

Sulfonic acid resin & copper salts: A novel heterogeneous catalytic system for direct hydroxylation of haloarenes

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Experimental Section

General Remarks

All chemicals were purchased from Sigma Aldrich and were used as received. All solvents used were analytical grade and were used as received from Merck India Pvt. Ltd. The INDION-770 resin was purchased from Ion Exchange India Ltd. The Thin Layer Chromatography (TLC) was carried out on Merck silica gel 60 F₂₅₄ plates using ethyl acetate and hexanes as eluting agents. Purification of products was carried out by flash chromatography using silica gel (100-200 mesh) and a mixture of ethyl acetate and hexane as eluting agent. All products were characterized by ¹H-NMR and Mass Spectrometry. The ¹H spectra of samples were acquired on a Bruker Avance 300 MHz or a Varian Unity Inova 500 MHz Spectrometer using TMS as an internal standard in CDCl₃ or DMSO-d₆ as solvent. Mass spectra (ESI-MS) of samples were acquired with a Micromass Quattro premier tandem quadrupole mass spectrometer.

General procedure for Cuprous Iodide and INDION 770 resin catalyzed direct hydroxylation of haloarenes. A pressure tube (15 mL volume) charged with cuprous iodide (19 mg; 0.1 mmol), INDION-770 resin (60 mg; ~ 0.25 mmol of active sulfonic acid groups) and DMSO (0.6 mL) is stirred using a magnetic stirrer at 125 °C for 10 minutes. To this was added CsOH.H₂O (504 mg, 3 mmol), H₂O (0.3 mL) and haloarenes (1 mmol), respectively. Then, the reaction was performed by stirring at the indicated temperature and reaction time as described in Table 1 and 2 in the main manuscript. The progress of the reaction was monitored by TLC studies using ethyl acetate and hexane as eluting agent. After the completion of reaction, the reaction mixture was cooled to room temperature, and filtered through a sintered funnel. The filtrate was made slightly acidic by careful addition of 2N HCl (for entries 13 & 17-20, a neutral pH was maintained) and is extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and filtered. Then, the solvent was evaporated under reduced pressure to give the crude product which was purified by flash column chromatography to afford the desired products in good yields.

Procedure for preparation of Copper-exchanged INDION-770 catalyst: Cuprous iodide (0.1 mmol, 19 mg) and INDION-770 resin (60 mg) were stirred in DMSO (1 mL) at 125 °C for 30 minutes to form copper exchanged INDION-770. It is filtered through a sintered funnel, washed with DMSO and methanol respectively, and oven dried to yield around 65 mg of Copper exchanged INDION-770 catalyst. Use of such preformed copper-exchanged INDION-770 resin catalyst also works well for synthesis of 4-methoxyphenol from 4-iodoanisole as illustrated in Table 1; entry 24. Such, freshly prepared Copper-exchanged INDION-770 resin catalyst can be easily recovered from the reaction mixture by simple filtration, washing with DMSO and methanol, respectively, and oven dried so as to be recycled for multiple reaction experiments (up to five-cycles) under optimized reaction conditions described in Table 2 (entry 1; with foot note c) without significant drop in both yield and catalytic activity.

Procedure for recycling studies for direct hydroxylation reaction of 4-iodoanisole catalyzed by Copper exchanged INDION-770 catalyst. Spent and recovered copper exchanged INDION-770 catalyst (63 mg, ~ 0.1 mmol of copper), CsOH.H₂O (3 mmol) and 4-iodoanisole (1 mmol) were stirred in 2:1 DMSO/H₂O mixture (0.9 mL) at 125 °C for 8 h. The progress of the reaction was monitored by TLC studies using ethyl acetate and hexane as eluting agent. After the completion of reaction, the reaction mixture was cooled to room temperature, and filtered through a sintered funnel. The filtrate was made slightly acidic by careful addition of 2N HCl, and is extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and filtered. Then, the solvent was evaporated under reduced pressure to give the crude product which was purified by flash column chromatography to afford the desired products in good yields. The filtered resin is washed with methanol, dried and reused for up to five-cycles (see Table 2; entry 1 and foot note c in the main manuscript for more details).

