

# A Facile Protocol for the Synthesis of Benzofuran Derivatives by the Reaction of *o*-Hydroxy Aryl Ketone, Amine and Chloroacetyl Chloride

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A facile and effective method has been developed for the synthesis of a novel series of benzofuran derivatives via *N*-acylation, *O*-alkylation and intramolecular condensation reactions, starting from readily available substituted *o*-hydroxy aryl ketone, and chloroacetyl arylamides. This metal-free transition process is characterized by mild reaction conditions, atom economy, short reaction time and a high yield with a decreased amount of by-products.

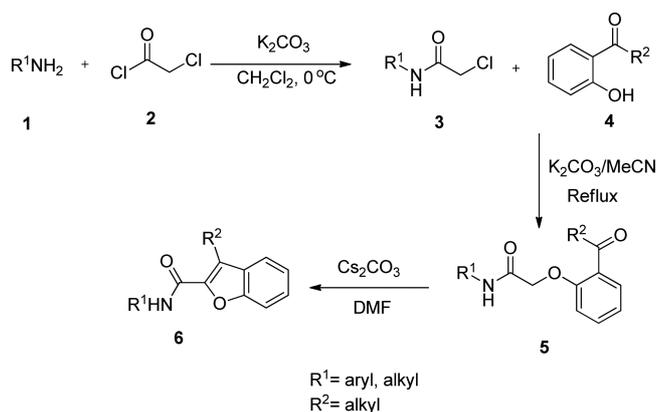
**Key Words** : Benzofuran, *o*-Hydroxy aryl ketone, Amine, Synthesis, Intramolecular condensation

## Introduction

Benzofuran moiety is abundant in both natural and artificial molecules. Substituted benzofurans are pharmaceutically important heterocycles that display numerous biological activities such as antimicrobial,<sup>1,2</sup> antifungal,<sup>3</sup> antitubercular,<sup>3,4</sup> antiprotozoal,<sup>5</sup> anti-HIV-1, anticancer,<sup>6,7</sup> antimalarial,<sup>7</sup> antiretroviral,<sup>8</sup> antioxidant,<sup>9</sup> cytotoxic,<sup>10</sup> anticonvulsant,<sup>11</sup> anti-inflammatory<sup>12</sup> activities. They have also been exhibited some properties as steroidogenic inhibitors,<sup>13</sup> MMP-13 inhibitors,<sup>14</sup> cathepsin K inhibitors,<sup>15</sup> local anesthetic,<sup>16</sup> monoamine oxidase inhibitors,<sup>17</sup> dual 5-HT<sub>1A</sub> receptor agonists, and serotonin reuptake inhibitors.<sup>18</sup> In addition, several benzo[*b*]furan ring systems bearing various substituents are widely distributed in nature, *e.g.*, aianthoidol,<sup>1</sup> (–)-concentricolide,<sup>19</sup> (+)-frondosin B<sup>20</sup> and the eupomatenoid family.<sup>21</sup>

Owing to their important applications in medicinal chemistry, it is of great significance to develop systematic and novel approaches to benzofurans. The conventional strategies for the construction of furan rings are *via* the conversion of various arene derivatives,<sup>22,23</sup> through C–O bond formation<sup>24,25</sup> or with the assistance of expensive transition-metal catalyzed reactions,<sup>26–36</sup> most of which suffer from the limitations such as the requirement of expensive metal reagents, multi-step processes, harsh reaction conditions, and unavailability of starting materials. Furthermore, there are still no typical efficient protocols for the preparation of benzofuran skeleton, making it urgent for searching new methods.

Herein, in the interest of the impressive results of various benzofuran series and in continuation of our previous work in the synthesis of heterocycles,<sup>37–39</sup> we reported an efficient protocol for the synthesis of a novel variety of benzofuran derivatives using readily available *o*-hydroxy aryl ketones,



**Scheme 1.** Synthetic route to benzo[*b*]furan derivatives **6**.

chloroacetyl chloride and amines *via* *N*-acylation, *O*-alkylation and intramolecular condensation, under mild basic conditions in relatively short time (Scheme 1).

