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Synthesis of crop protection agent mandipropamid

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A simple synthesis of a novel fungicide mandipropamid has been achieved in six steps, with an overall yield of 43%. Synthesis has been carried out from commercially available starting materials, 4-chloroacetophenone and vanillin. The key steps involved in the synthesis are Cannizzaro and Henry reactions, amide bond formation and *O*-propargylation.

Keywords: Mandipropamid, Fungicide, Cannizzaro reaction, Henry reaction, Amide

Crop protection agent, mandipropamid belongs to carboxylic acid amide (CAA) chemical class of compounds and used for the control of oomycete fungal pathogens[1-3]. The oomycetes or water molds, are a group of fungal organisms with around 800 different species. Some of them are the most devastating plant pathogens known and cause foliar diseases like blights, mildews, rust, mold, spots, *etc*., on crop plants like wheat, potato, grapes, soya, cereals, fruits, tomatoes, cucurbits, vegetables and ornamentals[4-7]. The control of these fungal diseases is not easy, because cell walls of the pathogens are made up of cellulose, glucans and hydroxyproline. The repeated use of chemical fungicides has led to resistance. The CAA compounds (Fig. 1) are showing tremendous activity against oomycete foliar disease by inhibiting the cellulose synthesis. Mandipropamid plays a vital role for recessive mutation in PvCesA3 to resistance and thus found as the best controlling agent for these fungal diseases[8,9].

In view of its bio-activity, fascination with the structural aspects of the molecule, and growing application in crop protection, mandipropamid has attracted the attention of synthetic chemists globally and led to its synthesis by various routes[10-12]. 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[13-18].

Results and Discussion

As shown in the retrosynthetic analysis (Scheme 1), the target molecule mandipropamid, could be derived from compound **5** and **8**. These intermediates could be synthesized from 4-chloroacetophenone **1** and vanillin **6** using Cannizzaro and Henry protocols respectively.

As per the plan, synthesis of mandipropamid started with readily available 4-chloroaceto phenone **1**. A modified Cannizzaro protocol was adopted for tandem one-pot oxidation with selenium dioxide, in presence of Lewis acid catalyst ytterbium triflate in a mixture of solvents [dioxane-water (3:1)] at 90°C to furnish, α-hydroxyacrylacetic acid **2**, in 93% yield[20]. Thereafter, further esterification in presence of *p*-TSA in methanol afforded compound **3** in excellent yields. The ester **3** was reacted with propargyl bromide and K_2CO_3 in acetonitrile to get compound **4**. The obtained propargylated product was subjected to ester hydrolysis with $LiOH.H_2O$ to furnish compound **5**. The other fragment, phenyl ethyl amine was prepared from commercially available starting material vanillin **6**. Vanillin was subjected to Henry reaction for making carbon-carbon bond under basic (ethylene diamine) conditions to yield nitroalkene **7** in excellent yields[19]. The obtained compound **7** was reacted with LAH for simultaneous reduction of double bond, as well as nitro group to afford, 4-(2-amino ethyl)-2-methoxyphenol **8** in very good yields[20].

Thereafter, the obtained fragments **5** and **8** were coupled in the presence of HOBt and EDCI at RT for 6 h to afford compound **9** in 84% yield[21-23]. The final step of the synthesis was *O*-propargylation of **9**, which was achieved by stirring with propargylbromide in

