Synthesis of chlorohomophthalic acids, key intermediates in the synthesis of chlorinated isocoumarins

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Efficient synthesis of chlorohomophthalic acids (**6**) and (**7**), key intermediates in the synthesis of chlorinated isocoumarins (**3**) and (**4**) is described.

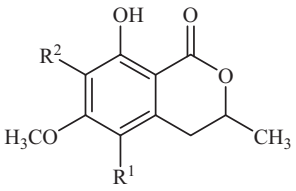
Keywords: chlorohomophthalic acid, chlorinated isocoumarins, sulfuryl chloride

Isocoumarins are important secondary metabolites isolated from fungi and are involved in the biosynthetic pathways of several metabolites. A large number of 3-alkyl and 3-aryl substituted 3,4-dihydroisocoumarins, isolated from natural sources are also known to possess significant biological properties

Amongst the various naturally occurring and biologically active isocoumarin derivatives, the chlorinated dihydroisocoumarins constitute an important class and have been the subject of interest of several researchers due to their widespread natural distribution and enhanced biological activity. Chlorinated dihydroisocoumarin (**1**), for example, which possesses fungicidal activity,[1] has been isolated from *Periconia macrospinosa*[2] while (**2**) and (**3**) have been found in *Sporormia affinis*.[3] Furthermore, the chlorinated isocoumarins (**4**) and (**5**) have been isolated from the trunkwood of *Swartzia laevicarpa*.[4]

In view of the natural abundance and notable biological properties of 3,4-dihydroisocoumarins, several interesting approaches have been developed for their synthesis. Conversely, very few synthetic routes[5,6] are known for the chlorinated dihydroisocoumarins and the most commonly traversed one which proceeds through the intermediary chlorohomophthalic acids (**6** and **7**) attracted our attention. We therefore required an easy access to these chlorohomophthalic acids (**6** and **7**), which would serve as vital precursors for building the naturally occurring and biologically active chlorinated isocoumarin derivatives. Thus, we selected 6-chloro-3,5-dimethoxyhomophthalic acid[6,7] (**6**) and 4,6-dichloro-3,5-dimethoxyhomophthalic acid[6] (**7**) as our target molecules and aspired to synthesise them by an efficient and high yielding route.

The acid (**6**) is a key intermediate for the synthesis of naturally occurring 5-chloro-8-hydroxy-6-methoxy-3-methyl



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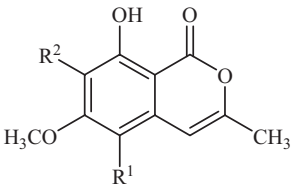

4; R^1 = Cl, R^2 = H
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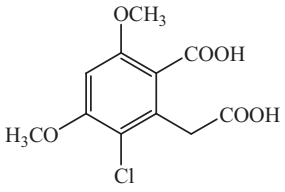

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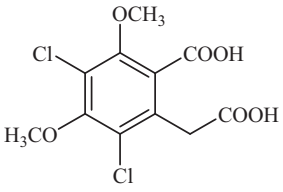

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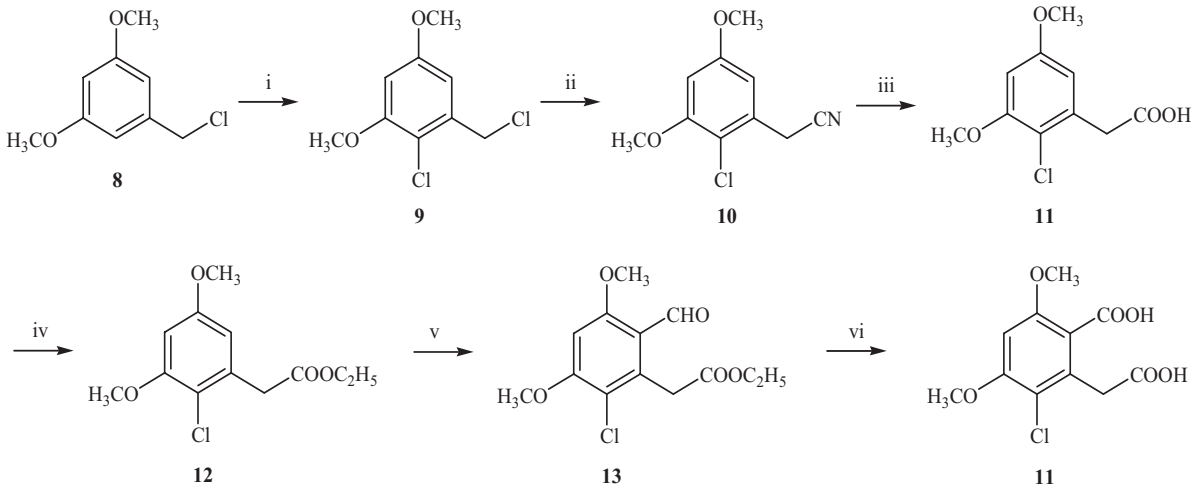
3,4-dihydroisocoumarin (**1**) and radicicol, isolated from *Cylindrocarpon radicicola*,[8] which is a 14-membered macrolide antibiotic and a potent tranquiliser of remarkably low toxicity.[9]

Initially we focussed on synthesising 6-chloro-3,5-dimethoxyhomophthalic acid (**6**) starting from 3,5-dimethoxybenzyl chloride (**8**) as depicted in Scheme 1.