## Experimental

**General.** All of the reagents were obtained from commercial sources. Solvents were dried and purified with known conventional methods. Melting points (uncorrected) were determined on a Gallenkamp apparatus. <sup>1</sup>H and <sup>13</sup>C NMR spectra (at 500 MHz, 400 MHz or 300 MHz and 125 MHz, 100 MHz or 75 MHz, respectively) were recorded in CDCl<sub>3</sub> with tetramethylsilane as internal reference. Chemical shifts were reported in parts per million. Mass spectra (MS) were measured by ESI. CDCl<sub>3</sub> was used as delivered from Sigma-Aldrich. Silica gel (70–230 mesh) was used for flash column chromatography. All reactions were monitored by TLC using 0.25 mm silica gel plates with UV indicator (Shanghai Jiapeng Technology Co., Ltd., China). Unless otherwise noted, other reagents were obtained from commercial suppliers and used without further purification.

<sup>39</sup>These authors contributed equally to this work.

**Representative Procedure for the Synthesis of *N*-Substituted-2-chloroacetamide (3).** To a magnetically stirred solution of substituted aniline **1** (10.0 mmol, 1.0 equiv) and  $K_2CO_3$  (15.0 mmol, 1.5 equiv) in  $CH_2Cl_2$  (100 mL), cooled in an ice bath, chloroacetyl chloride **2** (12.0 mmol, 1.2 equiv) was added slowly dropwise. The reaction mixture was stirred at room temperature and monitored by TLC. After the reaction was complete, solvent was removed under vacuum and ice water (200 mL) was added into the residue. The product **3** precipitated was filtered and washed with water, dried and used for the next step without further purification.

**Representative Procedure for the Synthesis of Substituted Acetamide (5).** The solution of *o*-hydroxy aryl ketone **4** (5.0 mmol, 1.0 equiv),  $K_2CO_3$  (6.0 mmol, 1.2 equiv), *N*-substituted-2-chloroacetamide **3** (5.0 mmol, 1.0 equiv) in  $CH_3CN$  (10 mL) was refluxed and monitored by TLC. After completion of the reaction, solvent was removed under vacuum and water (20 mL) was added to the residue. The mixture was then extracted with ethyl acetate (4 × 30 mL). The organic layers were combined, dried over anhydrous  $MgSO_4$ , and evaporated under vacuum to give the crude product. The residue obtained was purified by silica gel column chromatography to obtain corresponding compound **5**.

**Representative Procedure for the Synthesis of Substituted Benzo[*b*]furans (6).** Cyclization of substituted acetamide **5** (5.0 mmol, 1.0 equiv) by treating it with cesium carbonate (7.5 mmol, 1.2 equiv) in anhydrous DMF (10 mL) at 110 °C gave substituted benzo[*b*]furans **6**. After the completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and water (30 mL) was added into the residue. The mixture was then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine and dried over anhydrous  $MgSO_4$ , filtered and evaporated under vacuum to give the crude product. The pure product **6** was obtained by column chromatography on silica gel (ethyl acetate: petroleum ether = 1:10).

***N*-(2-Pyridyl)-(benzo[*b*]furan-2-yl)carboxamide 6a:** A white solid; mp 139.5–141 °C;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  9.08 (s, 1H), 8.39–8.37 (m, 2H), 7.78 (t,  $J$  = 7.6 Hz, 1H), 7.71 (d,  $J$  = 7.6 Hz, 1H), 7.63 (s, 1H), 7.55 (d,  $J$  = 8.4 Hz, 1H), 7.47 (t,  $J$  = 7.4 Hz, 1H), 7.33 (t,  $J$  = 7.4 Hz, 1H), 7.11 (t,  $J$  = 5.1 Hz, 1H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  158.2, 156.3, 152.3, 149.5, 149.4, 139.9, 129.0, 128.9, 125.4, 124.3, 121.6, 115.7, 113.4, 113.3; HRMS (ESI):  $m/z$  239.0843.

***N*-(2-Pyridyl)-(3-methyl-benzo[*b*]furan-2-yl)carboxamide 6b:** A light-yellow solid; mp 131.5–133 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  9.12 (s, 1H), 8.39 (d,  $J$  = 8.4 Hz, 1H), 8.36–8.33 (m, 1H), 7.79–7.74 (m, 1H), 7.65 (d,  $J$  = 7.4 Hz, 1H), 7.52–7.45 (m, 2H), 7.34–7.31 (m, 1H), 7.10–7.08 (m, 1H), 2.70 (s, 3H;  $CH_3$ );  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  158.3, 153.4, 151.1, 148.2, 142.0, 138.4, 129.7, 127.7, 124.6, 123.4, 121.1, 120.0, 114.1, 111.8, 9.1; HRMS (ESI):  $m/z$  253.0976.