Analytical Data

4-methoxyphenol (Table 2, entry 1); $^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 6.73\text{-}6.66$ (m, 4H), 5.59 (brs, 1H), 3.72 (s, 3H); MS (ESI): $m/z = 125$ $[\text{M}+\text{H}]^+$

***p*-cresol** (Table 2, entry 2); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 6.97$ (d, 2H, $J = 8.3$ Hz), 6.66 (d, 2H, $J = 8.3$ Hz), 4.90 (s, 1H), 2.26 (s, 3H); MS (ESI): $m/z = 109$ $[\text{M}+\text{H}]^+$

4-*tert*-butylphenol (Table 2, entry 3); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.19$ (d, 2H, $J = 8.7$ Hz), 6.70 (d, 2H, $J = 8.7$ Hz), 5.44 (brs, 1H), 1.28 (s, 9H); MS (ESI): $m/z = 151$ $[\text{M}+\text{H}]^+$

Phenol (Table 2, entry 4); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.18$ (t, 2H, $J = 7.8$ Hz), 6.87 (t, 1H, $J = 7.4$ Hz), 6.78 (d, 2H, $J = 7.6$ Hz), 5.95 (brs, 1H); MS (ESI): $m/z = 95$ $[\text{M}+\text{H}]^+$

4-nitrophenol (Table 2, entry 5); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 8.18$ (d, 2H, $J = 9.1$ Hz), 6.94 (d, 2H, $J = 9.1$ Hz), 6.59 (brs, 1H); MS (ESI): $m/z = 140$ $[\text{M}+\text{H}]^+$

4-(trifluoromethyl)phenol (Table 2, entry 6); $^1\text{H NMR}$ (300 MHz, DMSO-d_6): $\delta = 9.66$ (brs, 1H), 7.81 (d, 2H, $J = 8.7$ Hz), 6.77 (d, 2H, $J = 8.7$ Hz); MS (ESI): $m/z = 163$ $[\text{M}+\text{H}]^+$

1-(4-hydroxyphenyl)ethanone (Table 2, entry 7); $^1\text{H NMR}$ (300 MHz, DMSO-d_6): $\delta = 9.74$ (brs, 1H), 7.77 (d, 2H, $J = 8.7$ Hz), 6.80 (d, 2H, $J = 8.7$ Hz), 2.48 (s, 3H); MS (ESI): $m/z = 137$ $[\text{M}+\text{H}]^+$

3-methoxyphenol (Table 2, entry 8); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.02$ (s, 1H), 6.36-6.45 (m, 3H), 5.07 (brs, 1H), 3.74 (s, 3H); MS (ESI): $m/z = 125$ $[\text{M}+\text{H}]^+$

4-chlorophenol (Table 2, entry 9); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.13$ (d, 2H, $J = 8.9$ Hz), 6.71 (d, 2H, $J = 8.9$ Hz), 6.33 (brs, 1H); MS (ESI): $m/z = 129$ $[\text{M}+\text{H}]^+$

Naphthalen-2-ol (Table 2, entry 10); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.71$ (d, 2H, $J = 8.3$ Hz), 7.62 (d, 1H, $J = 8.3$ Hz), 7.37 (t, 1H, $J = 8.3$ Hz), 7.28 (d, 1H, $J = 8.3$ Hz), 7.11-7.02 (m, 2H), 4.83 (s, 1H); MS (ESI): $m/z = 145$ $[\text{M}+\text{H}]^+$

2-methoxyphenol (Table 2, entry 11); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 6.89\text{-}6.76$ (m, 4H), 5.56 (brs, 1H), 3.83 (s, 3H); MS (ESI): $m/z = 125$ $[\text{M}+\text{H}]^+$

Pyrocatechol (Table 2, entry 12); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 6.84\text{-}6.70$ (m, 4H), 5.16 (brs, 1H); MS (ESI): $m/z = 111$ $[\text{M}+\text{H}]^+$

2-aminophenol (Table 2, entry 13); $^1\text{H NMR}$ (500 MHz, DMSO-d_6): $\delta = 11.30$ (brs, 1H), 7.19-7.11 (m, 1H), 7.02-6.88 (m, 2H), 6.75 (t, 1H, $J = 7.4$ Hz), 4.59 (brs, 2H); MS (ESI): $m/z = 110$ $[\text{M}+\text{H}]^+$

2-nitrophenol (Table 2, entry 14); ^1H NMR (500 MHz, DMSO- d_6): δ = 10.63 (brs, 1H), 7.93 (d, 1H, J = 9.1 Hz), 7.54 (t, 1H, J = 8.4 Hz), 7.11 (d, 1H, J = 9.1 Hz), 6.98 (t, 1H, J = 8.4 Hz); MS (ESI): m/z = 140 $[\text{M}+\text{H}]^+$

Naphthalen-1-ol (Table 2, entry 15); ^1H NMR (300 MHz, CDCl_3): δ = 8.12 (t, 1H, J = 4.8 Hz), 7.75 (t, 1H, J = 4.8 Hz), 7.51-7.34 (m, 3H), 7.23 (t, 1H, J = 7.8 Hz), 6.70 (d, 1H, J = 7.4 Hz), 5.25 (brs, 1H); MS (ESI): m/z = 145 $[\text{M}+\text{H}]^+$

