Research Article

Synthesis of Phenols via Metal-Free Hydroxylation of Aryl Boronic Acids with Aqueous TBHP

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An alternate procedure for oxidative hydroxylation of aryl boronic acids with aqueous TBHP to access phenols is described. The protocol tolerated various functional groups substituted with aromatic rings. The reaction was performed in water and free from transition metal oxidants.

1. Introduction

In the past few decades, phenols have received great attention in modern synthetic chemistry [1–3], since ever Runge and Laurent made the first discovery in 1834 and 1841, respectively [4, 5], with regard to this motif, which is frequently found in natural products [6–8], flavonoids [9, 10], and pharmaceutically important compounds [11–17] associated with certain bioactivities, such as antibacterial [18–20], antifungal, antibiotic [21], anti-inflammatory [22, 23], antiviral [24], anxiolytic [25, 26], and antioxidant [27–33] activities.

In addition, they serve as a powerful building block and precursor in metal-catalyzed cross-coupling reactions [34–39] and synthesis of oxy-functionalized derivatives including o-alkenyl phenols [40], benzofurans and dibenzofurans [41–44], chromanones [45], coumarins [46–49], glycosides [50], and benzolactone [51], Representative examples of commercially important drugs are presented in Figure 1. Conventional methods for the large-scale synthesis of phenols include the Hock process, diazotization of aromatic amines, and nucleophilic substitution reactions. Academicians have focused on the development of alternative approaches, for example, C-H activation of arenes [52, 53] and oxidation of C-Si bonds [54] and C-halo bonds [55, 56]. Recently, the direct hydroxylation of aryl boronic acids to phenols has gained a lot of attention. In this context, a variety of oxidative methods employing metal catalysts, Cu(OAc)$_2$–H$_2$O$_2$ [57], CuSO$_4$–phenanthroline [58], CuCl$_2$–micellar systems [59], Cu$_2$O–NH$_3$ [60], [Ru(bpy)$_3$Cl$_2$]$\cdot$6H$_2$O [61], Al$_2$O$_3$–H$_2$O$_2$ [62], and H$_3$BO$_3$–H$_2$O$_2$ [63] has been developed. On the other hand, the metal-free oxidative process are also competitive, Oxone [64, 65], $n$Bu$_4$NHSO$_5$ [66], NH$_2$OH [67], H$_2$O$_2$–poly(N-vinylpyrrolidone) [68], I$_2$–H$_2$O$_2$ [69], Amberlite IR-120–H$_2$O [70], N-oxides [71], MCPBA [72], NaClO$_2$ [73], photoredox catalysis [74, 75], electrochemical oxidation [76, 77], (NH$_4$)$_2$S$_2$O$_8$ [78], PEG-400-H$_2$O$_2$ [79], WERSA-H$_2$O$_2$ [80], WEBPA-H$_2$O$_2$ [81], nanoparticles of Ag [82], Cu$_2$O [83], and Fe$_3$O$_4$/silica gel [84], and TBHP/Cl$_3$CCN [85]. Despite these efficient oxidative processes, developing a new methodology free from metal oxidants and organic solvents is highly desirable. As part of our research interest involving metal-free oxidation reactions [86], herein, a new protocol for the direct hydroxylation of aryl boronic acids with TBHP in the aqueous medium is reported (Scheme 1).

2. Results and Discussion

During a study of the Pd-Cu catalyzed cross-coupling reaction with phenylboronic acid as one of the components, surprisingly the reaction took a different course and resulted phenol as a new product. This unexpected product was observed after addition of aqueous TBHP as part of workup. Then, it was our interest to find detailed investigation of this
reaction. In order to find suitable reaction conditions, various reaction parameters have been considered and they are presented in Tables 1 and 2.

Table 1 describes the solvent effect for the hydroxylation reaction. We commenced our investigation by subjecting phenylboronic acid as a model substrate and aqueous 70% TBHP as an oxidant. Traces of phenol were observed under the reaction temperature of 0–25°C in the presence of Cs₂CO₃ as a base and THF solvent (Table 1, entries 1-2). When the reaction was performed in a 1:1 mixture of THF:H₂O solvent, to our surprise, only 22% of phenol was observed (Table 1, entry 3). However, combination of acetonitrile or dimethylformamide with water did not favor this hydroxylation process, although the temperature was raised to 70°C (entries 4-5). When the reaction was stirred in water as solvent, 47% of yield of the product was observed at 70°C (entry 8). It is important to conclude that water is necessary to form homogeneous reaction mixture.