***N*-(2-Pyridyl)-(3-ethyl-benzo[*b*]furan-2-yl)carboxamide 6c:** A white solid; mp 99–100 °C;  $^1H$  NMR (500 MHz,

$CDCl_3$ )  $\delta$  9.18 (s, 1H), 8.38 (d,  $J$  = 8.4 Hz, 1H), 8.34 (dd,  $J$  = 4.8, 0.9 Hz, 1H), 7.74–7.71 (m, 1H), 7.65 (d,  $J$  = 7.5 Hz, 1H), 7.46–7.41 (m, 2H), 7.29–7.26 (m, 1H), 7.06–7.04 (m, 1H), 3.21 (q,  $J$  = 7.6 Hz, 2H), 1.35 (t,  $J$  = 7.6 Hz, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  158.0, 153.5, 151.2, 148.1, 141.4, 138.4, 130.7, 128.8, 127.6, 123.3, 121.2, 119.9, 114.1, 111.9, 17.4, 14.3; HRMS (ESI):  $m/z$  267.1129.

***N*-(2-Pyridyl)-(3-propyl-benzo[*b*]furan-2-yl)carboxamide 6d:** A white solid; mp 107.5–109 °C;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  9.11 (s, 1H), 8.39–8.37 (m, 2H), 7.75 (t,  $J$  = 7.5 Hz, 1H), 7.68 (d,  $J$  = 7.8 Hz, 1H), 7.51–7.43 (m, 2H), 7.31 (t,  $J$  = 6.9 Hz, 1H), 7.08 (t,  $J$  = 5.7 Hz, 1H), 3.18 (t,  $J$  = 7.5 Hz, 2H), 1.86–1.77 (m, 2H), 1.04 (t,  $J$  = 7.3 Hz, 3H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  159.5, 154.9, 152.5, 149.5, 143.2, 139.8, 130.7, 130.6, 129.0, 124.7, 122.8, 121.4, 115.5, 113.3, 27.2, 24.5, 15.6; HRMS (ESI):  $m/z$  281.1285.

***N*-(2-Pyridyl)-(3-phenyl-5-methoxy-benzo[*b*]furan-2-yl)carboxamide 6e:** A light-yellow solid; mp 167–168.5 °C;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  9.02 (s, 1H), 8.33–8.31 (m, 2H), 7.70–7.68 (m, 3H), 7.55–7.46 (m, 4H), 7.06 (t,  $J$  = 5.4 Hz, 2H), 6.97 (d,  $J$  = 8.7 Hz, 1H), 3.92 (s, 3H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  162.2, 158.6, 156.3, 152.6, 149.5, 142.5, 139.7, 131.8, 131.4, 130.0, 129.8, 129.7, 123.9, 123.5, 121.3, 115.7, 115.3, 96.8, 57.2; HRMS (ESI):  $m/z$  345.1256.

***N*-(3-Pyridyl)-(3-methyl-benzo[*b*]furan-2-yl)carboxamide 6f:** A white solid; mp 180–182 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.76 (d,  $J$  = 2.5 Hz, 1H), 8.50 (s, 1H), 8.39 (dd,  $J$  = 5.0, 1.5 Hz, 1H), 8.36–8.33 (m, 1H), 7.64 (d,  $J$  = 8.0 Hz, 1H), 7.49–7.44 (m, 2H), 7.34–7.30 (m, 2H), 2.67 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  158.4, 153.4, 145.5, 141.9, 141.4, 134.4, 129.7, 127.8, 127.2, 124.6, 123.8, 123.5, 121.2, 111.7, 9.1; HRMS (ESI):  $m/z$  253.0972.

