Supporting Information

Copper-Mediated C-H Trifluoromethylation of Quinones

Nadia O. Ilchenko, Pär G. Janson and Kálmán J. Szabó*

Stockholm University, Arrhenius Laboratory, Department of Organic Chemistry
SE-106 91 Stockholm, Sweden. E-mail: kalman@organ.su.se. Fax: +46-8-15 49 08

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General Information

All manipulations were performed under air without using inert conditions and without degassing the solvents. Trifluoromethylating agent 1a was prepared by a literature procedure from 2-iodobenzoic acid\(^1\) and quinone 2j was synthesized according to a literature procedure from 1,2,3-trimethoxybenzene.\(^2\) All other chemicals were obtained from commercial sources and used as received. \(^1\)H NMR, \(^13\)C NMR and \(^19\)F NMR spectra were recorded in CDCl\(_3\) (internal standard: 7.26 ppm, \(^1\)H; 77.16 ppm, \(^13\)C) or acetone-\(d_6\) (internal standard: 2.05 ppm, \(^1\)H; 29.84 ppm, \(^13\)C), using 400 MHz spectrometers. High resolution mass data (HRMS) were obtained using ESI technique except for quinones 3i-k for which APCI technique was used. For column chromatography, silica gel (35-70 microns) was used.

Warning! The new quinone-CF\(_3\) compounds should be handled with care because of their unknown biological effects. Menadione (2b) itself has been banned from the US market of food supplements by the FDA (US Food and Drug Administration) because of its potential toxicity in human use. Large doses of 2b may cause neonatal brain or liver damages in some rare cases.

Experimental Procedures and Spectral Data

General procedure for trifluoromethylation of quinones: To a 3 ml screwtop vial was added copper cyanide 4 (9.0 mg, 0.1 mmol, 1 equiv.), bis(pinacolato)diboron 5 (1.3 mg, 0.005 mmol, 5 mol%), reagent 1a (47.4 mg, 0.15 mmol, 1.5 equiv.) and the corresponding quinone 2 (0.1 mmol, 1 equiv.) in CDCl\(_3\) (0.5 mL). The vial was equipped with a stirring bar, screwed shut and stirred at room temperature for 18 h. The products were isolated by column chromatography using pentane: dichloromethane systems as eluents.

2-(Trifluoromethyl)benzoquinone (3a)

This compound was prepared according to the general procedure. The product was isolated as fine yellow crystals using pentane:dichloromethane, 1:3 as eluent system (16 mg, 89 %). The reaction was also performed at larger scale (ten times scale) than described in the general procedure. In this case the reaction was performed according to the general procedure except 4 (90 mg, 1 mmol, 1 equiv.), 5 (13 mg,
0.05 mmol, 5 mol%) 1a (474 mg, 1.5 mmol, 1.5 equiv.) and 2a (109 mg, 1 mmol, 1 equiv.) in CDCl$_3$ (5 mL) were used in a 6 mL screwtop vial. The product was isolated as yellow crystals (128 mg, 72%). N.B. This compound can easily sublimate, and therefore the drying in high vacuum should be avoided. $^1$H-NMR (400 MHz, CDCl$_3$) δ 7.11 (br s, 1H), 6.89 (m, 2H); $^{19}$F-NMR (376 MHz, CDCl$_3$) δ -65.89 (s); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 185.6, 181.4, 137.1 (q, J$_{CF}$ = 1.5 Hz), 136.5, 135.1 (q, J$_{CF}$ = 31.5 Hz), 134.6 (q, J$_{CF}$ = 4.9 Hz), 120.6 (q, J$_{CF}$ = 274.5 Hz); HRMS (ESI): m/z calcd. for [C$_7$H$_3$F$_3$O$_2$+Na]$^+$ 198.9977, found: 198.9982.

2-(Trifluoromethyl)-1,4-naphthoquinone (3b)

This compound was prepared according to the general procedure. The product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (17 mg, 76%). The NMR data obtained for 3b is in agreement with literature values.$^3$

$^1$H-NMR (400 MHz, CDCl$_3$) δ 8.18 (m, 1H), 8.12 (m, 1H), 7.84 (m, 2H), 7.31(q, J$_{HF}$ = 0.9 Hz, 1H); $^{19}$F-NMR (376 MHz, CDCl$_3$) δ -65.51 (d, J$_{HF}$ = 0.9 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 183.5, 179.6, 136.9, (q, J$_{CF}$ = 4.9 Hz), 136.6 (q, J$_{CF}$ = 30.7 Hz), 134.9, 134.7, 131.6 (q, J$_{CF}$ = 1.4 Hz), 131.5, 127.1, 126.6, 120.9 (q, J$_{CF}$ = 275.3 Hz); HRMS (ESI): m/z calcd. for [C$_{11}$H$_5$F$_3$O$_2$+Na]$^+$ 249.0134, found: 249.0130.