Considering the role of the oxidant and base in the hydroxylation process, we then studied ratios of the oxidant and base, and the findings are outlined in Table 2. An initial study was conducted using 2:1 ratio of the oxidant and base in water solvent heated to 70°C (Table 2, entry 2). Although 50% of the desired product was obtained, substantial amount of unreactive phenylboronic acid was isolated. Changing the temperature and base K₂CO₃ did not favor the oxidative process (entries 3-4). On the other hand, organic bases such as pyridine, triethyl amine, and diethyl amine completely ruled out hydroxylation (entries 5–7). To our surprise, an improved yield of phenol (76%) was observed with NaOH (entry 8). Variations in temperature (25–80°C) resulted 45–60% yield of the product (entries 9–10). The control experiment either in the absence of an oxidant or base failed to give any product (entries 11–12). A significant improvement noticed with combination of aqueous TBHP and potassium tert-butoxide as an effective base in water provided high yield (92%) of phenol at 50°C (entry 14). Thus, the optimized reaction conditions for this hydroxylation process involved phenylboronic acid (1 mmol), aqueous TBHP (2 mmol), KOtBu (1 mmol), and H₂O (1 mL) heated to 50°C (entry 14).

Having the optimized reaction conditions in hand, we then pursued the scope of this hydroxylation process using a variety of substituted aryl boronic acids, and the results are presented in Table 3. Initially, the substrates bearing halides such as bromo, chloro, and iodo were tested, and as expected, the corresponding hydroxylated product was obtained in excellent yields (Table 3, entries 2–4). The aryl substitution did not alter the reaction, for example, the reaction of 4-phenyl-, 2-phenyl-, and naphthyl-boronic acids resulted 4-phenylphenol, 2-phenylphenol, and 2-naphthol in 90–92% yields, respectively (entries 5–7). Simple methyl groups at para positions proceed smoothly to give para-Cresol in 89% yields (entry 8). Some limitations appear when a strong electron-donating group such as para-methoxy boronic acid was subjected to the

![Figure 1: Bioactive compounds with phenol moiety.](image)

**Figure 1: Bioactive compounds with phenol moiety.**

**Scheme 1: Hydroxylation of aryl boronic acids.**

![Scheme 1](image)

