Electrochemical-induced hydroxylation of aryl halides in the presence of Et$_3$N in water

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1. General information

All reagents were purchased from commercial sources and used without further purification. All solvents were dried in a standard manner. Reactions were monitored by TLC on silica gel plates. Column chromatography was performed over silica gel (200-300 mesh) and petroleum ether/ethyl acetate. Shanghai chenhua CHI600E electrochemical workstation was used in the standard configuration as delivered, including proprietary software. All products were characterized by NMR. \(^1\)H NMR spectra were recorded at 500 and 400 MHz and \(^{13}\)C NMR spectra were recorded at 101 and 125 MHz (Bruker DPX) with CDCl\(_3\) and DMSO-\(d_6\) as solvent. Chemical shifts are reported in ppm using TMS as internal standard. NMR by the services provided at the Shandong Liaocheng University. HPLC were recorded on an SHIMDZU LC-20A instrument with a HP5-MS 30 m x 0.25 mm capillary apolar columns.

2. General procedure for the catalytic reactions

\[
\begin{align*}
\text{X} & \xrightarrow{\text{Pt}} \text{OH} \\
\text{Pt} & \xrightarrow{\text{Bu}_4\text{NPF}_6} \text{Et}_3\text{N} \\
\text{H}_2\text{O} & \xrightarrow{3 \text{mL}} I=15 \text{mA}, 6 \text{ h, r.t.} \\
1 & \xrightarrow{\text{under air}} (X=I, Br, Cl) \xrightarrow{2} 2 \\
\end{align*}
\]

A dried 10 mL quartz tube equipped was charged with iodobenzene (or bromobenzene, chlorobenzene) (0.5 mmol), \(\text{Et}_3\text{N} \) (2.0 equiv), \(\text{Bu}_4\text{NPF}_6 \) (2.0 equiv) and water (3 mL) in the presence of the air balloon. The mixture was stirred at room temperature with a voltage range of 6-8 V for 6 h with 15 mA (Pt anode (10.0 mm x 10.0 mm), Pt cathode (10.0 mm x 10.0 mm)). After the reaction was completed, the reaction vessel was opened and the organic layer was collected by ethyl acetate extraction. The solution of the crude product was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1) to afford the target product as a white solid.

3. General procedure for the gram scale experiment

A dried 50 mL quartz tube equipped was charged with iodobenzene (or bromobenzene, chlorobenzene) (10 mmol), \(\text{Et}_3\text{N} \) (2.0 equiv), \(\text{Bu}_4\text{NPF}_6 \) (2.0 equiv) and water (20 mL) in the presence of the air balloon. The mixture was stirred at room temperature with a voltage range of 6-8 V for 24 h with 25 mA (Pt anode (15.0 mm x 15.0 mm), Pt cathode (15.0 mm x 15.0 mm)). After the reaction was completed, the reaction vessel was opened and the organic layer was collected by ethyl acetate extraction. The product was purified by flash column chromatography on silica gel.

4. Synthesis of 1-(3-ethyl-2,4-dihydroxy-6-methoxyphenyl)butan-1-one (D1)

In a round-bottom flask, 1-(3-ethyl-2-hydroxy-4-iodo-6-methoxyphenyl)butan-1-one (0.5 mmol) was dissolved in 3 mL water and \(\text{Et}_3\text{N} \) (2.0 equiv), \(\text{Bu}_4\text{NPF}_6 \) (2.0 equiv) was added to the solution in the presence of the air balloon. The mixture was stirred at room temperature with a voltage range of 6-8 V for 6 h with 15 mA. After the reaction was completed, the reaction vessel was opened and the organic layer was collected by ethyl acetate extraction. The residue was purified by silica gel column chromatography to obtain the corresponding product 1-(3-ethyl-2,4-dihydroxy-6-methoxyphenyl)butan-1-one (D1) with the yield 86%.

5. Cyclic voltammetry experiment

Cyclic voltammograms were measured using Shanghai chenhua CHI600E electrochemical workstation with electrochemical analysis software, using a conventional three-electrode cell. The working electrode was a glassy carbon working electrode, the counter and reference electrodes consisted of a Pt wire and a SCE, respectively. The glassy carbon working electrode was polished with a polishing cloth before each measurement. The concentration of all tested compounds was 1 mmol L\(^{-1}\). The scan rate was 0.1 V/s.

To prove that the anodic oxidation of iodide is preferable than the oxidation of \(\text{Et}_3\text{N} \) in the proposed mechanism, we have used potassium iodide and \(\text{Et}_3\text{N} \) to carry out cyclic voltammetry experiments with water as the solvent. From the following figure, we have observed that the onset potential of potassium...
iodide oxidation (0.65 V) is lower than the onset potential for oxidation of Et₃N (0.89 V), which serves as evidence that iodide is more readily oxidized than Et₃N.