***N*-(3-Pyridyl)-(3-ethyl-benzo[*b*]furan-2-yl)carboxamide 6g:** A white solid; mp 132.5–134 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.77 (s, 1H), 8.46 (s, 1H), 8.41 (d,  $J$  = 4.4 Hz, 1H), 8.36 (d,  $J$  = 8.4 Hz, 1H), 7.70 (d,  $J$  = 8.0 Hz, 1H), 7.54–7.45 (m, 2H), 7.33 (t,  $J$  = 7.4 Hz, 2H), 3.22 (q,  $J$  = 7.5 Hz, 2H), 1.36 (t,  $J$  = 7.5 Hz, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  158.2, 153.5, 145.5, 141.3, 134.4, 130.8, 128.8, 127.7, 127.2, 123.7, 123.5, 121.4, 111.8, 17.3, 14.2; HRMS (ESI):  $m/z$  267.1125.

***N*-(3-Pyridyl)-(3-propyl-benzo[*b*]furan-2-yl)carboxamide 6h:** A white solid; mp 163.5–164.5 °C;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  8.76–8.75 (m, 1H), 8.46 (s, 1H), 8.41–8.36 (m, 2H), 7.70 (d,  $J$  = 7.8 Hz, 1H), 7.53–7.45 (m, 2H), 7.34 (t,  $J$  = 7.2 Hz, 2H), 3.18 (t,  $J$  = 7.6 Hz, 2H), 1.82–1.78 (m, 2H), 1.03 (t,  $J$  = 7.3 Hz, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  157.2, 152.5, 144.4, 140.7, 140.2, 133.4, 128.3, 128.2, 126.6, 126.2, 122.7, 122.4, 120.5, 110.7, 24.7, 22.0, 13.1; HRMS (ESI):  $m/z$  280.1349.

***N*-Phenyl-(3-methyl-benzo[*b*]furan-2-yl)carboxamide 6i:** A yellow solid; mp 126–128 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.34 (s, 1H), 7.70 (d,  $J$  = 7.5 Hz, 2H), 7.61 (d,  $J$  = 7.5 Hz, 1H), 7.48 (d,  $J$  = 8.0 Hz, 1H), 7.45–7.42 (m, 1H), 7.37 (t,  $J$  = 7.8 Hz, 2H), 7.30 (t,  $J$  = 7.5 Hz, 1H), 7.14 (t,  $J$  = 7.5 Hz, 1H), 2.66 (s, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  158.1, 153.3, 142.4, 137.5, 129.9, 129.1, 127.4, 124.5, 123.8,

123.3, 121.1, 120.0, 111.6, 9.1; HRMS (ESI):  $m/z$  252.1017.

***N*-Phenyl-((3-ethyl-benzo[*b*]furan)-2-yl)carboxamide 6j:** A yellow solid; mp 95–97 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (s, 1H), 7.71 (d,  $J = 8.0$  Hz, 2H), 7.67 (d,  $J = 8.0$  Hz, 1H), 7.51 (d,  $J = 8.0$  Hz, 1H), 7.44 (t,  $J = 7.5$  Hz, 1H), 7.37 (t,  $J = 8.0$  Hz, 2H), 7.31 (t,  $J = 7.5$  Hz, 1H), 7.15 (t,  $J = 7.5$  Hz, 1H), 3.22 (q,  $J = 7.5$  Hz, 2H), 1.35 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  157.9, 153.4, 141.9, 137.5, 129.9, 129.1, 129.0, 127.3, 124.5, 123.3, 121.2, 120.0, 111.7, 17.3, 14.3; HRMS (ESI):  $m/z$  266.1166.

***N*-Phenyl-((3-propyl-benzo[*b*]furan)-2-yl)carboxamide 6k:** A yellow solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.39 (s, 1H), 7.68 (d,  $J = 7.8$  Hz, 2H), 7.59 (d,  $J = 7.8$  Hz, 1H), 7.44–7.21 (m, 5H), 7.09 (t,  $J = 7.4$  Hz, 1H), 3.13 (t,  $J = 7.4$  Hz, 2H), 1.76 (s,  $J = 7.4$ , 7.4 Hz, 2H), 1.00 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  157.9, 153.4, 142.3, 137.5, 129.4, 129.1, 128.4, 127.3, 124.5, 123.3, 121.4, 120.0, 111.7, 25.8, 23.1, 14.2; HRMS (ESI):  $m/z$  280.1329.