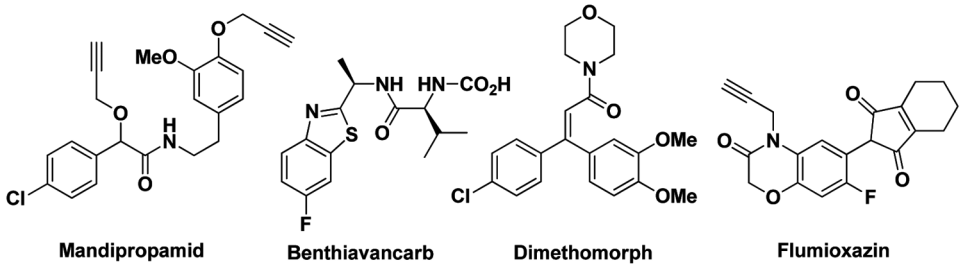
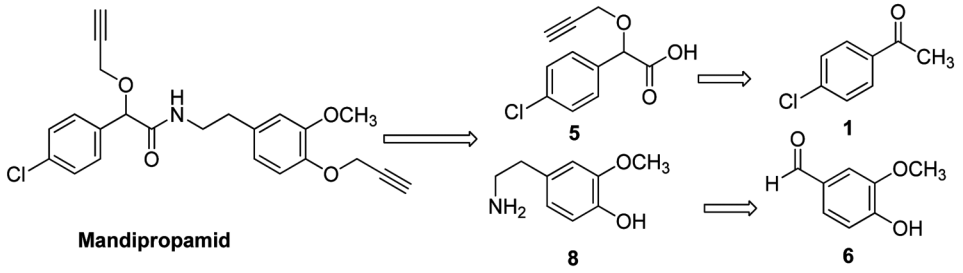
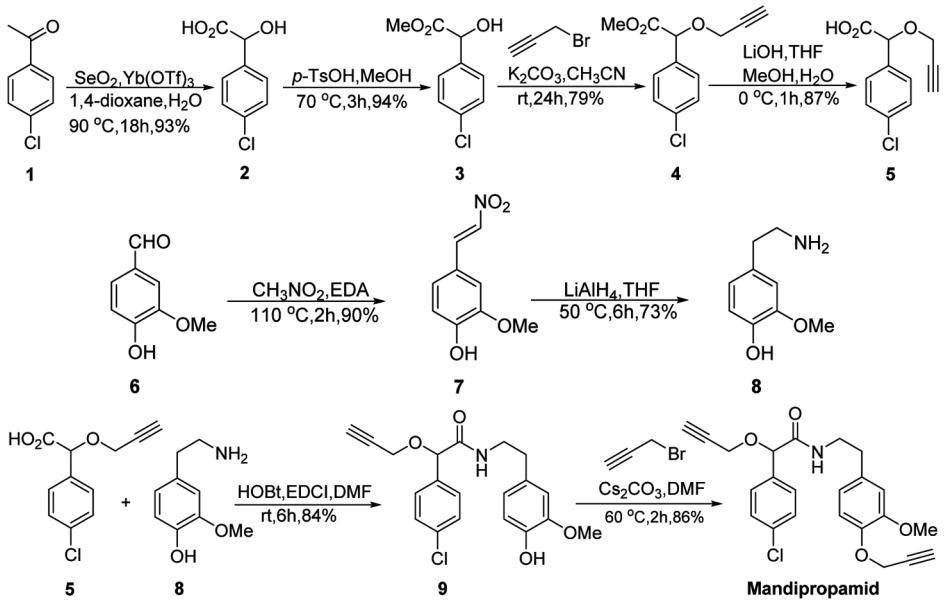


Fig. 1



Scheme 1



Scheme 2

presence of Cs_2CO_3 in DMF at 60 °C for 2 h to afford the target molecule mandipropamid in 86% yield, as shown in Scheme 2 [24]. Formation of the final product was confirmed from its spectral data and comparison with reported literature[11].

Experimental Section

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 over silica gel (60-120 mesh). ^{1}H NMR spectra were recorded in $CDCl_3$ and CD_3OD solvents on 400 MHz and 500 MHz spectrometers. ^{13}C NMR spectra were recorded in $CDCl_3$ and CD_3OD solvents on 101 MHz and 126 MHz spectrometers, at ambient temperature, using TMS as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer 683

infrared spectrophotometer, as neat. High resolution mass spectra (HRMS) [ESI$^+$] were obtained using either a TOF or a double focusing spectrometer. Melting points were obtained using Optics Technology.