The previously reported synthesis of 3b from 2b was performed in four steps$^3$:

(a) SnCl$_2$ (2.5 eq.), HCl (37%), EtOH, 10 min, RT; then (CH$_3$O)$_2$SO$_2$ (3.0 eq.), KOH (5.0 eq.) in MeOH, acetone, 2.5 h, 60 °C; (b) Br$_2$ (1.0 eq.), CHCl$_3$, 45 min, 0 °C, (c) CF$_3$COONa (3.0 eq.), CuI (2.0 eq.), DMA–toluene, 18 h, 145 °C. CAN (3.0 eq.), CH$_3$CN–H$_2$O, 15 min, r.t.

2-methyl-3-(Trifluoromethyl)-1,4-naphthoquinone (3c)
This compound was prepared according to the general procedure. The product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (17 mg, 71%).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 8.07 (m, 2H), 7.76 (m, 2H), 2.40 (q, J$_{HF}$ = 3.0 Hz, 3H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -57.88 (q, J$_{HF}$ = 3.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 183.8, 180.1, 148.8 (q, J$_{CF}$ = 1.6 Hz), 134.6, 134.1, 133.2 (q, J$_{CF}$ = 28.0 Hz), 131.7 (q, J$_{CF}$ = 1.5 Hz), 126.8, 126.6, 122.7 (q, J$_{CF}$ = 277.4 Hz), 12.9 (q, J$_{CF}$ = 3.6 Hz); HRMS (ESI): m/z calcd. for [C$_{12}$H$_7$F$_3$O$_2$]+Na$^+$ 263.0290, found: 263.0281.

2-Bromo-3-(trifluoromethyl)-1,4-naphthoquinone (3d)

This compound was prepared according to the general procedure. The product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (20 mg, 67%). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 8.15 (m, 2H), 7.83 (m, 2H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -59.34 (s); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 177.9, 176.6, 142.3 (q, J$_{CF}$ = 1.7 Hz), 136.9 (q, J$_{CF}$ = 29.4 Hz), 135.3, 134.6, 131.4 (q, J$_{CF}$ = 1.2 Hz), 129.9, 128.0, 127.4, 121.1 (q, J$_{CF}$ = 278.6 Hz); HRMS (ESI): m/z calcd. for [C$_{11}$H$_4$BrF$_3$O$_2$]+Na$^+$ 326.9239, found: 326.9234.

3,5-Dimethyl-2-(trifluoromethyl)-1,4-benzoquinone (3e)

This compound was prepared according to the general procedure except that 1 mL of CDCl$_3$ was used. The product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (14 mg, 72%). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.63 (q, J$_{HH}$ = 1.5 Hz, 1H), 2.29 (q, J$_{HH}$ = 3.2 Hz, 3H), 2.09 (d, J$_{HH}$ = 1.5 Hz, 3H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -57.74 (q, J$_{HF}$ = 3.2 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 186.6, 181.9, 146.5 (q, J$_{CF}$ = 1.8 Hz), 145.6, 133.8 (q, J$_{CF}$ = 1.5 Hz), 130.9 (q, J$_{CF}$ = 28.5 Hz), 122.1 (q, J$_{CF}$ = 277.5 Hz), 15.9, 12.64 (q, J$_{CF}$ = 3.4 Hz); HRMS (ESI): m/z calcd. for [C$_9$H$_7$F$_3$O$_2$]+Na$^+$ 227.0296, found: 227.0290.

2,6-Dimethyl-3,5-bis(trifluoromethyl)-1,4-benzoquinone (3f)

This compound was prepared according to the general procedure except that the amounts of the reactants were changed; 95 mg (0.3
mmol, 3 equiv.) of 1a, 18 mg (0.2 mmol) of CuCN 4 and 2.5 mg (0.010 mmol, 10 mol%) of B$_2$pin$_2$ 5 was used. The product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (13 mg, 50 %). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.33 (q, $J_{HF}$ = 3.0 Hz, 6H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -57.90 (q, $J_{HF}$ = 3.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 185.4, 177.1, 146.4, 131.7 (q, $J_{CF}$ = 29.7 Hz), 121.6 (q, $J_{CF}$ = 278.2 Hz), 12.9 (q, $J_{CF}$ = 3.3 Hz); HRMS (ESI): m/z calcd. for [C$_{10}$H$_6$F$_6$O$_2$+Na]$^+$ 295.0164, found: 295.0163.