***N*-(2-Nitrophenyl)-((3-methyl-benzo[*b*]furan)-2-yl)carboxamide 6l:** A yellow solid; mp 177–179 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.64 (s, 1H), 9.00 (dd,  $J = 8.4$ , 1.2 Hz, 1H), 8.30 (dd,  $J = 8.4$ , 1.6 Hz, 1H), 7.73–7.68 (m, 1H), 7.66 (d,  $J = 8.0$  Hz, 1H), 7.60 (d,  $J = 8.0$  Hz, 1H), 7.52–7.48 (m, 1H), 7.36–7.32 (m, 1H), 7.25–7.21 (m, 1H), 2.70 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.6, 153.6, 142.1, 136.6, 135.9, 134.8, 129.6, 128.0, 126.0, 125.4, 123.5, 123.3, 122.1, 121.1, 112.1, 9.2; HRMS (ESI):  $m/z$  297.0859.

***N*-(2-Nitrophenyl)-((3-ethyl-benzo[*b*]furan)-2-yl)carboxamide 6m:** A yellow solid; mp 131–133 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.64 (s, 1H), 8.99 (d,  $J = 8.5$  Hz, 1H), 8.28 (d,  $J = 8.5$  Hz, 1H), 7.71–7.67 (m, 2H), 7.59 (d,  $J = 8.4$  Hz, 1H), 7.50–7.47 (m, 1H), 7.35–7.31 (m, 1H), 7.24–7.19 (m, 1H), 3.22 (q,  $J = 7.6$  Hz, 2H), 1.36 (t,  $J = 7.6$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 153.8, 141.5, 136.5, 135.9, 134.8, 131.5, 128.8, 127.9, 125.9, 123.4, 123.3, 122.1, 121.2, 112.2, 17.4, 14.2; HRMS (ESI):  $m/z$  311.1019.

***N*-(2-Nitrophenyl)-((3-propyl-benzo[*b*]furan)-2-yl)carboxamide 6n:** A yellow solid; mp 134–136 °C;  $^1\text{H}$  NMR (400

MHz,  $\text{CDCl}_3$ )  $\delta$  11.64 (s, 1H), 8.99 (d,  $J = 8.4$  Hz, 1H), 8.29 (dd,  $J = 8.4$ , 0.9 Hz, 1H), 7.71–7.67 (m, 2H), 7.60 (d,  $J = 8.4$  Hz, 1H), 7.48 (t,  $J = 7.6$  Hz, 1H), 7.33 (t,  $J = 7.4$  Hz, 1H), 7.22 (t,  $J = 7.8$  Hz, 1H), 3.18 (t,  $J = 7.6$  Hz, 2H), 1.81 (s,  $J = 7.6$ , 7.4 Hz, 2H), 1.04 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 153.7, 141.9, 136.6, 135.9, 134.8, 130.0, 129.2, 127.9, 125.9, 123.4, 123.3, 122.1, 121.4, 112.2, 25.8, 23.0, 14.1; HRMS (ESI):  $m/z$  325.1165.

***N*-(2-Naphthyl)-((3-methyl-benzo[*b*]furan)-2-yl)carboxamide 6o:** A White floc solid; mp 171–177 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.82 (s, 1H), 8.19 (d,  $J = 7.6$  Hz, 1H), 8.03 (d,  $J = 8.0$  Hz, 1H), 7.91 (d,  $J = 7.6$  Hz, 1H), 7.74 (d,  $J = 8.4$  Hz, 1H), 7.68 (d,  $J = 8.0$  Hz, 1H), 7.62–7.47 (m, 5H), 7.35 (t,  $J = 7.6$  Hz, 1H), 2.72 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.6, 153.4, 142.7, 134.2, 131.7, 129.9, 128.9, 127.5, 127.0, 126.5, 126.1, 125.8, 125.8, 124.0, 123.4, 121.1, 120.5, 120.4, 111.7, 9.1; HRMS (ESI):  $m/z$  302.1189.