2-(4-Chlorophenyl)-2-hydroxyacetic acid, 2: To a stirred solution of 4-chloroacetophenone (2 g, 6.5 m mol) and SeO_2 (2.9 g, 26 mmol) in 1,4-dioxane-H_2O (20 mL, 3:1, v/v) mixture was added $Yb(OTf)_3$ (0.81 g, 1.3 mmol) and the resulting reaction mixture was stirred under reflux for 18 h. The mixture was filtered through a short pad of celite, the filtrate diluted with aq.NaOH (20 mL) and extracted with CH_2Cl_2 (2×20 mL). The aqueous solution was acidified to *p*H 1 with HCl (10%) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to furnish a yellow oil. The crude product was purified by column chromatography over silica gel (60-120 mesh) eluting with hexane-EtOAc (1:1) mixture to afford hydroxy acetic acid **2** as a white solid. Yield 2.24 g, 93%. M.p.115-116 °C. IR (neat): 3403, 2996, 2832, 2602, 1718, 1486, 1256, 1223, 1184, 1059, 908, 819, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 - 7.33 (m, 4H), 5.23 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3, 136.1, 134.8, 129.0, 128.1, 72.0; HRMS (ESI): *m/z* [M-H]$^+$ Calcd for $C_8H_6ClO_3$: 185.5835. Found: 185.5841.

Methyl-2-(4-chlorophenyl)-2-hydroxyacetate, 3: To a stirred solution of the above acid **2** (2 g, 10.7 m mol) in MeOH (20 mL) was added *p*-TsOH.H_2O (0.2 g, 1.1 mmol). The mixture was stirred at reflux for 3 h, then MeOH was evaporated and CH_2Cl_2 was added. The resulting solution was washed with a sat. $NaHCO_3$ and brine dried over Na_2SO_4 and evaporated to give the crude product as colorless oil. It was purified by column chromatography over silica gel eluting with hexane-EtOAc (4:1) mixture to afford, product **3**, as a white solid. Yield 2.02 g, 94%. M.p.51-52°C. IR (neat): 3528, 3441, 3032, 2978, 2827, 1738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.31 (m, 4H), 5.15 (d, *J* = 4.8 Hz, 1H), 3.75 (s, 3H), 3.53 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 136.6, 134.4, 128.8, 127.9, 72.2, 53.2.

Methyl-2-(4-chlorophenyl)-2-(prop-2-yn-1-yloxy) acetate, 4: To a stirred solution of ester **3** (1.5 g, 7.5 mmol) in acetonitrile (15 mL) was added K_2CO_3 (1.34 g, 9.7 mmol) and stirred at RT for 15 min, then propargyl bromide (1.21 mL, 11.3 mmol, 80 wt.% in toluene) was added drop wise and allowed to stir for 24 h. The reaction mixture was concentrated and the residue partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic extracts were dried over Na_2SO_4 and filtered, concentrated. The crude product was purified by column chromatography over silica gel (60-120 mesh) and eluted with hexane-EtOAc (4:1) mixture to afford, the product **4**, as a colorless liquid. Yield 1.41 g, 79%. IR (neat): 1764, 1491, 1436, 1342, 1257, 1211, 1173, 1109, 1087, 1027, 1014, 912, 825, 755, 667, 635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 - 7.33 (m, 4H), 5.19 (s, 1H), 4.30 (dd, *J* = 16.0, 2.4 Hz, 1H), 4.17 (dd, *J* = 16.1, 2.4 Hz, 1H), 3.72 (s, 3H), 2.50 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 134.9, 133.9, 128.9, 128.9, 78.3, 77.9, 75.9, 56.4, 52.5.

