

## Protecting group-free synthesis of the fungicide Mandipropamid

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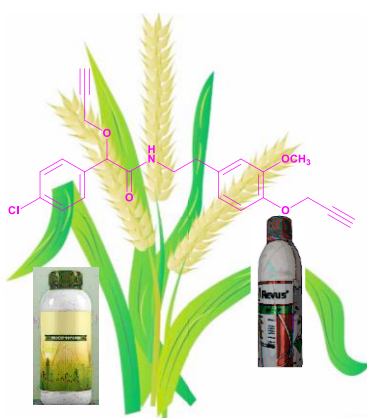
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### Abstract

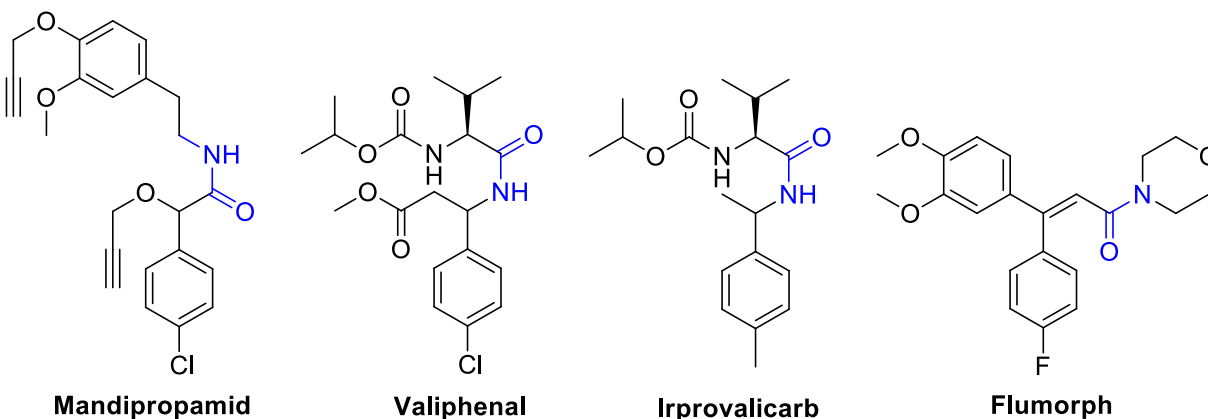
A simple and efficient protecting group free synthesis of a relatively new fungicide Mandipropamid has been achieved in five steps, with an excellent overall yield. The synthesis started from commercially available starting materials like vanillin and *p*-chloroacetophenone. The key steps involved in the synthesis are the Henry and Cannizzaro reactions, as well as amide formation through a carboxylic acid-amine coupling step.



**Keywords:** Mandipropamid, fungicide, Cannizzaro reaction, Henry reaction

## Introduction

Mandipropamid is a fungicide belonging to the mandelamide class (Figure 1) and was developed by Syngenta for the control of oomycete fungal pathogens in different crops.<sup>1-4</sup> The oomycetes are a group of fungal organisms with around 800 different species. Indeed, some of them are devastating plant pathogens, which causes foliar diseases like blights, mildews, rust, mold and spots etc., in various crops like wheat, potato, grapes, soya, cereals, fruits, tomatoes, cucurbits, vegetables and ornamentals.<sup>5-8</sup> The relatively new fungicide mandipropamid, plays a vital role in controlling oomycete foliar diseases by inhibiting the cellulose synthesis.<sup>9-10</sup>