## Results and Discussion

Our work began with the unexpected reaction of **3a** and 1-(2-hydroxyphenyl)ethanone (**4b**). At the beginning of the reaction, pyridin-2-amine (**1a**) (1.0 equiv) was reacted with chloroacetyl chloride (**2**) (1.5 equiv) in  $\text{K}_2\text{CO}_3/\text{CH}_2\text{Cl}_2$  at room temperature, giving 2-chloro-*N*-(pyridin-2-yl)acetamide (**3a**) as the product. The crude amide **3a** was then reacted with 1-(2-hydroxyphenyl)ethanone (**4b**) (1.2 equiv) in refluxing  $\text{K}_2\text{CO}_3/\text{CH}_3\text{CN}$ , afforded *O*-alkylated compound **5b**. However, under the basic condition, *O*-alkylated compound **5b** was quickly transformed into a kind of unknown white crystals in excellent yield, instead of undergoing Smiles rearrangement to give 1-(2-(pyridin-2-ylamino)phenyl)ethanone. Through complete analysis by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS, the unknown compound turned out to be 3-methyl-*N*-(pyridin-2-yl)benzo[*b*]furan-2-carboxamide (**6b**), as a new compound.

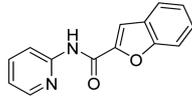
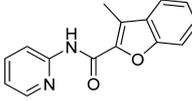
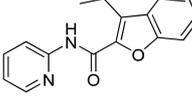
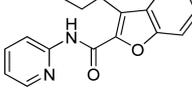
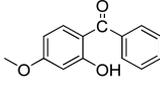
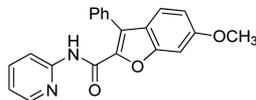
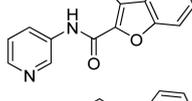
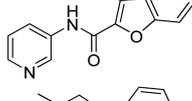
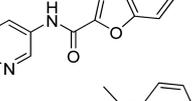
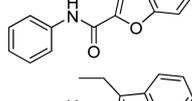
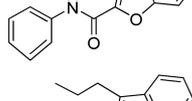
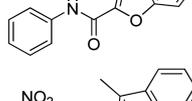
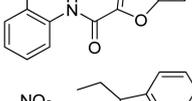
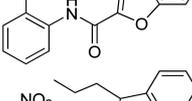
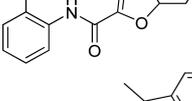
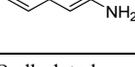
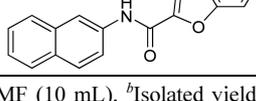
Inspired by above result, we then optimized the reaction condition. Since the best conditions of first two steps had

**Table 1.** Optimization of the reaction conditions to obtain **6b**<sup>a</sup>

Entry	Compound	Solvent	Base	Temperature (°C)	Time (min)	Yield (%) <sup>b</sup>
1	<b>5b</b>	DMF	$\text{K}_2\text{CO}_3$	80	–	trace
2	<b>5b</b>	DMF	$\text{Cs}_2\text{CO}_3$	80	30	72
3	<b>5b</b>	DMF	NaOH	80	55	51
4	<b>5b</b>	DMF	NaH	80	15	47
5	<b>5b</b>	$\text{CH}_3\text{CN}$	$\text{Cs}_2\text{CO}_3$	80	75	39
6	<b>5b</b>	DMF	$\text{Cs}_2\text{CO}_3$	50	45	20
7	<b>5b</b>	DMF	$\text{Cs}_2\text{CO}_3$	110	25	91
8	<b>5b</b>	DMF	$\text{Cs}_2\text{CO}_3$	150	10	85

<sup>a</sup>Reaction conditions: *O*-alkylated compound (**5b**) (1.0 mmol), base (1.5 mmol), solvent (10 mL). <sup>b</sup>Isolated yield after column purification in the condensation step.