2,5-Dimethyl-3-(trifluoromethyl)-1,4-benzoquinone (3g)

This compound was prepared according to general procedure except 0.2 mmol of quinone 2f, 0.2 mmol of CuCN 4, 0.01 mmol of B$_2$Pin$_2$ 5 and 0.15 mmol 1a was used. The yield is based on the amount of 1a used in this reaction. Product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (24 mg, 77 %). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.73 (q, $J_{HH}$ = 1.6 Hz, 1H), 2.26 (q, $J_{HF}$ = 3.3 Hz, 3H), 2.09 (d, $J_{HH}$ = 1.6 Hz, 3H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -58.29 (q, $J_{HF}$ = 3.3 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 185.7, 183.0, 146.7 (app. pent., $J_{CF}$ = 1.6 Hz), 146.5 (q, $J_{CF}$ = 1.8 Hz), 133.1, 131.6 (q, $J_{CF}$ = 28.5 Hz), 122.4 (q, $J_{CF}$ = 277.6 Hz), 15.9, 12.4 (q, $J_{CF}$ = 3.5 Hz); HRMS (ESI): m/z calcd. for [C$_9$H$_7$F$_3$O$_2$+Na]$^+$ 227.029, found: 227.0288.

2,5-Dimethyl-3,6-bis(trifluoromethyl)-1,4-benzoquinone (3h)

This compound was prepared according to the general procedure except 95 mg (0.3 mmol, 3 equiv.) of 1a, 18 mg (0.2 mmol) of CuCN 4 and 2.5 mg (0.010 mmol, 10 mol%) of B$_2$pin$_2$ 5 was used. The product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (14 mg, 49 %). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.33 (q, $J_{HF}$ = 3.1 Hz, 6H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -58.82 (q, $J_{HF}$ = 2.8 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 181.1, 147.3 (app. pent., $J_{CF}$ = 1.6 Hz), 131.8 (q, $J_{CF}$ = 29.6 Hz), 121.9 (q, $J_{CF}$ = 277.6 Hz), 12.7 (q, $J_{CF}$ = 3.5 Hz); HRMS (ESI): m/z calcd. for [C$_{10}$H$_6$F$_6$O$_2$+Na]$^+$ 295.0164, found: 295.0154.

2-Chloro-3-(trifluoromethyl)-1,4-benzoquinone (3i)
This compound was prepared according to general procedure. The product was isolated as yellow crystals using pentane:dichloromethane, 2:1 as eluent system (17 mg, 63 %). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.03 (d, $J_{HH} = 10.1$ Hz, 1H), 6.91 (d, $J_{HH} = 10.1$ Hz, 1H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -58.87 (s); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 179.7, 177.5, 145.2 (q, $J_{CF} = 1.8$ Hz), 137.5 (q, $J_{CF} = 1.2$ Hz), 135.3, 131.4 (q, $J_{CF} = 30.1$ Hz), 120.6 (q, $J_{CF} = 278.0$ Hz); HRMS (APCI): $m/z$ calcd. for [C$_7$H$_2$Cl$_2$F$_3$O$_2$]$^-$ 217.9701, found: 217.9700.

3,5-Dichloro-2-(trifluoromethyl)-1,4-benzoquinone (3j) This compound was prepared according to general procedure except 0.2 mmol of quinone 2h, 0.2 mmol of CuCN, 0.01 mmol of B$_2$Pin$_2$ 5 and 0.1 mmol 1a was used. Yield was calculated based on reagent 1a. Product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (15 mg, 58 %). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.11 (s, 1H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -58.84 (s); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 179.7, 177.5, 144.9 (q, $J_{CF} = 1.7$ Hz), 142.9, 134.3 (q, $J_{CF} = 1.3$ Hz), 131.4 (q, $J_{CF} = 30.5$ Hz), 120.4 (q, $J_{CF} = 278.1$ Hz); HRMS (APCI): $m/z$ calcd. for [C$_7$HCl$_2$F$_3$O$_2$]$^-$ 243.9311, found: 243.9320.

2,6-Dichloro-3,5-bis(trifluoromethyl)-1,4-benzoquinone (3k) This compound was prepared according to the general procedure except 95 mg (0.3 mmol, 3 equiv.) of 1a, 18 mg (0.2 mmol) CuCN 4 and 2.5 mg (0.010 mmol, 10 mol%) of B$_2$pin$_2$ 5 was added. The product was isolated as off-white crystals using pentane:dichloromethane, 1:1 as eluent system (25 mg, 77 %). $^{19}$F-NMR (376 MHz, acetone-$d_6$) $\delta$ -60.00 (s); $^{13}$C-NMR (100 MHz, acetone-$d_6$) $\delta$ 175.16, 172.39, 145.2 (q, $J_{CF} = 1.9$ Hz), 132.2 (qq, $J_{CF} = 30.3, 1.6$ Hz), 121.6 (q $J_{CF} = 276.8$ Hz); HRMS (APCI): $m/z$ calcd. for [C$_6$Cl$_2$F$_3$O$_2$]$^-$ 311.9185, found: 311.9199.