2,6-dimethoxyphenol (Table 2, entry 16); ^1H NMR (500 MHz, CDCl_3): δ = 6.77 (t, 1H, J = 8.3 Hz), 6.55 (d, 1H, J = 8.3 Hz), 5.54 (brs, 1H), 3.87 (s, 3H); MS (ESI): m/z = 155 $[\text{M}+\text{H}]^+$

Quinolin-3-ol (Table 2, entry 17); ^1H NMR (300 MHz, DMSO- d_6): δ = 9.92 (brs, 1H), 8.56 (s, 1H), 7.89 (d, 1H, J = 8.3 Hz), 7.63 (d, 1H, J = 7.7 Hz), 7.47-7.37 (m, 3H); MS (ESI): m/z = 146 $[\text{M}+\text{H}]^+$

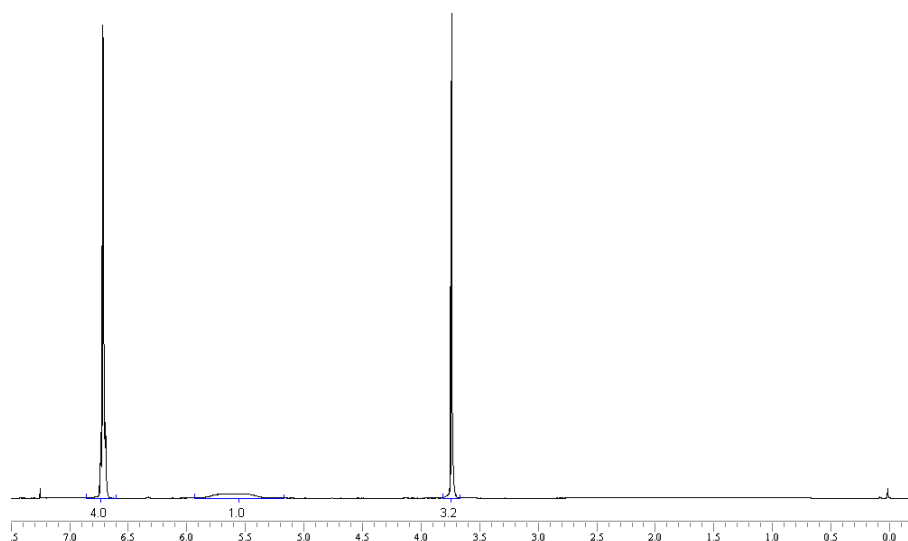
4-methylpyridin-2-ol:4-methylpyridin-2(1H)-one [1:1] (Table 2, entry 18); ^1H NMR (500 MHz, CDCl_3): δ = 8.35 (d, 1H, J = 5.5 Hz), 7.83-7.76 (m, 2H), 7.07 (d, 1H, J = 4.6 Hz), 6.38 (s, 1H), 6.08 (d, 1H, J = 7.3 Hz), 3.70-3.54 (m, 2H), 2.44 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 151.8, 148.3, 135.0, 123.9, 121.9, 120.1, 108.7, 96.3, 29.5, 21.2; MS (ESI): m/z = 110 $[\text{M}+\text{H}]^+$

Pyridin-3-ol (Table 2, entry 19); ^1H NMR (300 MHz, DMSO- d_6): δ = 9.91 (brs, 1H), 8.15 (s, 1H), 8.03 (s, 1H), 7.25-7.12 (m, 2H); MS (ESI): m/z = 96 $[\text{M}+\text{H}]^+$

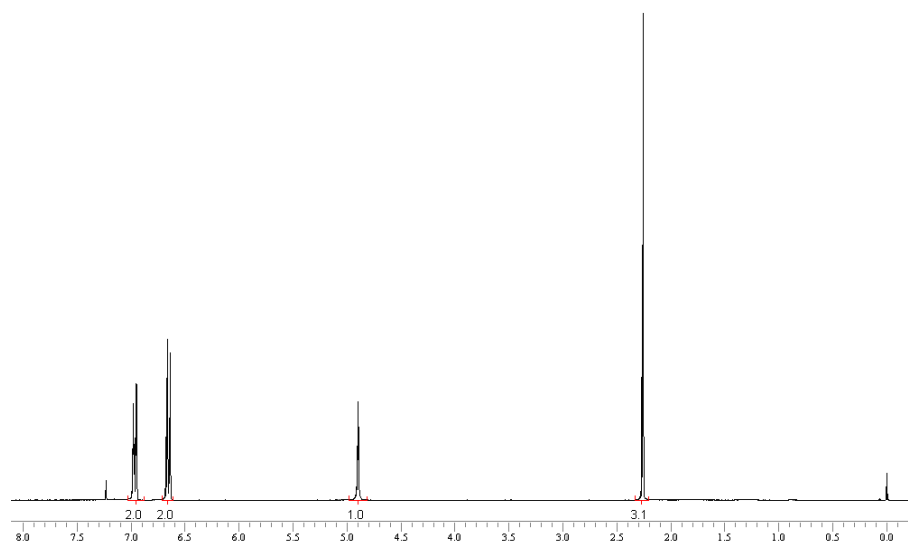
2-aminopyridin-3-ol (Table 2, entry 20); ^1H NMR (300 MHz, DMSO- d_6): δ = 7.41 (d, 1H, J = 4.9 Hz), 6.83 (d, 1H, J = 7.4 Hz), 6.44-6.34 (m, 1H), 5.33 (brs, 2H); MS (ESI): m/z = 111 $[\text{M}+\text{H}]^+$