**Table 2.** Synthesis of benzofuran derivatives **6a-o**<sup>a</sup>

Entry	Amine	<i>o</i> -Carbonyl phenol	Benzofuran	Yield (%) <sup>b</sup>
1	 <b>1a</b>	 <b>4a</b>	 <b>6a</b>	90
2	 <b>1a</b>	 <b>4b</b>	 <b>6b</b>	91
3	 <b>1a</b>	 <b>4c</b>	 <b>6c</b>	93
4	 <b>1a</b>	 <b>4d</b>	 <b>6d</b>	93
5	 <b>1a</b>	 <b>4e</b>	 <b>6e</b>	95
6	 <b>1b</b>	 <b>4b</b>	 <b>6f</b>	83
7	 <b>1b</b>	 <b>4c</b>	 <b>6g</b>	86
8	 <b>1b</b>	 <b>4d</b>	 <b>6h</b>	89
9	 <b>1c</b>	 <b>4b</b>	 <b>6i</b>	79
10	 <b>1c</b>	 <b>4c</b>	 <b>6j</b>	83
11	 <b>1c</b>	 <b>4d</b>	 <b>6k</b>	84
12	 <b>1d</b>	 <b>4b</b>	 <b>6l</b>	82
13	 <b>1d</b>	 <b>4c</b>	 <b>6m</b>	85
14	 <b>1d</b>	 <b>4d</b>	 <b>6n</b>	88
15	 <b>1e</b>	 <b>4b</b>	 <b>6o</b>	81

<sup>a</sup>Reaction conditions: *O*-alkylated compounds (**5**) (1.0 mmol), Cs<sub>2</sub>CO<sub>3</sub> (1.5 mmol), DMF (10 mL). <sup>b</sup>Isolated yield after column purification in the condensation step.

been investigated before, we herein focused on the conditions of intramolecular condensation reaction and results were summarized in Table 1. Firstly, the effect of base on the reaction was explored.  $\text{Cs}_2\text{CO}_3$  catalyzed reaction led to a very good yield of the desired benzofuran product **6b** (Table 1, entry 2), while using a range of other conventional bases as catalysts resulted in far less effectiveness (Table 1, entries 1, 3 and 4). Especially, only a trace amount of target molecule was obtained when the reaction underwent in  $\text{K}_2\text{CO}_3/\text{DMF}$  system, even with longer reaction time. The reactions with  $\text{NaOH}$  or  $\text{NaH}$  as the base in DMF generated the desired product in 51% and 47% yield, respectively, and the former reaction required very long reaction time. Then the  $\text{Cs}_2\text{CO}_3/\text{DMF}$  system assisted the reactions in higher yield and shorter reaction time, compared with the reactions in  $\text{Cs}_2\text{CO}_3/\text{CH}_3\text{CN}$  system (Table 1, entries 1, 5). Furthermore, DMF proved to be more efficient than the tested solvents such as dichloromethane and acetonitrile. Finally, the following investigation on the reaction condition suggested that  $\text{Cs}_2\text{CO}_3/\text{DMF}$  system at 110 °C is the best condition for this reaction (Table 1, entries 2, 6, 7 and 8).

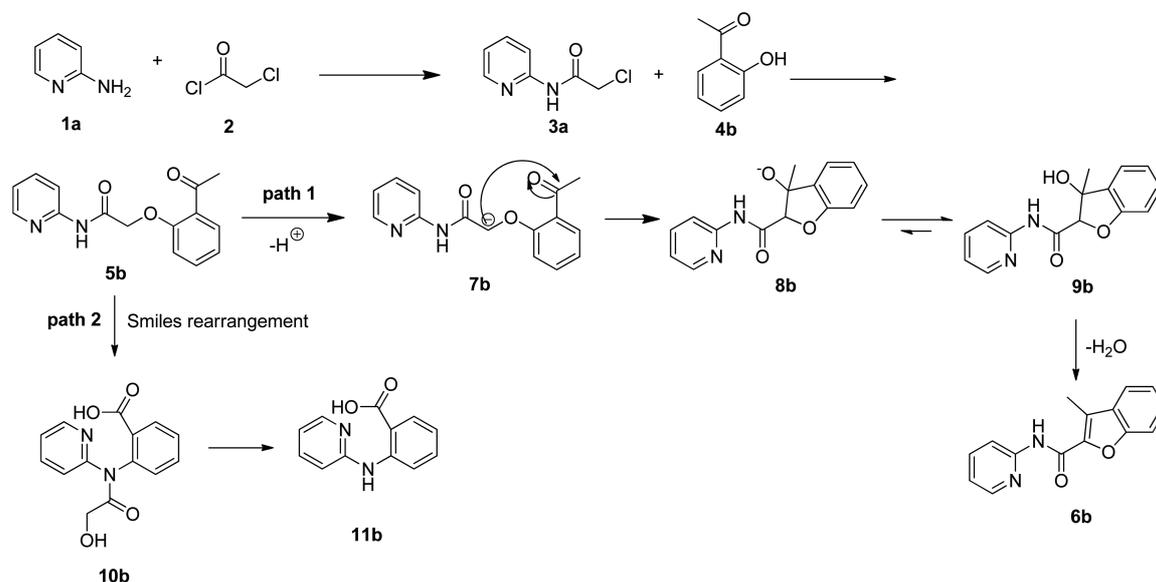
Under the optimized reaction conditions, we investigated the molecular diversity of novel substituted benzofurans. As depicted in Table 2, the yields of the condensation reaction of the new target compounds are between 79 and 95%. All the structures of newly synthesized compounds were clearly confirmed by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS spectral data, as well as by melting point. Using the above feasible reaction conditions, we are interested in investigating the effect of substituent introduced at various positions of the substrates of the reactions. As it can be seen from Table 2, a variety of *o*-hydroxy aryl ketones **4a-e** reacted smoothly with aniline, 2-nitroaniline, pyridin-2-amine or pyridin-3-amine to generate the corresponding target products in good yields with excellent selectivity. According to the experimental results, the *o*-hydroxy aryl ketone containing an ethyl