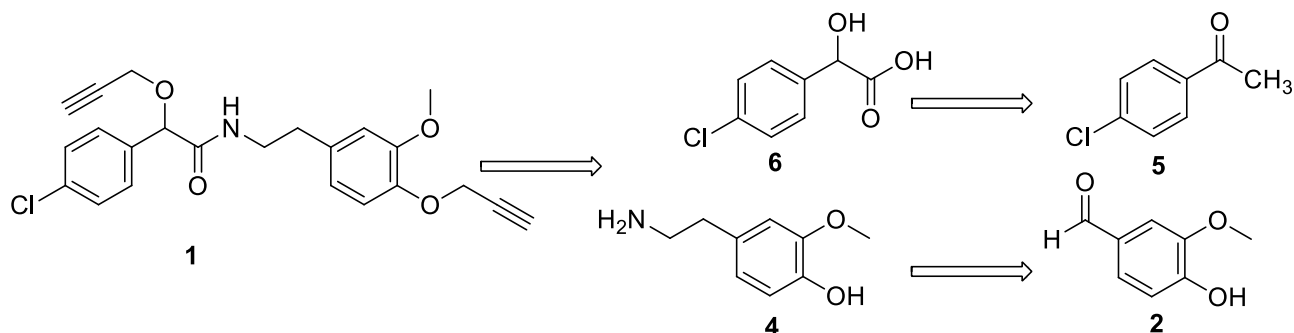


**Figure 1.** Amide based fungicides.

Due to its high demand, because of its effectiveness in the protection of crops from fungal diseases, mandipropamid has attracted the interest of synthetic chemists with the aim of developing efficient syntheses.<sup>1,11-13</sup> To the best of our knowledge, this is first report on the synthesis of mandipropamid starting from vanillin and *p*-chloroacetophenone in a highly convergent manner. As part of our regular research program in synthesis of biologically active molecules, herein we report a simple and protecting group free synthesis of mandipropamid.<sup>14-18</sup>

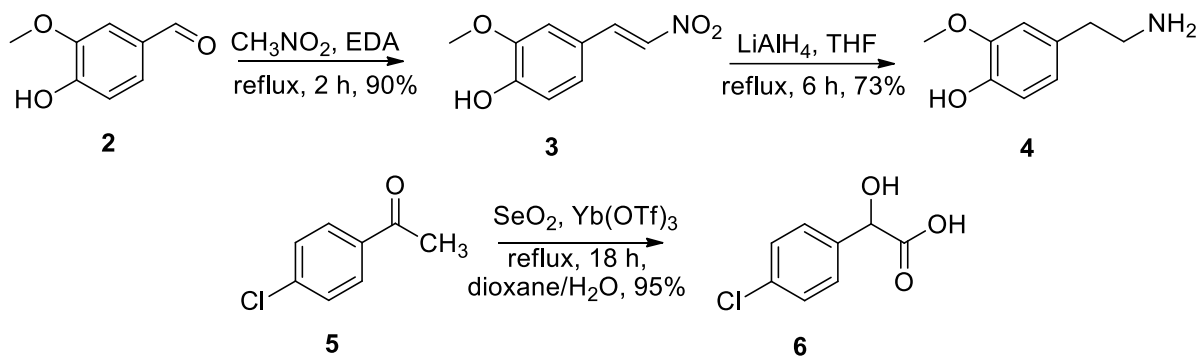
## Results and Discussion

Following our interest in the process development of crop protection agents, we herein report a simple and efficient method for the synthesis of mandipropamid, which is used as a fungicide for the control of foliar oomycete pathogens. The present method does not require any protection and deprotection of functional groups and is highly convergent. As shown in Scheme 1, mandipropamid (**1**) could be synthesized from amine **4** and  $\alpha$ -hydroxy acid **6**. These intermediates could be synthesized from vanillin (**2**) and *p*-chloroacetophenone (**5**) using Henry and Cannizzaro reaction protocols respectively.



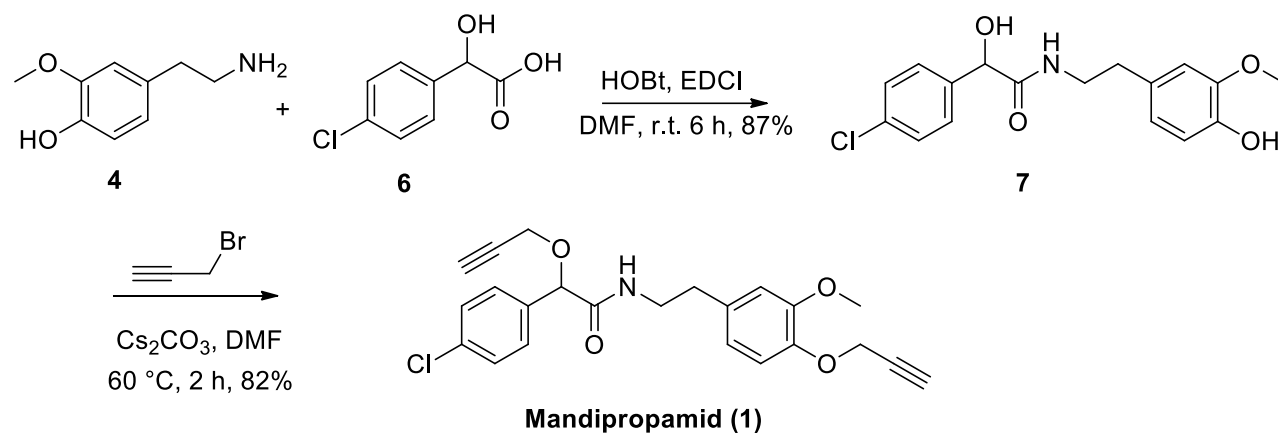
**Scheme 1.** Retrosynthesis of mandipropamid.