**Table 1: Solvent study: hydroxylation of phenylboronic acid.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>0</td>
<td>1</td>
<td>NR</td>
</tr>
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<td>THF</td>
<td>25</td>
<td>1</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>THF:H₂O</td>
<td>25</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN:H₂O</td>
<td>25</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>DMF:H₂O</td>
<td>70</td>
<td>3</td>
<td>&gt;5&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>THF:H₂O</td>
<td>50</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>H₂O</td>
<td>25</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>H₂O</td>
<td>70</td>
<td>3</td>
<td>47</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: phenylboronic acid (1 mmol), aqueous TBHP (1 mmol), Cs₂CO₃ (0.5 mmol), and solvent stirred at designated temperature and time;<sup>b</sup>isolated yield;<sup>c</sup>products were characterized by MP, FTIR, and 1H- and 13C-NMR;<sup>d</sup>traces of the product when CH₃CN and pyridine solvents were used.
Table 2: Optimization of hydroxylation parameters\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (equiv.)</th>
<th>Base (equiv.)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)\textsuperscript{b,c}</th>
</tr>
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<tbody>
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<td>1</td>
<td>TBHP (1)</td>
<td>Cs\textsubscript{2}CO\textsubscript{3} (1)</td>
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<td>3</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>TBHP (2)</td>
<td>Cs\textsubscript{2}CO\textsubscript{3} (1)</td>
<td>70</td>
<td>5</td>
<td>50\textsuperscript{d}</td>
</tr>
<tr>
<td>3</td>
<td>TBHP (2)</td>
<td>K\textsubscript{2}CO\textsubscript{3} (0.5)</td>
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<td>5</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>TBHP (2)</td>
<td>K\textsubscript{2}CO\textsubscript{3} (1)</td>
<td>25</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>TBHP (2)</td>
<td>Pyridine (1)</td>
<td>60</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>TBHP (2)</td>
<td>Et\textsubscript{3}N (1)</td>
<td>60</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
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<td>TBHP (2)</td>
<td>Et\textsubscript{2}NH (1)</td>
<td>60</td>
<td>5</td>
<td>22</td>
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<tr>
<td>8</td>
<td>TBHP (2)</td>
<td>NaOH (1)</td>
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<td>76</td>
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<tr>
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<td>45</td>
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<td>2</td>
<td>60</td>
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<td>11</td>
<td>—</td>
<td>NaOH (1)</td>
<td>50</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>TBHP (2)</td>
<td>—</td>
<td>50</td>
<td>5</td>
<td>Traces</td>
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<td>TBHP (2)</td>
<td>KOH (1)</td>
<td>50</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>14</td>
<td>TBHP (2)</td>
<td>KO\textsubscript{2}Bu (1)</td>
<td>50</td>
<td>5</td>
<td>92(87)\textsuperscript{e}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: phenylboronic acid (1 mmol), aqueous TBHP base, and water (1 mL) stirred at designated temperature and time; \textsuperscript{b}Isolated yield after workup; \textsuperscript{c}Products were characterized by MP, FTIR, and \textsuperscript{1}H- and \textsuperscript{13}C-NMR; \textsuperscript{d}THF was added to mix reactants; \textsuperscript{e}Yield after 2 hours.

Table 3: Substrate scope for the direct hydroxylation of aryl boronic acids\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b,c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![OH][B(OH)\textsubscript{2}]</td>
<td>![OH][B(OH)\textsubscript{2}]</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>![Br][B(OH)\textsubscript{2}]</td>
<td>![Br][B(OH)\textsubscript{2}]</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>![Cl][B(OH)\textsubscript{2}]</td>
<td>![Cl][B(OH)\textsubscript{2}]</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>![I][B(OH)\textsubscript{2}]</td>
<td>![I][B(OH)\textsubscript{2}]</td>
<td>87</td>
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<tr>
<td>5</td>
<td>![Ph][B(OH)\textsubscript{2}]</td>
<td>![Ph][B(OH)\textsubscript{2}]</td>
<td>92</td>
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<tr>
<td>6</td>
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<td>![Ph][B(OH)\textsubscript{2}]</td>
<td>90</td>
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<tr>
<td>7</td>
<td>![Ph][B(OH)\textsubscript{2}]</td>
<td>![Ph][B(OH)\textsubscript{2}]</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>![H\textsubscript{3}C][B(OH)\textsubscript{2}]</td>
<td>![H\textsubscript{3}C][B(OH)\textsubscript{2}]</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>![H\textsubscript{3}CO][B(OH)\textsubscript{2}]</td>
<td>![H\textsubscript{3}CO][B(OH)\textsubscript{2}]</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>![O\textsubscript{2}N][B(OH)\textsubscript{2}]</td>
<td>![O\textsubscript{2}N][B(OH)\textsubscript{2}]</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>![H\textsubscript{3}CO][B(OH)\textsubscript{2}]</td>
<td>![H\textsubscript{3}CO][B(OH)\textsubscript{2}]</td>
<td>47</td>
</tr>
<tr>
<td>12</td>
<td>![H\textsubscript{3}CO][B(OH)\textsubscript{2}]</td>
<td>![H\textsubscript{3}CO][B(OH)\textsubscript{2}]</td>
<td>nd\textsuperscript{d}</td>
</tr>
<tr>
<td>13</td>
<td>![NC][B(OH)\textsubscript{2}]</td>
<td>![NC][B(OH)\textsubscript{2}]</td>
<td>10\textsuperscript{e}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: aryl boronic acid (1 mmol), aqueous TBHP (2 mmol), TBHP (2 mmol), KO\textsubscript{2}Bu (1 mmol), and H\textsubscript{2}O (1 mL), 50°C; \textsuperscript{b}Isolated yield; \textsuperscript{c}products were characterized by MP, FTIR, and \textsuperscript{1}H- and \textsuperscript{13}C-NMR; \textsuperscript{d}the desired product was not isolated; \textsuperscript{e}Characterized by FTIR.
hydroxylation; the corresponding para methoxyphenol was isolated in 60% yield (entry 9), in addition to the side product because of the possibility of overoxidation. The presence of a strong electron-withdrawing substituent –NO₂ on aryl boronic acid quantitatively converted to the para-nitrophenol in excellent yield (entry 10). However, the expected 4-hydroxy-methyl-benzoate (entry 11) could be observed only in moderate yield when ester-boronic acid was tested; the corresponding acid was also formed during the course of hydroxylation.