or *n*-propyl group gave higher yields of the desired benzofuran products than that of the *o*-hydroxy aryl ketone with a methyl group (Table 2, entries 2–4, 6–8, 9–11, 12–14). Such a comparison of the data indicated that the larger steric hindrance in alkyl substitution group of *o*-hydroxy aryl ketone unit contributed to significantly higher substrate conversion rate. Notably, we were pleased to observe that the reaction of (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (**4e**) and **3a** proceeded well and generated corresponding products (**6e**) in marvelous yield (95%).

To assess the generality of this procedure, we then introduced a set of amines including pyridyl, aryl and naphthyl amines to the reaction. When pyridin-3-amine reacted with *o*-hydroxy acetophenone (**4b**), we found that the desired product (**6f**) was generated, yielding 83% (Table 2, entry 6). The other substituted amines showed properties similar to pyridin-3-amine, which is in accordance with the data given in Table 2. It was worth pointing out that the reaction of other amines with 1-(2-hydroxyphenyl)ethanone (**4b**) generated the benzofuran derivatives, but in a lower yield than compound (**6b**) (Table 2, entries 6, 9, 12 and 15).

According to our previous studies,<sup>40</sup> a plausible mechanism, which accounted for the formation of benzofuran has been shown in Scheme 2 (exemplified by **6b**) to illustrate the experimental consequences. The *O*-alkylated product **5b** was easily formed by the nucleophilic attack of compound **4b** on the amide **3a**.

The compound **5b** could proceed in two paths (path 1 and path 2). In path 1, which was the main approach, the next step involved the conversion of product **5b** to the intermediate **7b** by intramolecular condensation, followed by the dehydration of compound **9b** led to the formation of benzofuran product (**6b**) under  $\text{Cs}_2\text{CO}_3/\text{DMF}$  system condition. However, in path 2, the *O*-alkylated product **5b** underwent Smiles rearrangement, affording *N*-azaaryl anilines (**11b**) as the by-product of the reaction. In support of the proposed



Scheme 2. Proposed mechanism for the formation of **6b**.

mechanism, the substrate with larger steric hindrance had difficulty in undergoing Smiles rearrangement, leading to the lower yield of the by-products and higher yield of the desired products. Furthermore, the *O*-alkylated products containing the pyridin-2-amine moiety could not undergo Smiles rearrangement well, while they afforded benzofurans in excellent yields. Therefore, the process involved two competitive reactions, and the direct condensation (path 1) was proven to be dominant.

### Conclusions

In conclusion, a direct access to a range of benzofurans *via* *N*-acylation, *O*-alkylation and intramolecular condensation was developed. This method afforded a convenient and efficient route for preparing a variety of benzofurans by the reaction of chloroacetamides from substituted arylamines or pyridinamine and *o*-hydroxy aryl ketone, with only a trace amount of *N*-azaaryl anilines as a by-product. The use of simple inexpensive starting materials, moderate to excellent yields, metal-free procedure, short reaction time, mild reaction conditions and easy purification procedure present the notable advantages of this method. Studies on the biological activities of these products and the further application of the reactions are currently undergoing in our laboratory.

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