# Facile and metal-free synthesis of phenols from benzaldoxime and diaryliodonium salts

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A metal-free, base-promoted facile synthesis of phenol derivatives utilising diaryliodonium salts as the aryl source and benzaldoxime as the hydroxide surrogate has been developed. The reaction is fast and shows good substrate compatibility, giving the corresponding products in good to excellent yields. A gram-scale synthesis of phenols utilising this protocol has also been achieved.

Keywords: phenols, O-arylation, benzaldoxime, diaryliodonium salts, metal-free synthesis

Phenols and their derivatives have been found in numerous pharmaceutical, agrochemical, and natural products.1 They also serve as key synthetic intermediates in the preparation of complex compounds. Conventional methods for the synthesis of phenols including the transition metal-catalysed hydroxylation of aryl halides,<sup>2–7</sup> and the oxidative hydroxylation of aromatic boronic acids<sup>8-13</sup> (Scheme 1, a and b). Route (a) generally suffers from drawbacks such as harsh conditions (long reaction time and high temperature), the incompatibility of the substrates, as well as the requirement for a metal catalyst (Pd, Cu). In recent years, the oxidative hydroxylation of aromatic boronic acids (route b) has attracted attention since aromatic boronic acids have a low toxicity and are stable and readily available. However, these procedures still require a catalyst and a large amount of oxidant. Recently, Fier and co-workers reported a Pd or Cu-catalysed method to prepare phenols with benzaldehyde oxime as a hydroxide surrogate (route c).<sup>14,15</sup> It was found that a weak base such as Cs<sub>2</sub>CO<sub>3</sub> would promote the deprotonation of the oxime ether, thereby providing a new route to access phenols. However, specific ligands were necessary to promote this transformation. In the light of their contributions, we now report a modified base-promoted synthesis of phenols under mild reaction conditions using diaryliodonium salts as the aryl source and benzaldoxime as the hydroxide surrogate (route d).

# **Results and discussion**

This reaction involved two steps, namely the *O*-arylation and deprotonation process. When the first step was finished, the mixture was further stirred for another 1 h in the presence of

2 equiv. of Cs<sub>2</sub>CO<sub>3</sub> at 80 °C. Since the oxime ether generated from the benzaldoxime was readily deprotonated in the presence of Cs<sub>2</sub>CO<sub>3</sub><sup>14,15</sup> we focused on the optimisation of O-arylation process (step 1). Initially, benzaldoxime (1) and diphenyliodonium triflate (2a) were selected as the model substrates to optimise the reaction conditions (Table 1). As shown in the table, the base exhibited a significant influence on this transformation. The reaction did not occur in the absence of a base. Bases such as K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub> and KOH gave rather poor yields of the desired products at 60 °C after 12 h (entries 2-4). Pleasingly, switching the base to 'BuOK and 'BuONa provided the corresponding product 3a in 95% and 90% yields, respectively, in only 30 minutes (entry 5 and 6). The anion of diphenyliodonium salt was then examined, and an inferior yield was obtained (82%, entry 7). Other solvents including DMSO, toluene, dioxane, tetrahydrofuran and acetonitrile were also surveyed. However, lower yields were obtained (entries 8-12). Encouragingly, lowering the reaction temperature to room temperature affected neither the yield of the desired product nor the reaction time (entry 13). Decreasing the amounts of substrate 2a and base to 1.2 or 1.0 equiv. led to a decrease in the yield (entries 14 and 15).

To evaluate the scope and limitations of the current procedure, a series of diaryliodonium triflates were investigated under the optimised reaction conditions. The results are summarised in Table 2. In general, all the reactions proceeded smoothly to provide the desired products **3** in good to excellent yields. Substrates bearing either electron-donating or electron-withdrawing substituents including  $-CH_3$ ,  $-CH_3O$ , halogen



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#### Table 1 Optimisation of reaction conditions<sup>a</sup>

N <sup>OH</sup>		+	(1)	(1) base, temp, time		
		Ph <sup>-+</sup> Ph <sup>-</sup> (2) Cs <sub>2</sub> CO <sub>3</sub> , 80 °C, 1 h				111-011
- I		2a				3a
Entry	Х	Base (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%) <sup>b</sup>
1	0Tf	-	DMF	60	12	0
2	0Tf	K <sub>2</sub> CO <sub>3</sub> (1.5)	DMF	60	12	Trace
3	0Tf	Cs <sub>2</sub> CO <sub>3</sub> (1.5)	DMF	60	12	Trace
4	0Tf	KOH (1.5)	DMF	60	12	14
5	0Tf	<sup>t</sup> BuOK (1.5)	DMF	60	0.5	95
6	0Tf	<sup>t</sup> BuONa (1.5)	DMF	60	0.5	90
7	$BF_4$	<sup>t</sup> BuOK (1.5)	DMF	60	0.5	82
8	0Tf	<sup>t</sup> BuOK (1.5)	DMSO	60	0.5	89
9	0Tf	<sup>t</sup> BuOK (1.5)	Toluene	60	0.5	37
10	0Tf	<sup>t</sup> BuOK (1.5)	Dioxane	60	0.5	74
11	0Tf	<sup>t</sup> BuOK (1.5)	THF	60	0.5	60
12	0Tf	<sup>t</sup> BuOK (1.5)	CH <sub>3</sub> CN	60	0.5	72
13	0Tf	<sup>t</sup> BuOK (1.5)	DMF	r.t.	1	96
14	0Tf	<sup>t</sup> BuOK (1.2)	DMF	r.t.	1	85
15	0Tf	<sup>t</sup> BuOK (1.0)	DMF	r.t.	1	76