2-(4-Chlorophenyl)-2-(prop-2-yn-1-yloxy)acetic acid, 5: To a stirred mixture of propargyl ester **4** (1 g, 4.2 mmol) in THF-MeOH-H_2O (3:1:1, 10 mL) was added LiOH.H_2O (0.7 g, 16.8 mmol) at 0°C, and the reaction mixture was stirred at the same temperature for 1 h. After the completion of the reaction (monitored by TLC), the organic solvents were removed under vacuum, then added water (3 mL) and the reaction mixture was acidified with dil.HCl to *p*H 1. Then the reaction mixture was extracted with EtOAc (2×20 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give the crude product. It was purified by column chromatography over silica gel eluting with hexane-EtOAc (1:2) to afford, the pure product **5**, as a colorless solid. Yield 0.82 g, 87%. M.p.68-69°C. IR (neat): 3291, 3095, 2916, 1723, 1489, 1404, 1335, 1218, 1181, 1086, 1017, 976, 918, 820, 753, 675, 639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 - 7.34 (m, 4H), 5.20 (s, 1H), 4.32 (dd, *J* = 16.0, 2.3 Hz, 1H), 4.14 (dd, *J* = 16.0, 2.2 Hz, 1H), 2.51 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.40, 135.3, 133.2, 129.1, 128.9, 77.8, 77.5, 76.4, 56.5; HRMS (ESI): *m/z* [M-H]$^+$ Calcd for $C_{11}H_8ClO_3$: 223.0167. Found: 223.0156.

(*E*)-2-Methoxy-4-(2-nitrovinyl)phenol, 7: Vanillin (5.0 g, 32.9 mmol) was dissolved in nitro methane (20 mL, 328.6 mmol) and added ethylenediamine (0.04 mg, 0.65 mmol). Then the resulting reaction mixture was refluxed for 2 h. After the completion of reaction as indicated by TLC, rest of the nitromethane was removed by vacuum distillation to give a crude

yellowish solid, which was then triturated in aqueous methanol (CH_3OH-H_2O, 2:1, 20 mL). Pale yellow crystals were collected on a Buchner funnel by suction, and rinsed twice with aqueous methanol (CH_3OH-H_2O, 1:1, 2×10 mL). After being dried overnight under a warm air, compound **7** was obtained as yellow solid. Yield 5.76 g (90%). M.p.164-165°C. IR (neat): 3071, 2951, 1604, 1482, 1363, 1295, 1210, 1161, 1021, 972, 815, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.7, 147.1, 139.5, 135.0, 124.9, 122.4, 115.3, 110.1, 56.1; HRMS (ESI): *m/z* $[M-H]^+$ Calcd for $C_9H_8NO_4$: 194.1665. Found: 194.1715.

4-(2-Aminoethyl)-2-methoxyphenol,8: A solution of compound **7** (5g, 25.6 mmol) in THF (50 mL) was dropwise added into a stirred suspension of $LiAlH_4$ (4.86 g, 128 mmol) in THF (40 mL) at 0°C over 20 min. After the addition was finished, the mixture was then heated and stirred 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 drop wise into the reaction mixture over 30 min, and $NaHCO_3$ (10.76 g, 128.2 mmol) was then slowly added into the mixture at 0°C. The ice-bath was removed, and the mixture was further stirred at reflux for 3 h. After cooled to RT, the mixture was filtered on celite bed, and the filter cake was washed twice with MeOH (2×30 mL). The filtrates were combined and dried over Na_2SO_4. The filtrate was concentrated under vacuum to give crude product, as brown viscous oil, which was purified by column chromato graphy on neutral alumina by eluenting with CH_2Cl_2-CH_3OH (90:10) mixture to afford, pure compound **8**, as white solid. Yield 3.12 g (73%). M.p.157-158°C. IR (neat): 3150, 2918, 2846, 2616, 2502, 1594, 1482, 1227, 1125, 1021, 801 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): 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); ^{13}C NMR (126 MHz, CD_3OD): δ 147.6, 144.7, 130.8, 120.8, 114.8, 112.0, 54.9, 42.9, 38.1; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_9H_{14}NO_2$: 168.2155. Found: 168.2215.