3. Conclusion
An alternate method for the direct hydroxylation of aryl boronic acid to phenol promoted by aqueous TBHP as an oxidant using metal- and solvent-free conditions has been described. The products were obtained in good to excellent yields. It is important to note that the reaction works only with aryl boronic acids and not with heteroaryl or base-sensitive functional groups. The methodology is free from chromatographic purification because the desired products were obtained in pure form after acidic workup. Since this protocol is free from chromatographic purification, it could be extended for large-scale synthesis.

4. Materials and Methods
FTIR spectra of the synthesized compounds were recorded on a Shimadzu 4000 instrument using the KBr pellet within the range of 400 ± 10 to 4000 ± 10 cm⁻¹. ¹H-NMR and ¹³C-NMR spectra of all compounds were recorded on a Bruker NMR spectrometer using deuterated solvent CDCl₃ and DMSO TMS as an internal standard. Chemical shift values are expressed in δ (ppm).

All the starting materials, chemicals, and reagents were commercially available and used without further purification unless otherwise stated. TBHP was purchased from Rankem, India. Other reagents such as Cs₂CO₃, K₂CO₃, respectively. TLC plates and commercial grades solventssuch as tert-butyl alcohol, water, ethanol, and acetone were procured from Sigma Aldrich and Rankem, India, respectively. The products were isolated in pure form after acidic workup. Since this protocol is free from chromatographic purification, it could be extended for large-scale synthesis.

4.1. General Procedure for Hydroxylation. To a 5 mL screw top sample vial equipped with a magnetic stirrer bar, phenylboronic acid (0.2 mmol, 1 equiv), water (1 mL), and potassium tert-butoxide were introduced and stirred at room temperature. To this mixture, 70% aqueous TBHP was added with continuous stirring, and the reaction mixture was further heated at 50 °C for 5 h. The formation of phenol was monitored with the help of TLC. After completion of the reaction, the vial was cooled to room temperature, followed by addition of aqueous 6N HCl. The resultant mixture was extracted with ethyl acetate. The organic layer was washed with cold water and then dried over anhydrous sodium sulphate. The ethyl acetate was evaporated using a rotary evaporator to yield the corresponding phenol in pure form.

4.2. Spectral Data. Phenol (Table 2, entry 1): colorless solid; MP 41–42°C (lit. 41–42°C); FTIR (KBr, cm⁻¹) 692, 815, 1065, 1220, 1365, 1470, 1592, 1920, 2350, and 3325; ¹H-NMR (400 MHz, CDCl₃): δ 6.78–7.22 (m, 2H), 6.96–6.91 (m, 1H), 6.85–6.82 (m, 2H), and 5.03 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃): δ 155.0, 129.7, 121.0, and 115.3.

4-Methoxyphenol (Table 2, entry 2): colorless solid; MP 60–62°C; FTIR (KBr, cm⁻¹) 604, 810, 1030, 1207, 1405, 1500, and 1595, and 3402; ¹H-NMR (400 MHz, CDCl₃): δ 5.10 (br s, 1H), 6.71 (d, J = 8.5 Hz, 2H), and 7.30 (d, 2H J = 8.5 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 113.1, 117.3, 132.7, and 154.4.

