.0 mmol, 100 mol%) and trifluoroacetic acid (0.1 mmol, 10 mol%). The reaction mixture is stirred, open to the atmosphere, at reflux for 2 h. The mixture will become clear, then the reaction mixture is cooled down to room temperature and a second addition of paraformaldehyde (2.0 mmol, 200 mol%) is performed. Next, the reaction mixture is stirred at reflux for an additional 6 h open to the atmosphere. The reaction mixture is cooled down and the solvent is removed under reduced pressure, dissolved in Et₂O and washed with 1N HCl, 1N NaOH, and brine. The solution mixture is dried (Na₂SO₄) and concentrated under vacuum. The crude product is purified by silica gel column chromatography using 5% (Et₂O-Hexanes or EtOAc-Hexanes) as the eluent.



N-methylbenzenaminium 2,2,2-trifluoroacetate (I)^{S13}: To a stirred mixture of *N*-methyl aniline (100 mmol, 10.7 g) in Et₂O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et₂O (20 mL), dried under vacuum to afford

pure compound I (21.04 g, 96%) as white solid; IR (thin film) v 3418, 3002, 2717, 2496, 1676, 1601, 1204 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 10.02 (bs, 2NH), 7.46–7.38 (m, 5H), 2.98 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 162.6 (q, J = 35 Hz), 137.9, 130.2, 128.9, 121.8, 116.3 (q, J = 288 Hz), 37.6. HRMS (ESI+) calcd for C₇H₁₀N requires m/z 108.0808, found 108.0822. HRMS (ESI–) calcd for C₂F₃O₂ requires m/z 112.9856, found 112.9684.

 $\begin{array}{c} \textcircled{\begin{tabular}{ll} \hline \label{eq:hyperbolic} \hline \end{tabular} } & N-\text{methylbenzenaminium acetate (II): To a stirred neat freshly distilled$ *N* $-methyl aniline (100 mmol, 10.7 g) at 0 °C was added freshly distilled acetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min to afford pure compound II (21.8 g, 99%) as colorless oil; IR (thin film) n 3413, 3051, 2907, 2814, 1713, 1606, 1510 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) <math>\delta$ 7.23 (t, *J* = 8.2 Hz, 2H), 6.99 (bs, 2NH), 6.76 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 2H), 2.85 (s, 3H), 2.11 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 177.7, 149.0, 129.1, 117.5, 112.7, 30.7, 20.8. HRMS (ESI+) calcd for C₇H₁₀N requires *m/z* 108.0808, found 108.0804. HRMS (ESI-) calcd for C₂H₃O₂ requires *m/z* 59.0139, found 59.0138. \\ \end{array}



N-methylbenzenaminium chloride (III): To a stirred mixture of *N*-methyl aniline (100 mmol, 10.7 g) in Et_2O (100 mL) at 0 °C was bubbled excess hydrochloric acid gas (from ammonium chloride and sulfuric acid) for 10 min. The reaction mixture was stirred at 0 °C for an

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additional 5 min. The new-formed crystals were filtered and washed with Et₂O (20 mL), dried under vacuum to afford pure compound III (8.54 g, 64%) as colorless crystals; IR (thin film) v 3417, 2689, 2458, 1600, 1497 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 11.23 (bs, 2NH), 7.50 (d, J = 5.5 Hz 2H), 7.26 (m, 3H), 2.87 (s, 3H). ¹³C NMR $(CDCl_3, 75 \text{ MHz}) \delta 136.8, 129.8, 129.2, 122.3, 37.7.$ HRMS (ESI+) calcd for $C_7H_{10}N$ -Cl requires m/z 108.0808, found 108.0826.



1,2,3,4-tetrahydroquinolinium 2,2,2-trifluoroacetate (IV): To a stirred mixture of 1,2,3,4tetrahydroquinoline (100 mmol, 13.3 g) in Et₂O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for and additional 5 min. The new-formed crystals were filtered and washed with Et₂O (20 mL), dried under vacuum to afford

pure compound IV (22.3 g, 91%) as white solid; IR (thin film) v 3424, 2945, 2750, 1503, 1663, 1190 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 11.05 (bs, 2NH), 7.36-7.19 (m, 4H,), 3.48 (t, J = 5.5 Hz, 2H), 2.91 (t, J = 6.7 Hz, 2H), 2.18 (q, J = 5.5 Hz, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 162.6 (q, J = 37 Hz), 131.3, 130.4, 130.3, 128.2, 127.4, 122.8, 116.4 (q, J = 288 Hz), 42.3, 25.0, 19.6. HRMS (ESI+) calcd for C₉H₁₂N requires m/z 134.0964, found 134.1021. HRMS (ESI-) calcd for $C_2F_3O_2$ requires m/z 112.9856, found 112.9818.



Piperidinium 2,2,2-trifluoroacetate (V): To a stirred mixture of piperidine (100 mmol, 8.5 g) in Et₂O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et₂O (20 mL), dried under vacuum to afford pure compound V (16.15 g, 82%) as white solid; IR

(thin film) v 3430, 2966, 2867, 2550, 1697, 1203 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 9.03 (bs, 2NH), 3.03 (m, 4H), 1.76 (m, 4H), 1.60 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 162.2 (q, J = 35 Hz), 116.5 (q, J = 293 Hz), 44.4, 22.4, 22.2. HRMS (ESI+) calcd for $C_5H_{12}N$ requires m/z 86.0964, found 86.1046. HRMS (ESI-) calcd for C₂F₃O₂ requires *m/z* 112.9856, found 112.9865.