^1H NMR & ^{13}C NMR Spectra

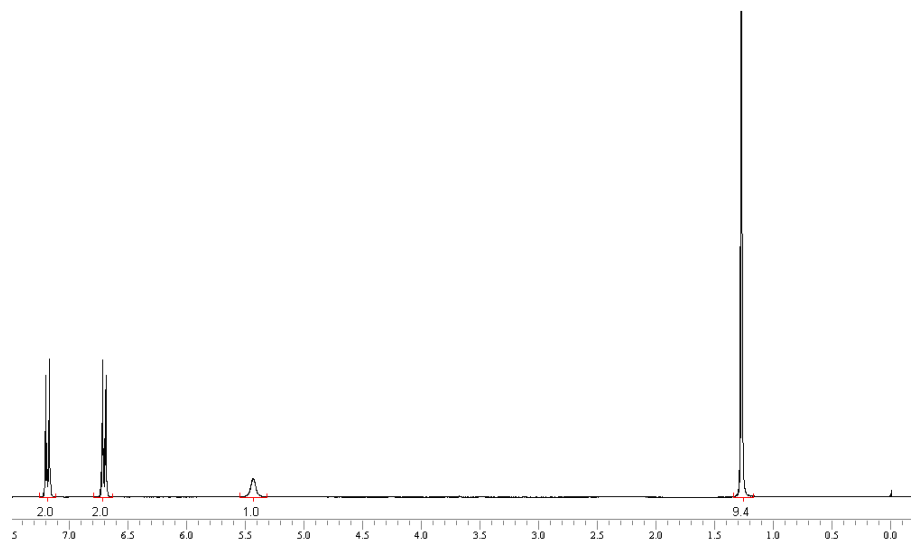
4-methoxyphenol (Table 2, entry 1)



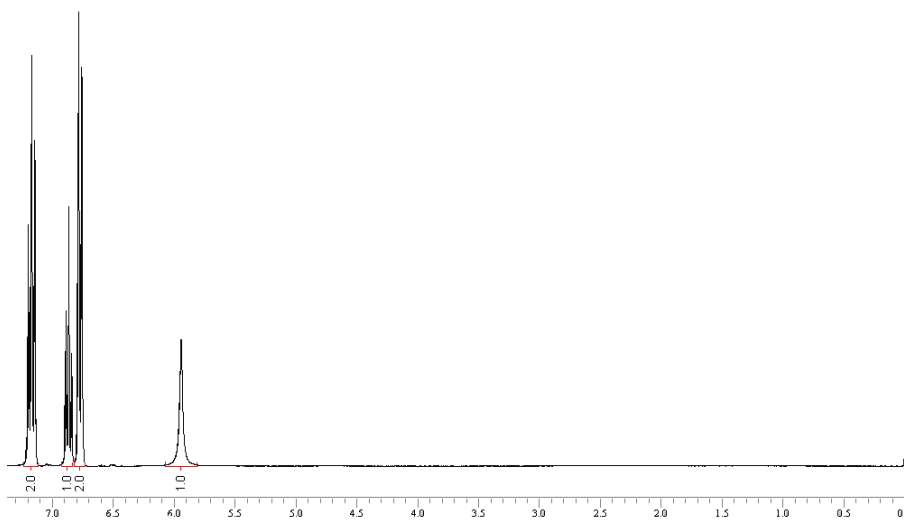
***p*-cresol** (Table 2, entry 2)



