

A novel strategy of the preparation of arylhydroxylamines: chemoselective reduction of aromatic nitro compound using bakers' yeast

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Supplementary information

Experimental procedures

In a typical reaction, bakers' yeast was suspended in 0.2 M phosphate buffer pH 6.5 (100 ml) containing glucose (2.5 g) and incubated at 30 °C for 0.5 h, then the substrate (100 mg) dissolved in ethanol (~5 ml) was added. The reaction mixture was vigorously stirred at 30 °C and the progress of the reaction was monitored by HPLC. At end of reaction, ethyl acetate (500 mL) was added to the reaction mixture. The separated organic phases was filtered through a celite pad and dried over anhydrous MgSO₄. After filtration and removal of organic solvent under reduced pressure, the crude products were analyzed with respect to the conversion (*via* ¹H NMR and HPLC).

Purification procedures

When the reduction did not show excellent chemoselectivity, it is difficult to separate the hydroxylamines and amines by a chromatography because their polarities are very similar.

1-2c: The crude products were purified by chromatography on a silica gel column using hexane-ethyl acetate (10:1, v/v) as an eluent to give **1c** in 83% yield and **2c** in 70% yield, respectively.

3-6c: The crude products were purified by a flash chromatography on a silica gel column using hexane-ethyl acetate (5 : 1, v/v) as an eluent to give the mixture of **3c** and **3d** in 78% yield, **5c** and **5d** in 72% yield, **6c** and **6d** in 69% yield, respectively. The crude product of reduction of **4a** was purified by a chromatography on a silica gel column using hexane-ethyl acetate (10 : 1, v/v) as an eluent to give the mixture of **4c** and **4d** in 70% yield, and 1-(4-nitrophenyl)ethanol in 7% yield. And the pure hydroxylamines **3-6c** were obtained by using prepared HPLC.

7c: The crude product was purified by a flash chromatography on a silica gel column using

hexane-ethyl acetate (5 : 1, v/v) as an eluent to give **7c** only in 90% yield.

8-10c: Since the corresponding amines **8-10d** are fluorescence compounds, it is easy to distinguish between the hydroxylamines and amines in the column. The crude products were purified by a chromatography on a silica gel column using hexane-ethyl acetate (10 : 1, v/v) as an eluent to give **8c** in 80% yield, **9c** in 71% yield and **10c** in 72% yield, respectively.

Spectroscopic Data

General.

Chemical shifts of ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra are expressed in ppm using residual DMSO- d_6 (2.52) and DMSO- d_6 (39.5), respectively, as the internal standards.

Spectroscopic Data for known compounds

- 1c** ^1H NMR (400 MHz, DMSO- d_6) δ 9.67 (s, -NH), 9.13 (s, -OH), 8.08 (d, $J = 7.59$ Hz, 2H), 6.85 (d, $J = 7.59$ Hz, 2H).
- 2c** ^1H NMR (400 MHz, DMSO- d_6) δ 9.85 (s, -NH), 9.33 (s, -OH), 8.06 (d, $J = 8.79$ Hz, 1H), 7.62 (dd, $J = 8.39, 7.19$ Hz, 1H), 7.49 (d, $J = 8.79$ Hz, 1H), 6.83 (dd, $J = 8.39, 7.19$ Hz, 1H).
- 3c** ^1H NMR (400 MHz, DMSO- d_6) δ 9.09 (s, -NH), 8.75 (s, -OH), 7.67 (d, $J = 8.39$ Hz, 2H), 6.91 (d, $J = 8.39$ Hz, 2H), 3.08 (s, 3H).
- 4c** ^1H NMR (400 MHz, DMSO- d_6) δ 8.93 (s, -NH), 8.83 (s, -OH), 7.76 (bs, 2H), 6.81 (bs, 2H), 2.41 (s, 3H).
- 5c** ^1H NMR (400 MHz, DMSO- d_6) δ 9.12 (s, -NH), 8.78 (s, -OH), 7.55 (d, $J = 8.39$ Hz, 2H), 6.87 (d, $J = 8.39$ Hz, 2H).
- 6c** ^1H NMR (400 MHz, DMSO- d_6) δ 7.75 (dd, $J = 4.6, 1.1$ Hz, 1H), 7.48 (dd, $J = 7.9, 1.1$ Hz, 1H), 7.30 (dd, $J = 4.6, 7.9$ Hz, 1H).