2-(4-Chlorophenyl)-*N*-(4-hydroxy-3-methoxy-phenethyl)-2-(prop-2-yn-1-yloxy)acetamide, 9: To a stirred solution of 1-hydroxybenzotriazole hydrate (HOBt) (0.45 g, 3.35 mmol) and *N*-(3-dimethyl amino propyl)-*N*'-ethylcarbodiimide hydrochloride (0.51 g, 2. 67 mmol) in DMF (10 mL) was added acid compound **5** (0.5 g, 2.23 mmol) at RT. After 15 min, amine compound **8** (0.56 g, 3.35 mmol) was added, reaction mixture was stirred at RT for 6 h. After completion, the reaction mixture was poured into ice-cold water (20 mL) and the product was extracted with EtOAc (3×10 mL). The combined organic phases were dried over Na_2SO_4. The solution was concentrated under vacuum to give crude product as viscous oil, which was purified by silica gel column chromatography by eluenting with EtOAc/hexane (1:1) mixture to afford, pure compound **9**, as white solid. Yield 0.7 g (84%). M.p.94-96°C. IR (neat): 3403, 3291, 2929, 2856, 1663, 1601, 1519, 1448, 1365, 1268, 1158, 1083, 1024, 821, 754, 675, 634, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.29 (m, 2H), 7.27 - 7.23 (m, 2H), 6.86 - 6.82 (m, 1H), 6.75 (t, *J* = 5.2 Hz, 1H), 6.67 - 6.63 (m, 2H), 5.57 (s, 1H), 4.96 (s, 1H), 4.19 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.97 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.82 (s, 3H), 3.62 - 3.43 (m, 2H), 2.83 - 2.71 (m, 2H), 2.48 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 146.6, 144.3, 134.7, 134.6, 130.4, 128.8, 128.7, 121.4, 114.4, 111.2, 79.6, 78.1, 75.8, 56.4, 55.8, 40.3, 35.2; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{20}H_{21}ClNO_4$:374.1154. Found: 374.1153.

2-(4-Chlorophenyl)-*N*-(3-methoxy-4-(prop-2-yn-1-yloxy)phenethyl)-2-(prop-2-yn-1-yloxy)aceta mide (mandipropamid): To a stirred solution of compound **9** (0.2 g, 0.59 mmol) in DMF (4 mL) was added Cs_2CO_3 (0.48 g, 1.47 mmol) and followed by propargyl bromide (0.13 mL, 1.47 mmol, 80 wt.% in toluene) and the resulting suspension was stirred at 60°C for 2 h. After completion, reaction mixture was poured into ice-cold water (5 mL) and the product was extracted with EtOAc (3×5 mL). The combined organic phases were dried over Na_2SO_4. The solution was concentrated under vacuum to give crude product as a viscous oil, which was purified by silica gel column chromatography (eluent: EtOAc-hexane, 30: 70) to afford, the target molecule Mandipropamid as white solid. Yield 0.2 g (86%). M.p.97-98°C. IR (neat): 3293, 2924, 2860, 2355, 1668, 1596, 1517, 1455, 1263, 1220, 1145, 1086, 1021, 905, 723, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 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); ^{13}C NMR (101 MHz,

$CDCl_3$): δ 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* $[M+H]^+$ Calcd for $C_{23}H_{23}ClNO_4$: 412.8895. Found: 412.8905.

Conclusion

In conclusion, a simple and efficient method is described for the synthesis of Mandipropamid from commercially available 4-chloroacetophenone and vanillin by using mild reaction conditions and simple work-up procedures. All the reactions are very clean with very good to excellent yields (73-94%). The present synthesis makes a significant contribution to cater to the needs of farmers for crop protection from fungal diseases.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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