Accordingly, we began the synthesis of mandipropamid (**1**) from the readily available vanillin (**2**), which was converted into nitroalkene (**3**) in 90% yield, under Henry reaction conditions (Scheme 2).<sup>19</sup> One-pot reduction of both double bonds and the nitro functionality in **3**, using lithium aluminium hydride, afforded the desired amine, 4-(2-aminoethyl)-2-methoxyphenol (**4**) in 73% yield.<sup>20</sup> The carboxylic acid fragment **6** was prepared by a modified Cannizzaro protocol. This started from commercially available, *p*-chloroacetophenone (**5**), which was treated with selenium dioxide in the presence of the Lewis acid, ytterbium triflate, in a solvent mixture of dioxane-water (3:1) at 90 °C. This protocol afforded the *p*-chloromandelic acid in excellent yield, as shown in Scheme 2.<sup>21</sup>



**Scheme 2.** Synthesis of key fragments 4 and 6.

Next, we attempted the coupling of amine **4** with the carboxylic acid **6** using EDCI and HOBT. This reaction proceeded smoothly at room temperature to afford the amide **7** in 87% yield after 6 h.<sup>22-24</sup> Finally, the *O*-propargylation of both hydroxyl groups of amide **7** was accomplished with propargyl bromide in the presence of Cs<sub>2</sub>CO<sub>3</sub> in DMF at 60 °C. After 2 h reaction time, the target molecule mandipropamid (**1**) was isolated in 82% yield after work-up, as described in Scheme 3.<sup>25</sup> The structure of this product was confirmed by spectral data and by comparison with the data reported in the literature.<sup>12</sup>



Scheme 3. Mandipropamid synthesis.

## Conclusions

In conclusion, we have developed a protection free strategy for the synthesis of mandipropamid from readily available precursors like vanillin and *p*-chloroacetophenone. This synthetic route is short, simple and potentially scalable and also offers several advantages such as cleaner reaction profiles, operational simplicity and ease of work up with good to high conversions (73–95%), which makes this synthetic route a useful contribution to preparative methods for the important crop protection agent, mandipropamid.

## Experimental Section

**General.** All air and moisture sensitive reactions were carried out under nitrogen atmosphere. Oven dried glass apparatus were used to perform all the reactions. Dry solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as received. Purification of compounds was carried out by column chromatography using silica gel (60-120 mesh). <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> or CD<sub>3</sub>OD solvents on 400 MHz and 500 MHz spectrometers, <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> or CD<sub>3</sub>OD solvents on 101 MHz and 126 MHz spectrometers, at ambient temperature and using TMS as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer 683 infrared spectrophotometer, as neat samples. High resolution mass spectra (HRMS) [ESI<sup>+</sup>] were obtained using either a TOF or a double focusing spectrometer. Melting points were obtained using an Optics Technology melting point apparatus.

**(E)-2-Methoxy-4-(2-nitrovinyl)phenol (3).** Ethylene diamine (40 μL, 0.65 mmol) was added to a solution of vanillin (5.0 g, 33 mmol) in nitromethane (20.0 mL, 329 mmol) and the resulting reaction mixture was heated at reflux for 2 h. Volatiles were removed by vacuum distillation to give a yellowish solid, which was triturated in aqueous methanol (CH<sub>3</sub>OH-H<sub>2</sub>O, 2:1, 20 mL). Pale yellow crystals were collected by filtration and rinsed twice with aqueous methanol (CH<sub>3</sub>OH-H<sub>2</sub>O, 1:1, 2 × 10 mL). After being dried overnight under warm air, the compound **3** was obtained as a yellow solid.