6. Cell cytotoxicity assay

MTT assay was used to test cell cytotoxicity and a drug concentration required to inhibit cell growth by 50% (IC₅₀) was used to measure the sensitivity of cell to compound as described previously. Briefly, cells growing in logarithmic phase were seeded at a density of 3000~7000 cells per well in 96-well plates. After the cells adhered 24 h, a range of different concentrations of D1 and control were added to the wells. After 48 h incubation, MTT (5 mg/mL, 20μL) was added into each well, and 4 h later, the medium was discarded and 150 μL DMSO was added into the wells to dissolve. Finally, optical density was measured at 570 nm by a Model 550 Microplate Reader (Bio-Rad, Hercules, CA, USA). IC₅₀ was calculated from survival curves using the Bliss method. All experiments were repeated at least three times.

7. Characterization data

phenol (2a)

1H NMR (400 MHz, CDCl₃) δ 7.28-7.15 (m, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.83 (dd, J = 8.4, 0.8 Hz, 2H), 5.09 (br, 1H); 13C NMR (100 MHz, CDCl₃) δ 155.22, 129.67, 120.83, 115.34; MS (EI, m/z): 94 [M⁺].

p-cresol (2b)

1H NMR (400 MHz, CDCl₃) δ 7.10-6.95 (m, 2H), 6.79-6.69 (m, 2H), 5.70 (br, 1H), 2.29-2.23(m, 3H); 13C NMR (100 MHz, CDCl₃) δ 152.97, 130.06, 115.17, 115.14, 20.39; MS (EI, m/z): 108 [M⁺].

4-methoxyphenol (2c)

1H NMR (400 MHz, CDCl₃) δ 6.85-6.72 (m, 4H), 5.47 (br, 1H), 3.76 (s, 3H); 13C NMR (100 MHz, CDCl₃) δ 153.58, 149.52, 116.11, 114.96, 55.87; MS (EI, m/z): 124 [M⁺].

hydroquinone (2d)

1H NMR (400 MHz, DMSO-d₆) δ 8.61 (s, 2H), 6.57 (s, 4H); 13C NMR (100 MHz, DMSO-d₆) δ 149.73, 115.67; MS (EI, m/z): 110 [M⁺].

4-fluorophenol (2e)

1H NMR (400 MHz, CDCl₃) δ 6.98-6.84 (m, 2H), 6.82-6.68 (m, 2H), 6.12 (br, 1H); 13C NMR (100 MHz, CDCl₃) δ 158.53, 156.17, 150.98, 116.34, 116.26, 116.14, 115.91; MS (EI, m/z): 112 [M⁺].

4-chlorophenol (2f)

1H NMR (400 MHz, CDCl₃) δ 7.22-7.14 (m, 2H), 6.80-6.72 (m, 2H), 5.09 (s, 1H); 13C NMR (100 MHz, CDCl₃) δ 153.99, 129.52, 125.71, 116.64; MS (EI, m/z): 128 [M⁺].
4-bromophenol (2g)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.48, 132.47, 117.18, 112.96; MS (EI, m/z): 172 [M$^+$].

4-(tert-butyl) phenol (2h)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 153.05, 143.56, 126.43, 114.74, 128.39, 115.79; MS (EI, m/z): 150 [M$^+$].

p-cyanophenol (2i)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.37, 134.31, 119.25, 116.48, 102.75; MS (EI, m/z): 119 [M$^+$].

4-hydroxybenzaldehyde (2j)
$^{13}$C NMR (125 MHz, DMSO-d$_6$) $\delta$ 190.86, 163.26, 132.04, 128.39, 115.79; MS (EI, m/z): 122 [M$^+$].

4-nitrophenol (2k)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.60, 142.85, 126.30, 115.73; MS (EI, m/z): 139 [M$^+$].

1-(4-hydroxyphenyl) ethan-1-one (2l)
$^{13}$C NMR (125 MHz, DMSO-d$_6$) $\delta$ 195.89, 161.91, 130.59, 128.53, 115.06, 26.11; MS (EI, m/z): 136 [M$^+$].

4-hydroxybenzoic acid (2m)
$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 167.18, 161.60, 131.54, 121.36, 115.12; MS (EI, m/z): 138 [M$^+$].

o-cresol (2n)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 153.68, 131.01, 127.09, 123.74, 120.74, 114.88, 15.66; MS (EI, m/z): 108 [M$^+$].

2-aminophenol (2o)
$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 143.94, 136.45, 119.47, 116.43, 114.34; MS (EI, m/z): 109 [M$^+$].

2-methoxyphenol (2p)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.54, 145.61, 121.39, 120.08, 114.50, 110.70, 55.79; MS (EI, m/z): 124 [M$^+$].