Spectroscopic Data for new compounds

- 7c** ^1H NMR (400 MHz, DMSO- d_6) δ 9.68 (s, -NH), 9.17 (s, -OH), 7.79 (d, $J = 8.79$ Hz, 1H), 7.22 (s, 1H), 7.07 (d, $J = 8.79$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 154.77, 134.77, 117.21, 116.36, 115.46, 115.00, 114.70, 100.87; IR (neat, cm^{-1}) 3444.2, 3286.1, 2225.5, 1596.8; HRMS-EI (70 eV) m/z calcd for $\text{C}_8\text{H}_5\text{N}_3\text{O}$ 159.0433, found 159.0432; mp. 124.6-125.7 $^\circ\text{C}$.
- 8c** ^1H NMR (400 MHz, DMSO- d_6) δ 10.95 (s, -NH), 9.34 (s, -NH), 8.98 (s, -OH), 7.60 (d, $J = 5.60$ Hz, 1H), 7.09 (s, 1H), 7.06 (d, $J = 5.60$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 169.52, 169.32, 157.24, 134.81, 124.24, 121.40, 115.48, 105.12; IR (neat, cm^{-1}) 3371.0, 3322.9, 3195.5, 1760.7, 1718.3; HRMS-EI (70 eV) m/z calcd for $\text{C}_8\text{H}_6\text{N}_2\text{O}_3$ 178.0378, found 178.0376; mp >300 $^\circ\text{C}$.
- 9c** ^1H NMR (400 MHz, DMSO- d_6) δ 11.06 (s, -NH), 9.07 (s, -NH), 8.86 (s, -OH), 7.64 (t, $J =$

7.59 Hz, 1H), 7.40 (d, $J = 7.59$ Hz, 1H), 7.13 (d, $J = 7.59$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 169.93, 169.50, 148.89, 135.69, 133.24, 118.00, 112.65, 111.69; IR (neat, cm^{-1}) 3374.8, 3318.9, 3197.4, 1762.6, 1720.2; HRMS-EI (70 eV) m/z calcd for $\text{C}_8\text{H}_6\text{N}_2\text{O}_3$ 178.0378, found 178.0370; mp >300 °C.

10c ^1H NMR (400 MHz, DMSO- d_6) δ 10.85 (s, -NH), 9.59 (s, -OH), 8.52 (d, $J = 8.5$ Hz, 1H), 8.45 (d, $J = 7.4$ Hz, 1H), 8.35 (d, $J = 8.5$, 1H), 7.73 (dd, $J = 8.5, 7.4$ Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 161.61, 160.21, 152.62, 135.99, 132.50, 131.49, 129.40, 124.98, 118.37, 117.58, 108.32, 104.55; IR (neat, cm^{-1}) 3439.0, 3301.59, 1759.0, 1702.3; HRMS-EI (70 eV) m/z calcd for $\text{C}_{12}\text{H}_7\text{NO}_4$, 229.0378, found 229.0375; mp > 300 °C.

HPLC Data for all compounds

General.

Instrument: Agilent 1100 HPLC-DAD (USA, Agilent)

Column: HIQ SIL C_{18} 4.6 mm \times 250 mm, 5 μm (Japan)

1a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 60% over 26 min, UV detection at 254 nm, flow 0.80 mL min^{-1} , retention time: **1a**, 19.9 min; **1c**, 11.3 min; **1d**, 12.4 min.

2a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 60% over 26 min, UV detection at 254 nm, flow 0.80 mL min^{-1} , retention time: **2a**, 20.0 min; **2c**, 15.9 min; **2d**, 19.0 min.

3a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 51% over 18 min, UV detection at 264 nm, flow 0.80 mL min^{-1} , retention time: **3a**, 11.7 min; **3c**, 5.0 min; **3d**, 5.7 min.

4a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 60% over 26 min, UV detection at 300 nm, flow 0.80 mL min^{-1} , retention time: **4a**, 21.8 min; **4c**, 8.2 min; **4d**, 9.5 min; 1-(4-nitrophenyl)ethanol, 20.2 min.

5a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 60% over 26 min, UV detection at 254 nm, flow 0.80 mL min^{-1} , retention time: **5a**, 15.6 min; **5c**, 8.2 min; **5d**, 9.7 min.

6a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 54.5% over 21 min, UV detection at 294 nm, flow 0.80 mL min^{-1} , retention time: **6a**, 17.5 min; **6c**, 6.8 min; **6d**, 8.1 min.

7a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 60% over 26 min, UV detection at 286 nm, flow 0.80 mL min^{-1} , retention time: **7a**, 12.5 min; **7c**, 10.2 min; **7d**, 11.7 min.

8a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B),

a linear gradient of 30% of B to 51% over 18 min, UV detection at 254 nm, flow 0.80 mL min⁻¹, retention time: **8a**, 14.3 min; **8c**, 6.5 min; **8d**, 7.7 min.

9a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 60% of B over 15 min, UV detection at 254 nm, flow 0.80 mL min⁻¹, retention time: **9a**, 7.4 min; **9c**, 6.4 min; **9d**, 7.2 min.

10a-d Eluent: citric acid (1g/L) in water (solvent A) + citric acid (1g/L) in methanol (solvent B), a linear gradient of 30% of B to 100% of B over 60 min, UV detection at 254 nm, flow 0.80 mL min⁻¹, retention time: **10a**, 28.3 min; **10c**, 18.3 min; **10d**, 20.0 min.