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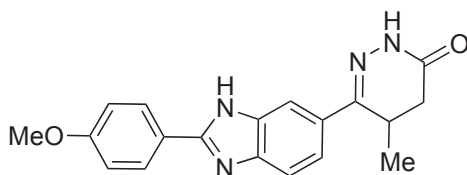
## PRACTICAL SYNTHESIS OF PIMOBENDAN

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**Abstract** – Pimobendan is a calcium sensitizer and a selective inhibitor of phosphodiesterase III (PDE3) with positive inotropic and vasodilator effects. Several attempts have been made to synthesize this drug. In this work, a facile synthetic route for the preparation of pimobendan from readily available starting materials and easily handled reagents is provided.

It is well known that serious damage of myocardial constringency might result in chronic heart failure and the heart could not transport blood to related tissues. This type of heart failure is called as congestive heart failure (CHF), a common and serious disease.<sup>1</sup> Mostly, partial lacking blood of myocardial, high blood pressure, non-emphractic myocardial pathological change and congenital heart attack could cause CHF.<sup>2</sup> Currently, the mortality caused by CHF is continuously increasing.<sup>3</sup> Thus, developing a better drug for treating CHF attracted great interest from scientists, and a lot of effective drugs for treating CHF were developed and marketed.<sup>4</sup> As a very impactful drug for treating CHF, pimobendan (**1**) (**Figure 1**) is an inotropic agent with phosphodiesterase inhibiting and calcium-sensitizing effects. This drug was developed by Boehringer Ingelheim and firstly came to the