Yield: 5.76 g (90%); mp 164–165 °C.; IR (neat): ν 3071, 2951, 1604, 1482, 1363, 1295, 1210, 1161, 1021, 972, 815, 607 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.96 (d, *J* 13.6 Hz, 1H), 7.52 (d, *J* 13.6 Hz, 1H), 7.14 (dd, *J* 8.2, 1.9

Hz, 1H), 6.99 (dd, *J* 10.8, 5.1 Hz, 2H), 6.05 (s, 1H), 3.96 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 149.7, 147.1, 139.5, 135.0, 124.9, 122.4, 115.3, 110.1, 56.1; HRMS (ESI): *m/z* [M-H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>8</sub>NO<sub>4</sub>: 194.0459; found: 194.0464.

**4-(2-Aminoethyl)-2-methoxyphenol (4).** A solution of compound **3** (5.0 g, 26 mmol) in THF (50 mL) was added dropwise into a stirred suspension of LiAlH<sub>4</sub> (4.86 g, 128 mmol) in THF (40 mL) at 0 °C over 20 min. After the addition was complete, the stirred mixture was heated at reflux for 8 h. The mixture was cooled to 0 °C by an ice-bath. While the mixture was vigorously stirred, water (20 mL) was added dropwise into the reaction mixture over 30 min, and NaHCO<sub>3</sub> (10.8 g, 128 mmol) was slowly added into the mixture at 0 °C. The ice-bath was removed, and the mixture was further stirred and heated at reflux for 3h. The mixture was cooled to room temperature and filtered through celite. The filter cake was washed twice with MeOH (2 × 30 mL). The combined filtrate was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give a brown viscous oil, which was purified by neutral alumina (Al<sub>2</sub>O<sub>3</sub>) column chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>-CH<sub>3</sub>OH, 90:10) to afford the pure compound **4**, as a white solid.

Yield: 3.12 g (73%); mp 157–158 °C; IR (neat): ν 3150, 2918, 2846, 2616, 2502, 1594, 1482, 1227, 1125, 1021, 801 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 6.78 (d, *J* 1.9 Hz, 1H), 6.72 (d, *J* 8.0 Hz, 1H), 6.64 (dd, *J* 8.0, 1.9 Hz, 1H), 3.84 (s, 3H), 2.84 (t, *J* 7.1 Hz, 2H), 2.66 (t, *J* 7.1 Hz, 2H); <sup>13</sup>C NMR (126 MHz, CD<sub>3</sub>OD): δ 147.6, 144.7, 130.8, 120.8, 114.8, 112.0, 54.9, 42.9, 38.1; HRMS (ESI): *m/z* [M+H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>14</sub>NO<sub>2</sub>: 168.1019; found: 168.1019.

**2-(4-Chlorophenyl)-2-hydroxyacetic acid (6).** To a solution of 4-chloroacetophenone **5** (1.0 g, 6.5 mmol) in a 3:1 mixture dioxane-H<sub>2</sub>O (12 mL), SeO<sub>2</sub> (1.4 g, 13 mmol) and Yb(OTf)<sub>3</sub> (0.4 g, 0.7 mmol) were added and the resulting suspension was stirred at 90 °C for 18 h. The mixture was filtered through celite bed, the filtrate was diluted with NaOH (aq.1%, 20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL). The aqueous solution was acidified to pH=1, with 10% aq. HCl and then extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residual pale-yellow oil was purified by silica gel column chromatography, eluting with a gradient mixture of EtOAc-hexane (80:20) to afford, the pure compound **6**, as a white solid.

Yield: 1.15 g (95%); mp 115–116 °C.; IR (neat): ν 3403, 2996, 2832, 2602, 1718, 1486, 1256, 1223, 1184, 1059, 908, 819, 747 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.42 - 7.33 (m, 4H), 5.23 (s, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 176.3, 136.1, 134.8, 129.0, 128.1, 72.0; HRMS (ESI): *m/z* [M-H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>6</sub>ClO<sub>3</sub>: 185. 0011; found: 185.0006.