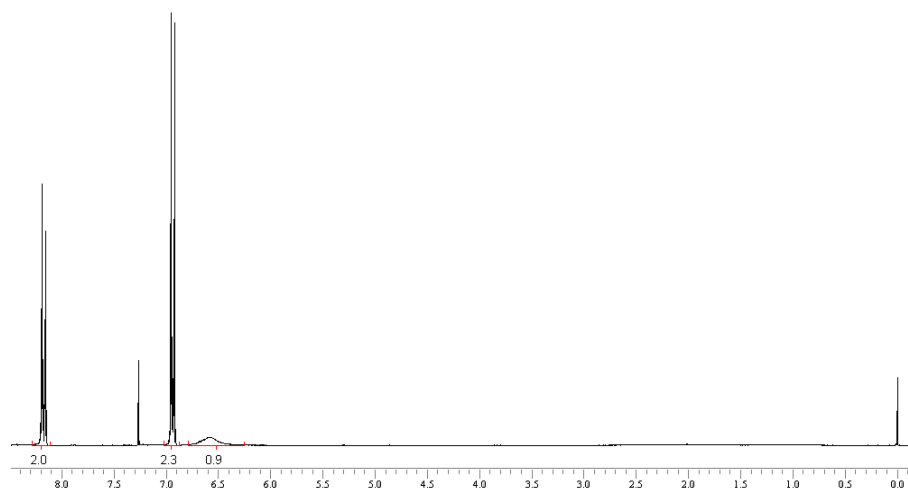
4-*tert*-butylphenol (Table 2, entry 3)



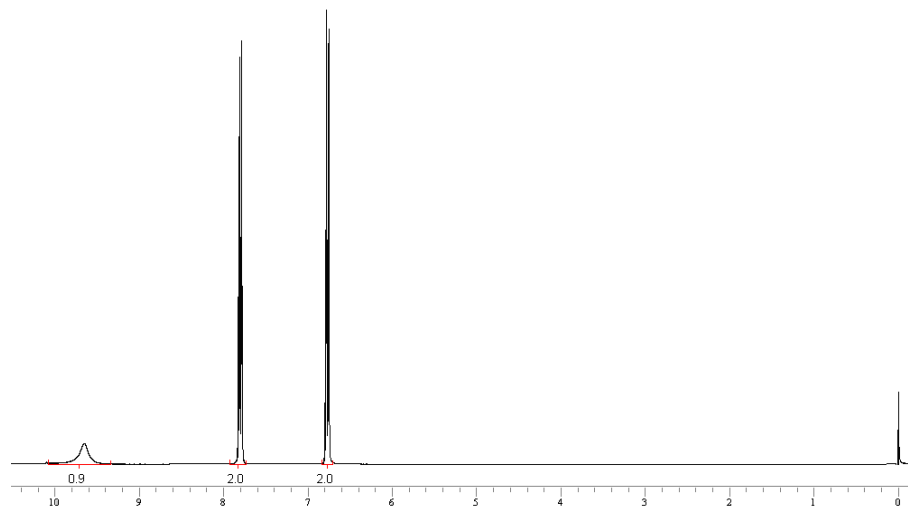
Phenol (Table 2, entry 4)



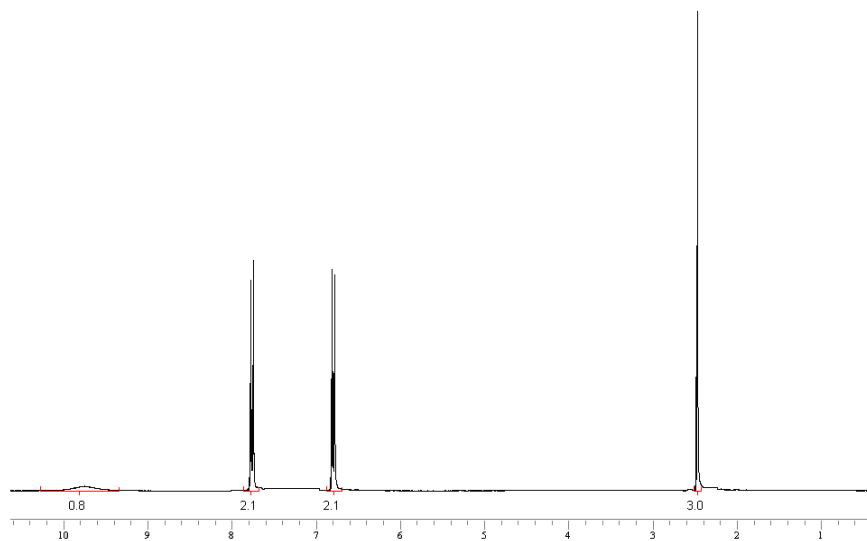
4-nitrophenol (Table 2, entry 5)