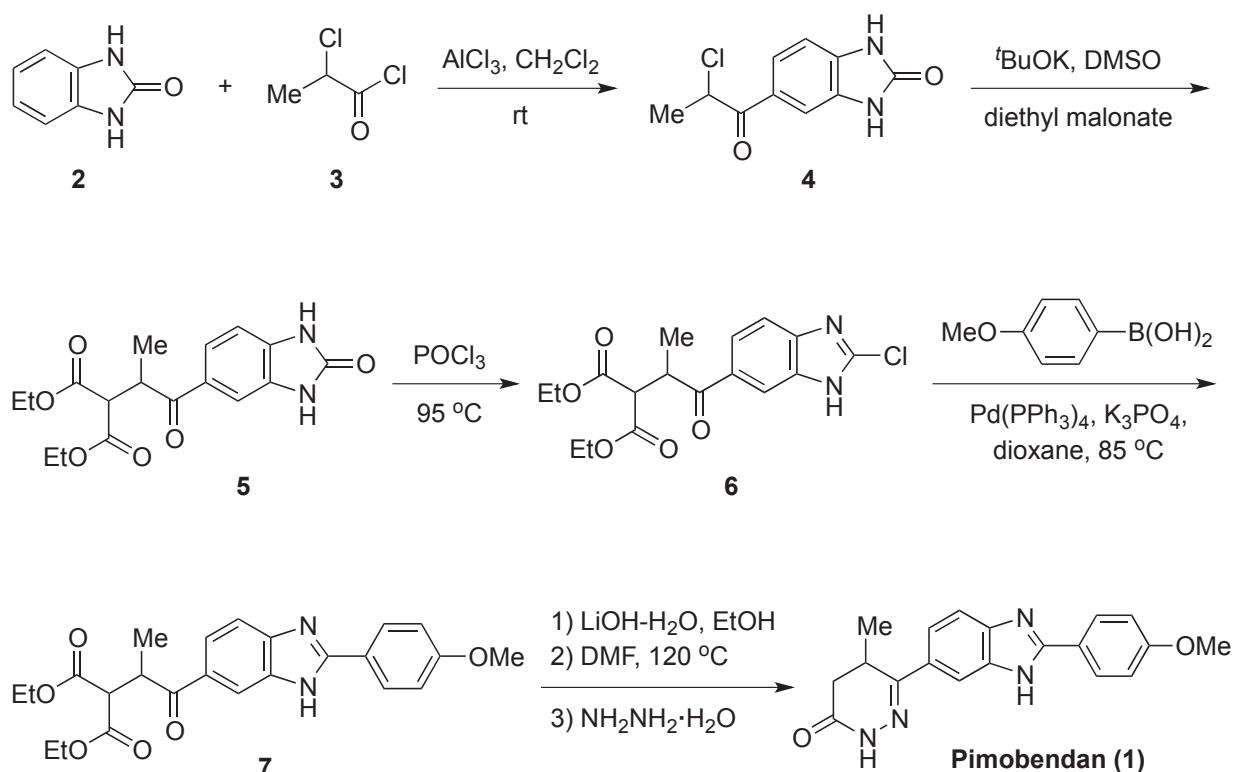


Pimobendan (**1**)

Figure 1

market in Japan in 1994.<sup>5</sup> Many studies have clearly demonstrated that pimobendan (**1**) is a positive inotropic vasodilator and is effective for treating myocardial transmural blood flow.<sup>6</sup>

Pimobendan (**1**) is a benzimidazole-pyridazinone derivative, which has attracted much attention from the synthetic community leading to the exploration of a number of synthetic routes. Early in 1982, Austel's group reported the first synthesis of pimobendan (**1**) from chlorobenzene.<sup>7</sup> Austel's synthesis of pimobendan (**1**) involved 13 steps of transformation, including Friedel-Crafts reaction, nitration, bromination, ammonolysis, hydrogenation, however the overall yield was very low. Piao and co-workers reported the synthesis of pimobendan (**1**) in 11 steps using acetanilide as starting material.<sup>8</sup> Piao's synthetic route featured the Friedel-Crafts reaction, Mannich reaction, cyanation, nitration, hydrogenation, however the overall yield was only 3%. In 1999, Xu et al. developed an improved synthetic approach to pimobendan (**1**) within 8 steps starting from acetanilide and 3-chloro-2-methylpropionyl chloride, with an overall yield of 17.3%.<sup>9</sup> More recently, Hao et al. reported a new synthesis route of pimobendan (**1**) in 6 steps utilizing acetanilide and methyl 4-chloro-3-methyl-4-oxobutanoate as starting materials.<sup>10</sup> However, 4-chloro-3-methyl-4-oxobutanoate was not easily available. Despite these great advances have been achieved, the development of more efficient and mild protocols for the synthesis of pimobendan (**1**) is still highly desirable. Herein, we would like to report an efficient synthesis of pimobendan (**1**) within seven steps of transformation without the use of difficult-to-operated and dangerous reaction conditions.<sup>11</sup> As shown in **Scheme 1**, our synthesis started from an AlCl<sub>3</sub>-mediated Friedel-Crafts reaction between readily available 2(3*H*)-benzimidazolone (**2**)<sup>12</sup> and 2-chloropropionyl chloride (**3**).<sup>13</sup> Gratifyingly, the Friedel-Crafts reaction proceeded smoothly with high regioselectivity to afford the desired chlorinated benzimidazolone (**4**) in 98% yield when reaction was conducted in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature. Then, nucleophilic substitution of compound (**4**) with diethyl malonate furnished diester (**5**) in excellent yield.<sup>14</sup> After screening a variety of bases, such as *t*-BuOK, DBU, K<sub>2</sub>CO<sub>3</sub>, NaH and KHMDS, we identified *t*-BuOK as an ideal base in this nucleophilic substitution, with the diester (**5**) obtained in 82% yield. Chlorination of intermediate (**5**) was performed with POCl<sub>3</sub> as a chlorination reagent, and compound (**6**) was delivered in 68% yield.<sup>15</sup> Next, Suzuki coupling between compound **6** and 4-methoxyphenylboronic acid was performed with tetrakis(triphenylphosphine)palladium as a catalyst and potassium phosphate as a base to provide the key intermediate (**7**) in 62% yield.<sup>16</sup> The key Suzuki coupling was extensively investigated in regards of catalyst loading, reaction temperature and reaction time. However, quite amount of material (**6**) was remained unconsumed with unknown side-products formed. Gratifyingly, the crude product could be facilely purified by filtration through silica, followed by refining and purification in methanol/heptane. Finally, hydrolysis of diester (**7**) with sodium hydroxide, followed by thermolytic decarboxylation and hydrazine-mediated cyclization afforded pimobendan (**1**) in 72% overall yield (3 steps).