 $\oplus NH_2$ CF₃CO₂

Morpholin-4-ium 2,2,2-trifluoroacetate (VI): To a stirred mixture of morpholine (100 mmol, 8.7 g) in Et₂O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et₂O (20 mL), dried under vacuum to afford pure compound VI (16.71 g, 84%) as white solid; IR (thin film) v 3426, 3004, 2872, 2513, 1681, 1204 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 8.39 (bs, 2NH), 3.89 (m, 4H), 3.16 (m, 4H). ¹³C NMR (CDCl₃, 75 MHz) δ 162.3 (q, J = 35 Hz), 116.5 (q, J = 290 Hz), 63.6, 43.2. HRMS (ESI+) calcd for C₄H₁₀NO requires m/z 88.0757, found 88.0812. HRMS (ESI-) calcd for C₂F₃O₂ requires m/z 112.9856, found 112.9866.

Pyrrolidinium 2,2,2-trifluoroacetate (VII): To a stirred mixture of pyrrolidine (100 mmol, 7.1 g) in Et₂O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed

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with Et₂O (20 mL), dried under vacuum to afford pure compound VII (17.01 g, 93%) as white solid; IR (thin film) v 3413, 2994, 2785, 2491, 1676, 1202 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 9.57 (bs, 2 NH), 3.20 (t, J = 6.15 Hz, 4 H), 1.97 (m, 4 H). ¹³C NMR (CDCl₃, 75 MHz) δ 162.1 (q, J = 34.4 Hz), 116.5 (q, J = 292 Hz), 44.9, 24.1. HRMS (ESI+) calcd for $C_4H_{10}N$ requires m/z 72.0808, found 72.0859. HRMS (ESI-) calcd for $C_2F_3O_2$ requires m/z 112.9856, found 112.9799.



Diisopropylammonium 2,2,2-trifluoroacetate (VIII): To a stirred mixture of diisopropylamine (100 mmol, 10.1 g) in Et₂O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The newformed crystals were filtered and washed with Et₂O (20 mL), dried under vacuum to afford pure compound VIII (20.23 g, 95%) as white solid; IR (thin film) v 3436, 3048, 2794, 2503, 1675, 1601, 1190 cm⁻¹;

¹H NMR (CDCl₃, 300 MHz) δ 8.91 (bs, 2NH), 3.35 (h, J = 6.5 Hz, 2H), 1.31 (d, J = 6.6 Hz, 12H). 13C NMR (CDCl3, 75 MHz) δ 161.6 (q, J = 35.5 Hz), 116.5 (q, J = 288 Hz), 46.8, 18.7. HRMS (ESI+) calcd for C₆H₁₆N requires m/z 102.1283, found 102.1286. HRMS (ESI-) calcd for C₂F₃O₂ requires m/z 112.9850, found 112.9853.

Me

Me

5-(triethylsilyl)pent-1-en-4-yn-3-one (17): To a mixture of a 4-(triethylsilyl)but-3-yn-2one (58 mg, 0.313 mmol) and paraformaldehyde (17 mg, 0.626 mmol) in dry THF (3 mL) was added salt VIII (68 mg, 0.313 mmol) and *i*-PrNH₂ (89 µL, 0.626 mmol) at room temperature. The reaction mixture was stirred at reflux until completion (2 h). Then, the reaction mixture was cooled down to room temperature and the solvent was removed under reduce pressure. The crude mixture was purified by silica gel column chromatography using 10% (EtOAc-Hexanes) as the eluent, to afford pure compound 17 (38 mg, 62% yield) as colorless oil; IR (thin film) v 2958, 2877, 1655, 1612, 1275, 1243, 991, 819, 729 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.62 (dd, J = 1.25, 17.4 Hz, 1H), 6.41 (dd, J = 1.03, 17.4 Hz, 1H), 6.22 (dd, J = 1.24, 10.3 Hz, 1H), 1.05 (t, J = 8.33 Hz, 9H), 0.72 (q, J = 8.03 Hz, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ 178.6, 137.9, 133.9, 100.9, 97.5, 7.3, 3.5. HRMS (ESI+) calcd for C₁₁H₁₉OSi requires m/z 195.1205, found 195.1272.

> (S)-3,7-Dimethyl-2-methylene-6-octanal (20). The reaction was carried out following the General Procedure using (S)-citronellal to yield 153 mg (92%) of **20** as a colorless oil. Lit. $[\alpha]_{D}^{20} = +5.2$ (c = 13.4 in CHCl₃).^{S8} Obtained $[\alpha]_{D}^{20} = +5.35$ (c = 1.00 in CHCl₃).; ¹H NMR

 $(CDCl_3, 300 \text{ MHz}): \delta 9.53 \text{ (s, 1H)}; 6.22 \text{ (s, 1H)}; 5.98 \text{ (s, 1H)}; 5.07 \text{ (tt, 1H, } J = 1.2, 7.2 \text{ Hz}); 2.71 \text{ (sext., 1H, } J = 6.8 \text{ Hz});$ 1.93 (m, 2H); 1.66 (s, 3H); 1.56 (s, 3H); 1.51 (m, 1H); 1.37 (m, 1H) 1.06 (d, 3H, J = 6.8 Hz) ¹³C NMR (CDCl₃, 75 MHz): δ 194.6, 155.5, 132.9, 131.6, 124.1, 35.5, 30.9, 25.7, 25.6, 19.5, 17.6.



¹³C NMR (CDCl₃, 75 MHz)







Supporting Information



¹³C NMR (CDCl₃, 75 MHz)









¹³C NMR (CDCl₃, 75 MHz)





¹³C NMR (CDCl₃, 75 MHz)







¹³C NMR (CDCl₃, 75 MHz)









¹³C NMR (CDCl₃, 75 MHz)

































¹³C NMR (CDCl₃, 75 MHz)





¹³C NMR (CDCl₃, 75 MHz)



¹H NMR (CDCl₃, 300 MHz)

















































¹³C NMR (CDCl₃, 75 MHz)