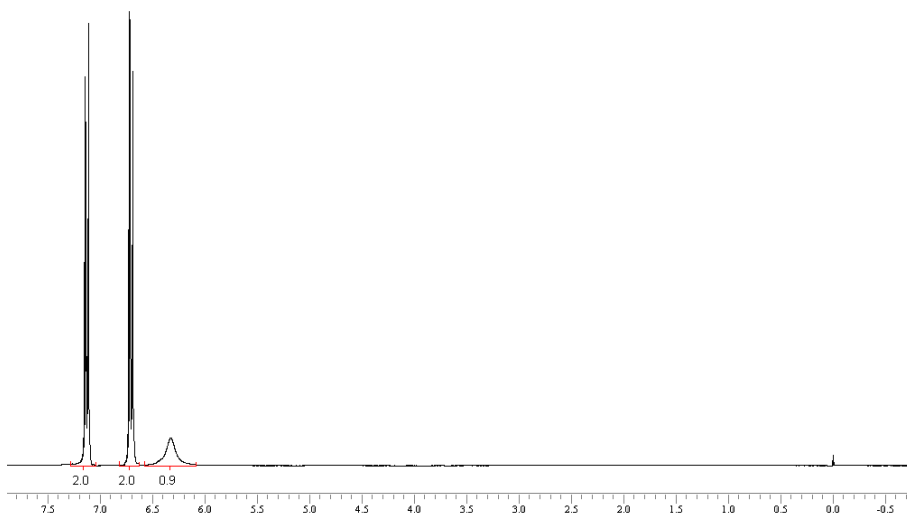
4-(trifluoromethyl)phenol (Table 2, entry 6)



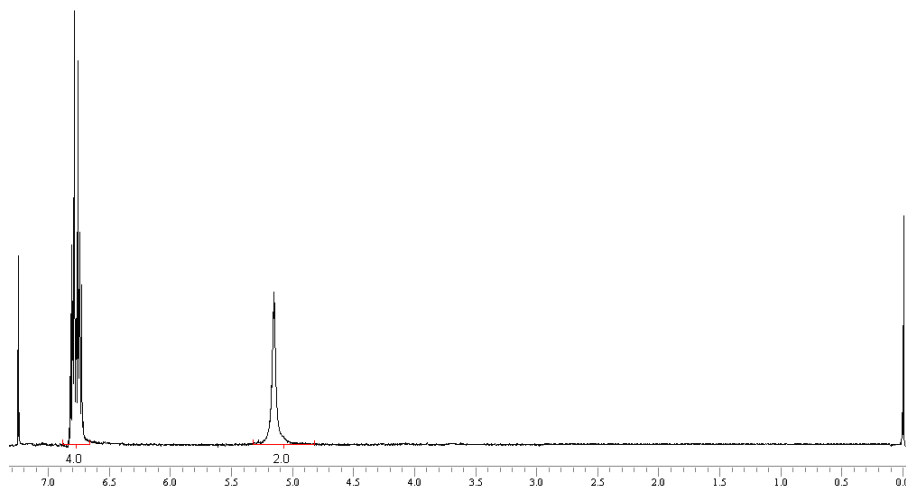
1-(4-hydroxyphenyl)ethanone (Table 2, entry 7)



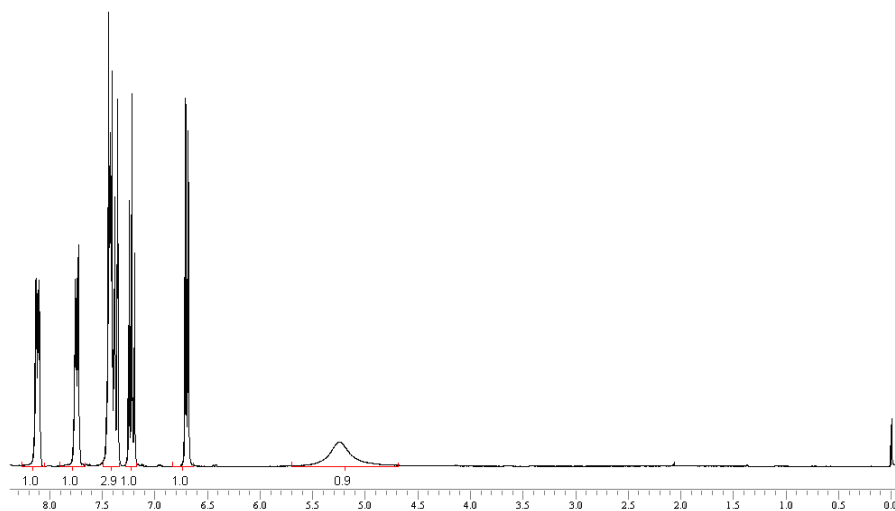
4-chlorophenol (Table 2, entry 9)