In summary, a facile seven-step synthetic route for the preparation of pimobendan (**1**) has been achieved using readily available starting materials. This method provides obvious advantages, such as good yields, easy workup and purification, and the usage of readily available starting materials and easily handled reagents.

## EXPERIMENTAL

All the reagents and chemicals were pure, procured commercially and were used without further purification unless otherwise stated.  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were recorded with a Bruker WM-400 MHz spectrometer.  $\text{CDCl}_3$  was used as the NMR solvent. The chemical shifts ( $\delta$ -scale) for the  $^1\text{H-NMR}$  data are reported in ppm relative to TMS ( $\delta = 0.00$  ppm) or residual  $\text{CHCl}_3$  ( $\delta = 7.26$  ppm). The  $^1\text{H-NMR}$  data are reported as follows: chemical shift ( $\delta$ , ppm), multiplicity [s (singlet), d (doublet), t (triplet), m (multiplet or unresolved), br s (broad singlet)], coupling constant (s) in Hz, integration. Solvents for flash chromatography (FC) were of technical grade and distilled prior to use. Column chromatography was performed on silica gel (200–300 mesh) by eluting with EtOAc and hexanes. TLC was performed on glass-backed silica plates.

**5-(2-Chloropropanoyl)-1,3-dihydro-2H-benzimidazol-2-one (4):** Under  $\text{N}_2$  protection, 2(3H)-benzimidazolone **2** (20 g, 149 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (75 mL). The solution was cooled to

5 °C and AlCl<sub>3</sub> (48 g, 358 mmol) was carefully added as a solid in three equal portions over 10 min. Then, 2-chloropropionyl chloride **3** (21 g, 169 mmol) was added dropwise. After the addition, the reaction mixture was warmed up and stirred for 17 h at room temperature. Then, AlCl<sub>3</sub> (10 g, 75 mmol) was added and the reaction mixture was stirred for 2 h at 25 °C. The reaction mixture was slowly poured into a cooled mixture (pre-cooled to 5 °C) of heptane (300 mL) and H<sub>2</sub>O (300 mL). The result mixture was stirred for 15 h at 25 °C. Filtration of the mixture gave a wet cake, which was washed by H<sub>2</sub>O (200 mL), followed by heptane (100 mL). The resulting cake was dried over 50 °C for 3 h to give compound **4** (33 g, 98%); a brown solid; mp 142-144 °C; IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3197, 3095, 2987, 2857, 1750, 1674, 1473, 1276, 1201, 872, 708 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 1.60 (d, *J* = 4.8 Hz, 3H), 5.75 (q, *J* = 4.8 Hz, 1H), 7.06 (d, *J* = 6.3 Hz, 1H), 7.55 (s, 1H), 7.66 (d, *J* = 6.3 Hz, 1H), 10.98 (br s, 1H), 11.16 (br s, 1H) ppm; <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 20.62, 53.66, 108.63, 109.14, 123.86, 127.02, 130.37, 135.23, 155.90, 193.11 ppm; HRMS (ESI): calcd. for C<sub>10</sub>H<sub>10</sub>ClN<sub>2</sub>O<sub>2</sub> 225.0431 [M+H]<sup>+</sup>; found 225.0431. Anal. Calcd for C<sub>10</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 53.47; H, 4.04; Cl, 15.78; N, 12.47. Found: C, 53.40; H, 3.95; Cl, 15.71; N, 12.38.