**2-(4-Chlorophenyl)-2-hydroxy-N-(4-hydroxy-3-methoxyphenethyl)acetamide (7).** To a stirred solution of 1-hydroxybenzotriazole (HOBt) (0.54 g, 4.0 mmol) and *N*-(3-dimethyl aminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.61 g, 3.2 mmol) in DMF (10 mL) was added compound **6** (0.5 g, 2.7 mmol) at room temperature. After 15 min, the amino compound **4** (0.66 g, 4.0 mmol) was added, the resulting mixture was stirred at room temperature for 6 h. After completion, the reaction mixture was poured into ice-cold water (20 mL) and the whole was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residual viscous oil was purified by silica gel column chromatography by elution with EtOAc/hexane (1:1) afford, the pure compound **7**, as a white solid.

Yield: 0.78 g (87%); mp 108–110 °C.; IR (neat): ν 3387, 2930, 1653, 1519, 1452, 1268, 1228, 1121, 1080, 1028, 907, 725, 640 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.30 (d, *J* 8.5 Hz, 2H), 7.23 (d, *J* 8.5 Hz, 2H), 6.79 (d, *J* 8.0 Hz, 1H), 6.59 (d, *J* 1.7 Hz, 1H), 6.51 (dd, *J* 8.0, 1.7 Hz, 1H), 6.20 (s, 1H), 5.58 (s, 1H), 4.93 (s, 1H), 3.81 (s, 3H), 3.69 (s, 1H), 3.55–3.41 (m, 2H), 2.76–2.62 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 171.5, 146.6, 144.3, 137.8, 134.4, 130.0, 128.9, 128.0, 121.3, 114.4, 111.0, 73.4, 55.8, 40.6, 35.1; HRMS (ESI): *m/z* [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>19</sub>ClNO<sub>4</sub>: 336.0997; found: 336.0997.

**2-(4-Chlorophenyl)-N-[3-methoxy-4-(prop-2-yn-1-yloxy)phenethyl]-2-(prop-2-yn-1-yloxy)acetamide (1).** To a solution of compound **7** (0.20 g, 0.59 mmol) in DMF (4 mL), Cs<sub>2</sub>CO<sub>3</sub> (0.48 g, 1.5 mmol) and propargyl bromide

(0.13 mL, 1.5 mmol, 80 wt.% in toluene) were added and the resulting suspension was stirred at 60 °C for 2 h. After completion, the reaction mixture was poured into ice-cold water (5 mL) and the whole was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residual viscous oil was purified by silica gel column chromatography (eluent: EtOAc-hexane, 30:70) to afford, the target molecule **1**, as a white solid.

Yield: 0.20 g (82%); mp 97–98 °C [96–97 °C]<sup>12</sup>; IR (neat):  $\nu$  3293, 2924, 2860, 2355, 1668, 1596, 1517, 1455, 1263, 1220, 1145, 1086, 1021, 905, 723, 646 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.35–7.24 (m, 4H), 6.97 (d, *J* 8.0 Hz, 1H), 6.76 (t, *J* 5.6 Hz, 1H), 6.73–6.68 (m, 2H), 4.96 (s, 1H), 4.75 (d, *J* 2.4 Hz, 2H), 4.19 (dd, *J* 15.8, 2.4 Hz, 1H), 3.97 (dd, *J* 15.8, 2.4 Hz, 1H), 3.84 (s, 3H), 3.62–3.45 (m, 2H), 2.79 (td, *J* 6.9, 2.3 Hz, 2H), 2.51 (t, *J* 2.4 Hz, 1H), 2.48 (t, *J* 2.4 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  169.5, 149.7, 145.5, 134.6, 134.6, 132.6, 128.8, 128.6, 120.5, 114.6, 112.3, 79.6, 78.7, 78.1, 75.8, 75.7, 56.8, 56.4, 55.8, 40.2, 35.2; HRMS (ESI): *m/z* [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>23</sub>ClNO<sub>4</sub>: 412.1273; found: 412.1310.

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## Supplementary Material

Available as separate file downloadable from journal website.

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