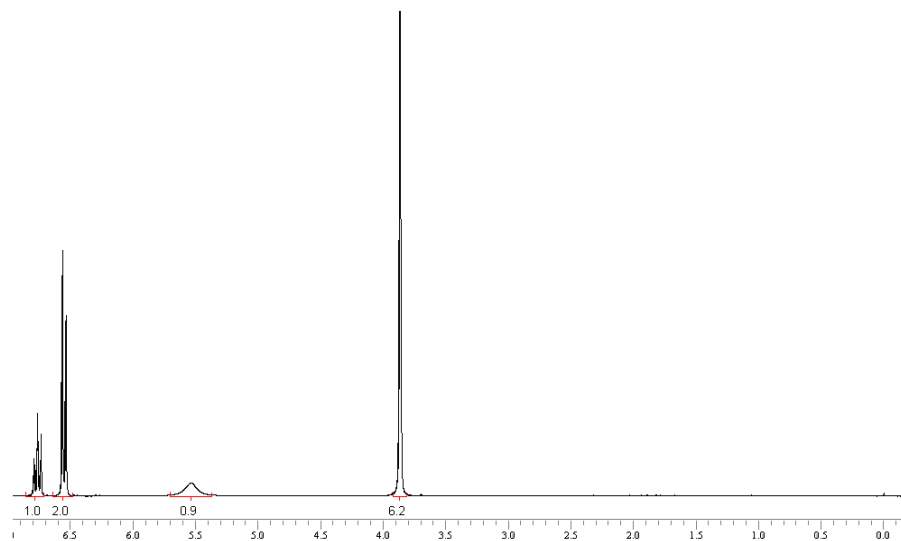
Pyrocatechol (Table 2, entry 12)



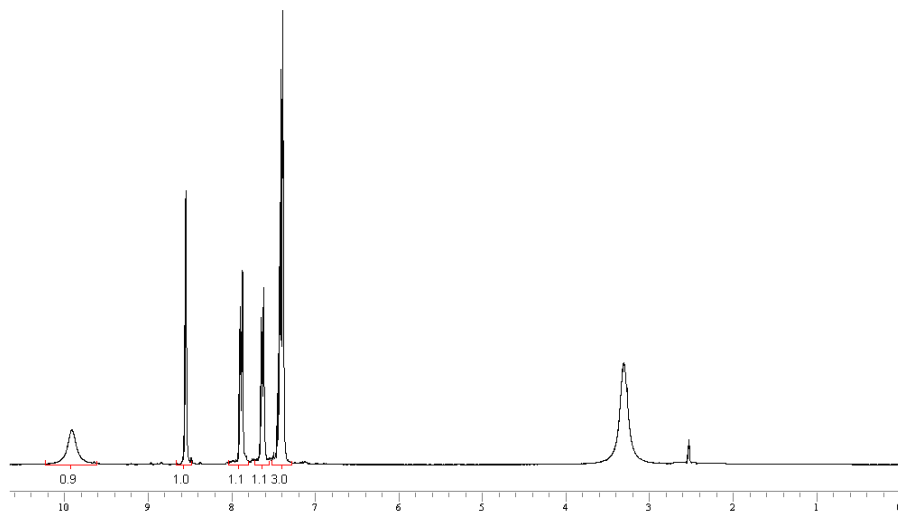
Naphthalen-1-ol (Table 2, entry 15)