**Diethyl 2-(1-oxo-1-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)propan-2-yl)malonate (5):** Under N<sub>2</sub> protection, to anhydrous DMSO (240 mL) was added *t*-BuOK (60 g, 535 mmol) and the resulting mixture was stirred for 20 min at 30 °C. Then, diethyl malonate (81 g, 506 mmol) was added dropwise over 1 h. After the addition, the mixture was stirred for another 1 h. Compound **4** (80 g, 356 mmol) was added in several portions. The resultant mixture was stirred for 2 h at 30 °C. AcOH (18 g, 300 mmol) was added to quench the reaction. Then, H<sub>2</sub>O (300 mL) and CH<sub>2</sub>Cl<sub>2</sub> (300 mL) were added. After being stirred for 30 min, the organic phase was isolated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 300 mL). The combined organic phases were washed with brine (2 × 200 mL). After removal of the solvent, the residue was purified by chromatography (hexanes/EtOAc = 3:1) on silica gel to afford compound **5** (102 g, 82%); a brown solid; mp 186-188 °C; IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 2982, 1750, 1674, 1627, 1473, 1369, 1303, 1199, 744 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 1.08 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 3.77 (d, *J* = 10.4 Hz, 1H), 3.98-4.11 (m, 3H), 4.18-4.24 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.49 (s, 1H), 7.72 (m, 1H), 10.98 (br s, 1H), 11.16 (br s, 1H) ppm; <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 13.67, 13.87, 15.97, 39.63, 54.50, 61.05, 61.27, 108.00, 108.11, 122.70, 127.73, 129.88, 134.34, 155.35, 167.71, 168.07, 199.54 ppm; HRMS (ESI): calcd. for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>6</sub> 349.1400 [M+H]<sup>+</sup>; found 349.1398. Anal. Calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.54; H, 3.78; N, 8.04.

**Diethyl 2-(1-(2-chloro-1*H*-benzo[*d*]imidazol-6-yl)-1-oxopropan-2-yl)malonate (6):** A mixture of compound **5** (10 g, 28.7 mmol) and POCl<sub>3</sub> (50 mL, 536.4 mmol) was heated to 95 °C, and was stirred for

5 h at 95 °C. Then, the reaction mixture was cooled to room temperature and POCl<sub>3</sub> was removed under reduced pressure. To the residue were added CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and Na<sub>3</sub>PO<sub>4</sub>·NaH<sub>2</sub>PO<sub>4</sub> buffer (pH = 6.5, 200 mL). After separating the organic phase, the obtained organic phases were washed with brine (2 × 100 mL) and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> (50 g). Filtration and removal of the solvent, the residue was purified by chromatography (heptane/EtOAc = 5:2) on silica gel to afford compound **6** (7.2 g, 68%); a brown solid; mp 156-158 °C; IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 2979, 1734, 1675, 1499, 1369, 1301, 1248, 744 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 1.07 (t, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 7.2 Hz), 1.23 (t, *J* = 7.0 Hz, 3H), 3.80 (d, *J* = 10.4 Hz, 1H), 3.98-4.08 (m, 2H), 4.17-4.24 (m, 3H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.90-7.92 (m, 1H), 8.22 (s, 1H), 13.68 (br s, 1H) ppm; <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.61, 12.81, 14.83, 38.87, 53.45, 60.02, 60.22, 110.36, 116.89, 121.99, 127.52, 128.50, 137.2, 140.43, 166.70, 166.99, 199.23 ppm; HRMS (ESI): calcd. for C<sub>17</sub>H<sub>20</sub>ClN<sub>2</sub>O<sub>5</sub> 366.0982 [M+H]<sup>+</sup>; found 367.0985. Anal. Calcd for C<sub>17</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>5</sub>: C, 55.67; H, 5.22; Cl, 9.66; N, 7.64. Found: C, 55.69; H, 5.22; Cl, 9.65; N, 7.61.