4-Chlorophenol (Table 2, entry 3): white solid; MP 44–45°C; FTIR (KBr, cm⁻¹) 635, 715, 820, 1089, 1210, 1352, 1490, 2850, 2900, 3240, and 3335; ¹H-NMR (400 MHz, CDCl₃): δ 4.76 (br s, 1H), 6.73 (d, J = 8.5, 2H), and 7.20 (d, J = 8.5, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 116.2, 125.3, 129.2, and 153.2.

2-Naphthalenol (Table 2, entry 7): white solid; MP 165–167°C; FTIR (KBr, cm⁻¹) 400, 604, 810, 1030, 1207, 1405, and 3402; ¹H-NMR (400 MHz, CDCl₃): δ 4.87 (br s, 1H), 6.55–6.61 (m, 2H), and 7.45–7.51 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 82.6, 118.1, 138.5, and 155.2.

4-Phenylphenol (Table 2, entry 5): yellow-brown solid; MP 165–167°C; FTIR (KBr, cm⁻¹) 640, 750, 810, 1195, 1225, 1370, 1440, 1510, 1600, 1605, 3005, 3010, and 3395; ¹H-NMR (400 MHz, CDCl₃): δ 2.0, 2H), and 7.34–7.50 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃): δ 119.7, 126.0, 129.4, 138.5, 142.0, and 158.0.

2-Phenylphenol (Table 2, entry 6): FTIR (KBr, cm⁻¹) 696, 745, 805, 1175, 1405, 1425, 1596, 3020, 3240, and 3521; ¹H-NMR (400 MHz, CDCl₃): δ 4.96 (br s, 1H), 6.92–7.02 (m, 2H), 7.26–7.59 (m, 2H), 7.34–7.40 (m, 1H), and 7.43–7.50 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃): δ 116.0, 120.9, 127.8, 128.0, 129.1, 129.9, 130.2, 130.7, 130.8, and 152.2.

2-Naphthalenol (Table 2, entry 7): white solid; MP 122–124°C; FTIR (KBr, cm⁻¹) 720, 805, 940, 1180, 1395, 1600, and 3240; ¹H-NMR (400 MHz, CDCl₃): δ 5.02 (br s, 1H), 7.02–7.10 (m, 2H), 7.24–7.29 (m, 1H), and 7.78 (d, J = 7.2, 2H), 7.32 (d, J = 8.3, 1H), and 7.76–7.71 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 109.0, 117.2, 123.2, 126.0, 126.2, 127.3, 128.5, 129.6, 134.1, and 153.0.

P-Cresol (Table 2, entry 8): FTIR (KBr, cm⁻¹) 725, 925, 1235, 1260, 1461, 1610, 1700, 2545, 2920, and 3345; ¹H-NMR (400 MHz, CDCl₃): δ 2.24 (s, 3H), 4.66 (br s, 1H), 6.70 (d, J = 8.5 Hz, 2H), and 7.05 (d, J = 8.4 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 20.2, 115.0, 130.1, 130.4, and 153.1.

4-Methoxyphenol (Table 2, entry 9): colorless; FTIR (KBr, cm⁻¹) 725, 805, 1030, 1175, 1225, 1432, 1602, 2830, 2952, and 3375; ¹H-NMR (400 MHz, CDCl₃): δ 3.72 (s, 3H), 4.75 (br s, 1H), and 6.73–6.80 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃): δ 55.7, 115.0, 116.2, 149.0, and 153.2.
4-Nitrophenol (Table 2, entry 10): yellow solid; MP 111–114°C; FTIR (KBr, cm⁻¹) 735, 922, 1245, 1352, 1545, 1605, 1697, 2535, 2915, and 3340; ¹H-NMR (400 MHz, CDCl₃): δ 6.73–6.76 (m, 2H) and 7.93–7.97 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 116.2, 126.1, 141.2, and 164.7.

1-Hydroxybenzoic acid (Table 2, entry 11): white solid; MP 215–217°C; FTIR (KBr, cm⁻¹) 730, 850, 948, 1135, 1220, 1295, 1305, 1415, 1580, 1603, 1700, 2530, 2640, and 3395; ¹H-NMR (400 MHz, CDCl₃): δ 6.65–6.70 (m, 2H) and 7.71–7.76 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 116.0, 122.4, 133.2, 163.0, and 170.0.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The author declares that there are no conflicts of interest.

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References