2-hydroxybenzoic acid (2q)
$^{13}$C NMR (125 MHz, DMSO-d$_6$) $\delta$ 171.83, 161.06, 135.54, 130.17, 119.07, 116.99, 112.82; MS (EI, m/z): 138 [M$^+$].

pyrocatechol (2r)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.50, 121.29, 115.53; MS (EI, m/z): 110 [M$^+$].

2-nitrophenol (2s)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.11, 137.51, 125.04,
122.99, 120.19, 119.95; MS (EI, m/z): 139 [M+].

5-methylbenzene-1,3-diol (2i) 6

1H NMR (400 MHz, DMSO-d6) δ 9.03 (s, 2H), 6.05-5.97 (m, 3H), 2.10 (s, 3H); 13C NMR (100 MHz, DMSO-d6) δ 158.22, 139.19, 107.09, 99.75, 21.22; MS (EI, m/z): 124 [M+].

3-methoxyphenol (2u) 7

1H NMR (400 MHz, CDCl3) δ 7.10 (t, J = 7.6 Hz, 1H), 6.53-6.46 (m, 1H), 6.45-6.37 (m, 2H), 5.99 (br, 1H), 3.74 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 160.70, 156.61, 130.19, 107.99, 106.47, 101.59, 55.26; MS (EI, m/z): 124 [M+].

3,4-dimethylphenol (2v) 7

1H NMR (500 MHz, CDCl3) δ 6.95 (d, J = 8 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 5.32 (s, 1H), 2.18 (s, 3H), 2.16 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 153.27, 137.93, 130.45, 128.65, 116.62, 112.39, 19.75, 18.68; MS (EI, m/z): 122 [M+].

m-cresol (2w) 6

1H NMR (400 MHz, CDCl3) δ 7.10 (t, J = 7.6 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.68-6.59 (m, 2H), 5.54 (s, 1H), 2.30 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 155.18, 139.82, 129.40, 121.66, 116.05, 112.30, 21.25; MS (EI, m/z): 108 [M+].

4,6-dimethylpyrimidin-2-ol (2x) 8

1H NMR (400 MHz, D2O) δ 6.77 – 6.70 (m, 1H), 2.74 – 2.37 (m, 6H); 13C NMR (100 MHz, D2O) δ 170.34, 148.45, 106.43, 19.32; MS (EI, m/z): 124 [M+].

pyridin-3-ol (2y) 3

1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 8.27 – 7.85 (m, 2H), 7.36 – 6.94 (m, 2H); 13C NMR (101 MHz, DMSO-d6) δ 154.14, 140.72, 138.48, 124.56, 122.47; MS (EI, m/z): 95 [M+].

quinolin-8-ol (2z) 9

1H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1H), 8.85 (dd, J = 4.2, 1.7 Hz, 1H), 8.31 (dd, J = 8.3, 1.7 Hz, 1H), 7.60 – 7.35 (m, 3H), 7.10 (dd, J = 7.4, 1.5 Hz, 1H); 13C NMR (101 MHz, DMSO-d6) δ 153.78, 148.60, 138.97, 136.51, 129.27, 127.96, 118.19, 111.74; MS (EI, m/z): 145 [M+].

pyridin-2-ol (3a) 1

1H NMR (400 MHz, CDCl3) δ 13.50 (s, 1H), 7.45 (dd, J = 2.8, 0.8 Hz, 1H), 7.34 (dd, J = 4.4, 1.6 Hz, 1H), 6.61 – 6.42 (d, J = 8.7 Hz, 1H), 5.78 – 5.57 (d, J = 8.6 Hz, 1H); 13C NMR (100 MHz, DMSO-d6) δ 165.40, 136.32, 134.08, 120.16, 118.08; MS (EI, m/z): 95 [M+].

hydroquinone (3b) 1

1H NMR (400 MHz, CDCl3) δ 8.59 (s, 2H), 6.57 (s, 4H); 13C NMR (101 MHz, DMSO-d6) δ 150.21, 116.14; MS (EI, m/z): 110 [M+].

1-(3-ethyl-2,4-dihydroxy-6-methoxyphenyl)butan-1-one (D1) 10

1H NMR (400 MHz, MeOD) δ 6.00 (s, 1H), 3.86 (s, 3H), 2.96 (t, J = 7.4 Hz, 2H), 2.57 (q, J = 7.4 Hz, 2H), 1.69 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H); 13C NMR (100 MHz, MeOD) δ 205.6, 164.3, 162.1, 161.7, 110.0, 104.4, 89.8, 54.4, 45.8, 18.2, 14.9, 13.0, 12.4; MS (EI, m/z): 238 [M+].

8. References


9. $^1$H NMR and $^{13}$C NMR spectra for the products

2a
2b
2d
2f
2g
2h
2j