**Diethyl 2-(1-(2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-6-yl)-1-oxopropan-2-yl)malonate (7):** A mixture of 4-methoxyphenylboronic acid (2.65 g, 17.4 mmol), K<sub>3</sub>PO<sub>4</sub> (11.5 g, 54.2 mmol) and anhydrous dioxane (150 mL) was stirred at 30 °C for 1 h. Then, the solution of compound **6** (5.0 g, 13.6 mmol) in anhydrous dioxane (50 mL) was added. Under stirring, the gas in the reaction system was replaced with N<sub>2</sub> three times, and under N<sub>2</sub> protection, tetrakis(triphenylphosphine)palladium (1.6 g, 1.38 mmol) was added. Then, the reaction was heated to 85 °C and stirred for 15 h. The reaction mixture was cooled to room temperature. Removal of the solvent under reduced pressure gave a residue. To the residue were added CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and H<sub>2</sub>O (80 mL) and the resultant mixture was stirred for 2 h. After the organic phase was separated, the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 mL). The combined organic phases were washed with brine (2 × 30 mL). After removal of all the solvent, the residue was purified by chromatography (hexanes/EtOAc = 4:1) on silica gel to afford the compound **7** (3.7 g, 62%); a white solid; mp 152-154 °C; IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 2979, 1734, 1675, 1499, 1369, 1301, 1248, 744 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 1.08 (t, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 3.82 (dd, *J* = 2.4, 3.0 Hz, 1H), 3.86 (s, 3H), 3.99-4.10 (m, 2H), 4.20-4.28 (m, 3H), 7.15 (d, *J* = 5.6 Hz, 2H), 7.67 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 8.10-8.33 (m, 3H), 13.13 (d, *J* = 9.6 Hz, 1H) ppm; <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 14.24, 14.44, 16.59, 40.42, 55.12, 55.89, 61.59, 61.81, 111.73, 115.01, 118.84, 120.14, 122.39, 122.51, 123.34, 139.34, 144.18, 148.29, 154.14, 155.29, 161.71, 168.32, 168.68, 200.86 ppm; HRMS (ESI): calcd. for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub> 439.1869 [M+H]<sup>+</sup>; found 439.1872. Anal. Calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.76; H, 5.92; N, 6.39.

**Pimobendan (1):** To a mixture of compound **7** (3.0 g, 6.85 mmol) and EtOH (50 mL) was added the solution of NaOH (1.1 g, 27.5 mmol) in H<sub>2</sub>O (15 mL). The reaction mixture was stirred overnight at room

temperature. After that, H<sub>2</sub>O (100 mL) was added and 3M HCl was added to the reaction mixture to adjust pH value to 2. The reaction mixture was extracted with EtOAc (3 × 70 mL). Removal of the combined organic phases gave a residue. To the obtained residue was added DMF (25 mL) and the resultant solution was heated to 125 °C and stirred for 6 h. DMF was then removed under reduced pressure to afford a residue. To this residue was added EtOH (25 mL) and hydrazine hydrate (5 mL). The reaction mixture was then heated to reflux for 12 h. The reaction mixture was cooled to room temperature. The solvent was removed under high vacuum to give a residue. To the obtained residue was added DMF (5 mL) and the resultant mixture was heated to 60 °C. Then, H<sub>2</sub>O (15 mL) was added dropwise and the mixture was cooled to room temperature. Filtration gave a cake, which was washed with EtOH (5 mL). The resulting cake was subjected to vacuum dry at 50 °C to give pimobendan (**1**) (1.65 g, 72%); a white solid; mp 147-150 °C; IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3232, 2902, 1670, 1610, 1491, 1253, 1181, 1029, 836, 812 cm<sup>-1</sup>; <sup>1</sup>H-NMR (600 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 1.15 (d, *J* = 7.2 Hz, 3H), 2.28 (d, *J* = 16.2 Hz, 1H), 2.75 (dd, *J* = 16.8, 6.6 Hz, 1H), 3.52 (m, 1H), 3.86 (s, 3H), 7.15 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.98 (br s, 1H), 8.17 (m, 2H), 10.98 (s, 1H), 12.94 (br s, 1H) ppm; <sup>13</sup>C-NMR (125 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 16.07, 27.48, 33.68, 55.35, 108.44, 111.17, 114.43, 118.38, 119.76, 122.40, 128.17, 128.11, 128.97, 135.86, 144.95, 152.85, 153.47, 160.81, 166.32 ppm; HRMS (ESI): calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>4</sub>O<sub>2</sub> 335.1508 [M+H]<sup>+</sup>; found 335.1502. Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.23; H, 5.46; N, 16.79.

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