2,5-Dichloro-3-(trifluoromethyl)-1,4-benzoquinone (3l)
This compound was prepared according to the general procedure. The product was isolated as yellow crystals using pentane:dichloromethane, 1:1 as eluent system (22 mg, 91%). ¹H-NMR (400 MHz, acetone-"d₆") δ 7.55 (s, 1H); ¹⁹F-NMR (376 MHz, CDCl₃) δ -59.25 (s); ¹³C-NMR (100 MHz, CDCl₃) δ 175.3, 172.9, 145.8 (q, J_CF = 1.5 Hz), 145.2 (q, J_CF = 1.7 Hz), 132.5, 131.5 (q, J_CF = 30.7 Hz), 120.5 (q, J_CF = 278.3 Hz); HRMS (APCI): m/z calcd. for [C₇HCl₂F₃O₂]⁻ 243.9311, found: 243.9311.

3,5-Dimethoxy-2-(trifluoromethyl)-1,4-benzoquinone (3m)

This compound was prepared according to the general procedure. The product was isolated as yellow crystals using pentane:dichloromethane, 1:4 as eluent system (12 mg, 51%). ¹H-NMR (400 MHz, CDCl₃) δ 5.90 (s, 1H), 4.18 (s, 3H), 3.82 (s, 3H). ¹⁹F-NMR (376 MHz, CDCl₃) δ -57.8 (s). ¹³C-NMR (100 MHz, CDCl₃) δ 181.8, 177.7, 156.9 (q, J_CF = 1.4 Hz), 156.8, 121.4 (q, J_CF = 274.0 Hz), 116.9 (q, J_CF = 28.5 Hz), 62.7, 56.7. ¹⁹F-NMR (376 MHz, CDCl₃) δ -65.13 (q, J_HF = 1.2 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 182.2, 178.5, 145.6, 145.4 (q, J_CF = 1.7 Hz), 133.6 (q, J_CF = 4.8 Hz), 133.2 (q, J_CF = 31.6 Hz), 120.5 (q, J_CF = 274.7 Hz), 61.8, 61.5; HRMS (ESI): m/z calcd. for [C₉H₇F₃O₄+Na]⁺ 259.0189, found: 259.0195.

2,3-Dimethoxy-5-(trifluoromethyl)-1,4-benzoquinone (3n)

This compound was prepared according to the general procedure except that 0.02 mmol (20 mol%) of B₂Pin₂ 5 and 0.5 mL of chloroform was used. The reaction was conducted in a microwave reactor at 100 °C for 60 min. The product was isolated as a deep red oil using pentane:dichloromethane, 1:9 as eluent system (12 mg, 51%). ¹H-NMR (400 MHz, CDCl₃) δ 6.94 (q, J_HF = 1.1 Hz, 1H), 4.06 (s, 3H), 4.05 (s, 3H); ¹⁹F-NMR (376 MHz, CDCl₃) δ -65.13 (d, J_HF = 1.2 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 182.2, 178.5, 145.6, 145.4 (q, J_CF = 1.7 Hz), 133.6 (q, J_CF = 4.8 Hz), 133.2 (q, J_CF = 31.6 Hz), 120.5 (q, J_CF = 274.7 Hz), 61.8, 61.5; HRMS (ESI): m/z calcd. for [C₉H₇F₃O₄+Na]⁺ 259.0189, found: 259.0188.

2,3-Dimethoxy-5-methyl-6-(trifluoromethyl)-1,4-benzoquinone (3o)

This compound was prepared according to the general procedure. The product was isolated as a deep red oil using
pentane:dichloromethane, 1:4 as eluent system (17 mg, 64 %). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 4.03 (s, 3H), 4.00 (s, 3H), 2.26 (q, J$_{HF}$ = 3.3 Hz, 3H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -57.46 (q, J$_{HF}$ = 3.2 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 182.6, 179.2, 145.3 (q, J$_{CF}$ = 1.8 Hz), 144.7, 144.6 (q, J$_{CF}$ = 1.8 Hz), 129.4 (q, J$_{CF}$ = 28.9 Hz), 122.2 (q, J$_{CF}$ = 277.2 Hz), 61.6, 61.4, 122.2 (q, J$_{CF}$ = 3.5 Hz); HRMS (ESI): $m/z$ calcd. for [C$_{10}$H$_9$F$_3$O$_4$+Na]$^+$ 273.0345, found: 273.0354.

References:

NMR spectra of products 3a-o
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