Table 2 Substrate scope<sup>a</sup>

N´    Ph	OH + Ar /	f (2)	(1) <sup>t</sup> BuOK, rt, time (2) Cs <sub>2</sub> CO <sub>3</sub> , 80 °C, 1 h		
່ 1	2				3
Entry	Ar	Time (h)	Product	Yield (%)⁵	M.p. (°C) <sup>lit.</sup>
1	$C_6H_5$	1	3a	96	40-42 (41-42)17
2	$4-CH_{3}C_{6}H_{4}$	1	3b	86	Yellow oil (yellow oil)18
3	4-MeOC <sub>6</sub> H <sub>4</sub>	6	3c	75	56-58 (57-58) <sup>17</sup>
4	4-CIC <sub>6</sub> H <sub>4</sub>	3	3d	90	43-44 (44-45)17
5	$4-BrC_6H_4$	3	3e	88	58-60 (55-58) <sup>19</sup>
6	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1	3f	85	42-45 (43)20
7	4-CHOC <sub>6</sub> H <sub>4</sub>	1	3g	87	114–116 (113–117) <sup>17</sup>
8	4-N0 <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1	3h	84	113-116 (113-114) <sup>17</sup>
9	4-CH <sub>3</sub> COC <sub>6</sub> H <sub>4</sub>	1	3i	85	108–110 (110) <sup>12</sup>
10	2-BrC <sub>6</sub> H <sub>4</sub>	3	3j	84	Yellow oil (colourless oil) <sup>21</sup>
11	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1	3k	89	Yellow oil (brown oil) <sup>12</sup>
12	1-Naphthyl	2	31	91	92-94 (91-93) <sup>17</sup>
13	3-Pyridyl	1	3m	82	125–126 (127)⁵

<sup>a</sup> Reaction conditions: 1 (0.5 mmol), **2a**/'BuOK (1:1 molar ratio, 1.5 equiv), DMF (5 mL), r.t., 1h. After step one, the mixture was further stirred for another 1 h in the presence of 2 equiv. of  $Cs_2CO_3$  at 80 °C. <sup>b</sup>Isolated yield.

<sup>a</sup> Reaction conditions: 1 (0.5 mmol), **2a**/base (1:1 molar ratio), solvent (5 mL). After step one, the mixture was stirred for another 1 h in the presence of 2 equiv. of  $Cs_2CO_3$  at 80 °C. <sup>b</sup> Isolated yield.



(1.

Scheme 2 Gram-scale reaction.

(Cl, Br),  $-CF_3$ , -CHO,  $-NO_2$ ,  $-C(O)CH_3$  survived the reaction conditions well, affording the corresponding products in 75– 96% yields. Among them, electron-rich bis(4-methoxyphenyl) iodonium triflate afforded the product **3c** in 75% yield due to byproduct formation.<sup>16</sup> Moreover, the steric effect was negligible, with the product **3j** and **3k** being obtained in 84% and 89% yields, respectively. Bis(1-naphthyl)iodonium triflate also showed good reactivity to deliver product **3l** in 91% yield. It was worth noting that bis(3-pyridyl)iodonium triflates was tolerated well under the reactions, affording **3m** in 82% yield.

To further demonstrate the practicality of the protocol which we have developed, the reaction was scaled-up (20 mmol). Under the optimised reaction conditions, the reaction proceeded smoothly to provide the phenol **3a** in 90% yield (Scheme 2).

# Conclusion

In summary, a metal-free and base-promoted facile synthesis of phenol derivatives has been developed. This protocol utilised diaryliodonium salts as the aryl source and benzaldoxime as the hydroxide surrogate. Substrates with different functional groups survived the reaction conditions to afford the desired products in good to excellent yields. Importantly, diaryliodonium salts are readily available and can be prepared from iodobenzene derivatives, thereby providing a new route to access phenols. A gram-scale synthesis utilising this protocol could also be achieved.

#### Experimental

All reagents were obtained from local commercial suppliers and used without further purification. Diaryliodonium salts were prepared according to the literature where necessary.<sup>22</sup> <sup>1</sup>H and <sup>13</sup>C NMR

spectra were recorded on a Bruker AV300 analyser in chloroform-d (CDCl<sub>3</sub>) using TMS as an internal standard. Melting points (m.p.) are determined with a MPA 100 apparatus and are not corrected. GC–MS were recorded on an Agilent Technologies 7890A instrument with an Agilent 5975C mass detector (EI).

### Synthesis of phenols; general procedure

In a sealed tube, benzaldoxime (0.5 mmol), diaryliodonium salt (0.75 mmol), 'BuOK (0.75 mmol) and DMF (5 mL) were mixed at room temperature. The reaction mixture was stirred for a given time. Then,  $Cs_2CO_3$  (2 equiv.) was added to the tube, and the reaction mixture was kept stirring for another 1 h at 80 °C. After completion of the reaction, the mixture was allowed to cool to room temperature, diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous MgSO<sub>4</sub> and then the solvent was removed under reduced pressure. The residue was further purified by silica gel chromatography using a mixture of petroleum ether/ethyl acetate to afford the desired product **3**. All of the products are known compounds, and their characterisation data were compared and found to be consistent with the reported literature.

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