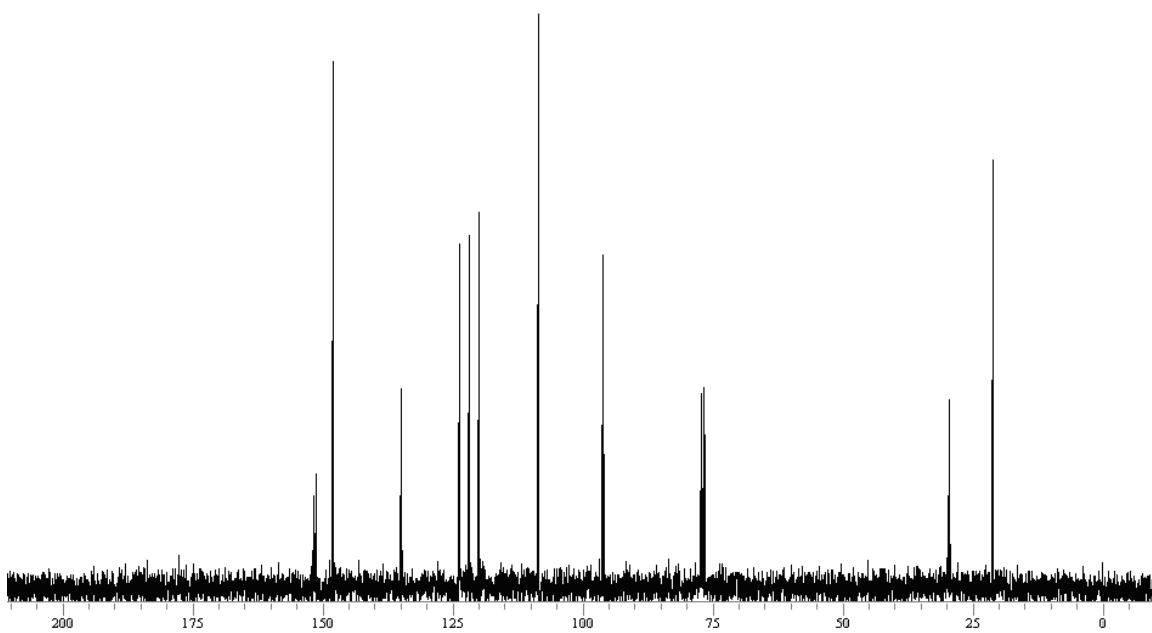
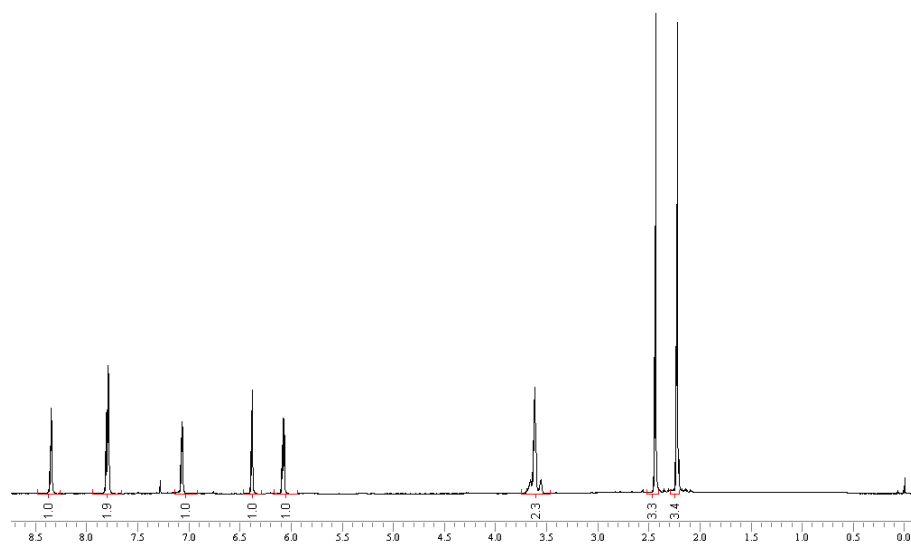
2,6-dimethoxyphenol (Table 2, entry 16)



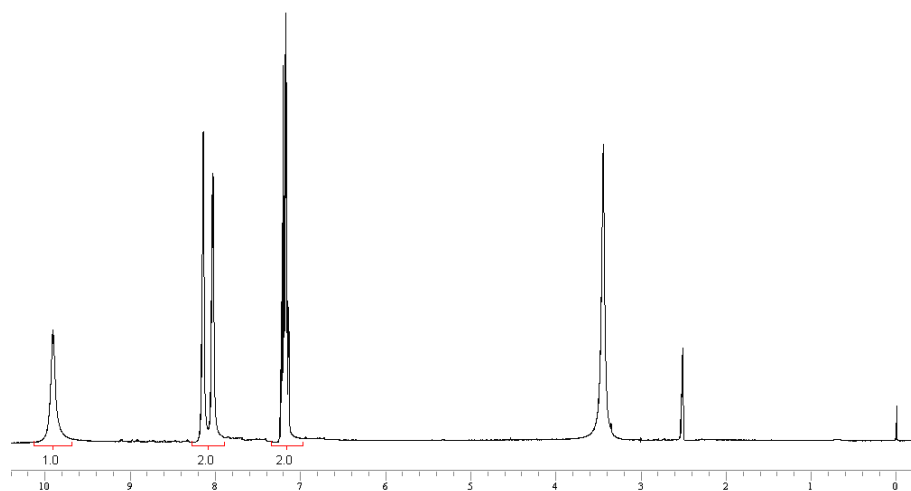
Quinolin-3-ol (Table 2, entry 17)



4-methylpyridin-2-ol ↔ **4-methylpyridin-2(1*H*)-one** (Table 2, entry 18)



Pyridin-3-ol (Table 2, entry 19)



2-aminopyridin-3-ol (Table 2, entry 20)