Reaction of (**8**) with sulfuryl chloride at low temperature afforded 2-chloro-3,5-dimethoxybenzyl chloride (**9**), which was converted into the ethyl ester (**12**) through a series of convenient chemical transformations. Vilsmeier–Haack formylation of the



8 **9** **10** **11**

12 **13** **11**

Scheme 1 *Reagents and conditions:* (i) SO_2Cl_2/dry ether, 0°C, (ii) KCN/DMF, RT, (iii) 20% alc. KOH, reflux; dil. HCl; (iv) ethanol, H_2SO_4, reflux, (v) DMF-$POCl_3$, 80°C and (vi) $KMnO_4$/dioxane, 80°C.

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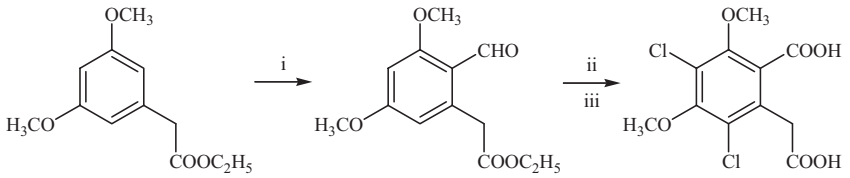

14 15 7

Scheme 2 *Reagents and conditions:* (i) DMF-$POCl_3$, 80°C, (ii) SO_2Cl_2 (excess), dioxan, reflux; and (iii) 5% aq. NaOH, heat followed by 1:1 HCl.

ester (**12**) provided the aldehyde (**13**) which was eventually oxidised to 6-chloro-3,5-dimethoxyhomophthalic acid (**6**), a key intermediate of the naturally occurring 5-chloro-8-hydroxy-6-methoxy-3-methyl-3,4-dihydro-isocoumarin (**1**), known to exhibit fungicidal activity.

After a lucrative and successful synthesis of (**6**), we focused on attaining the other target molecule *viz*. 4,6-dichloro-3,5-dimethoxyhomophthalic acid (**7**). In view of the fact that sulfuryl chloride is known to convert aromatic aldehydes to the corresponding acid chlorides we chose to synthesise (**7**), starting from ethyl 3,5-dimethoxyphenylacetate (**14**) as depicted in Scheme 2.

Vilsmeier–Haack formylation of (**14**) afforded the aldehyde (**15**), which was refluxed with excess sulfuryl chloride and the ensuing intermediate subjected to alkaline hydrolysis to furnish (**7**) in moderate yield.

To conclude, a successful synthesis of 6-chloro-3,5-dimethoxyhomophthalic acid (**6**) and 4,6-dichloro-3,5-dimethoxyhomophthalic acid (**7**), key intermediates for the naturally occurring isocoumarins (**3**) and (**4**), was accomplished using easily accessible starting materials, involving simple reaction conditions and convenient workup.

Experimental

Melting points were determined in capillaries and are uncorrected. ^{1}H NMR measured in $CDCl_3$ on a Varian 300 MHz spectrometer. The chemical shifts are expressed in parts per million (ppm) using TMS as an internal standard. Coupling constants are in Hertz. IR spectra were recorded on Perkin Elmer spectrometer and are reported in wavenumber (cm^{-1}). Elemental analyses were acquired using HOSLI semi-automatic CHN analyser.

2-Chloro-3,5-dimethoxybenzyl chloride (**9**): 3,5-Dimethoxybenzyl chloride (**8**) (5 g, 26.81 mmol) was dissolved in dry ether (50 ml) and cooled in ice–salt mixture. Then a solution of sulfuryl chloride (SO_2Cl_2) (2.15 ml, 26.81 mmol) in dry ether (15 ml) was slowly added and the mixture was stirred for 30 min under ice-cooling. The reaction mixture was poured into ice-water (50 ml), stirred well and the ethereal layer was separated, washed with water, 10% $NaHCO_3$ solution then again with water and dried over anhydrous Na_2SO_4. The residual solid obtained after removal of the solvent was recrystallised from methanol to give 2-chloro-3, 5-dimethoxybenzyl chloride (**9**) as colourless needles.

Yield: 95%; m.p. 87°C, (lit[7]. m.p. 87°C).

2-Chloro-3,5-dimethoxybenzyl cyanide (**10**): The chloride (**9**) (22.62 mmol) was dissolved in DMF (40 ml) and to this solution anhydrous, powdered potassium cyanide (67.03 mmol) was added. This heterogeneous reaction mixture was stirred vigorously at room temperature for 8 h and then it was carefully filtered under suction. The filtrate was diluted with water (75 ml) and cooled to 5°C. A cream coloured solid separated out which was filtered, dried, purified by column chromatography over silica gel using hexane as eluent and recrystallised from hexane–ethylacetate to obtain 2-chloro-3, 5-dimethoxybenzyl cyanide (**10**) as white crystals.

Yield: 85%; m.p. 115°C, IR: 2250 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz); data δ 3.79 (s, 6H), 3.87 (s, 2H), 6.46 (bs, 2H); Anal. calcd. for $C_{10}H_{10}ClNO_2$: C, 56.72; H, 4.76. Found: C, 56.75; H, 4.80.

2-Chloro-3,5-dimethoxyphenylacetic acid (**11**): To a solution of 2-chloro-3,5-dimethoxybenzyl cyanide (**10**) (23.64 mmol) in methyl alcohol (30 ml) was added, 20 ml of 20% alc. KOH solution and the resultant mixture was refluxed on a steam bath for 4 h. Excess methyl alcohol was then removed under reduced pressure and the residue was acidified by 1:1 HCl. A white solid separated out, which was filtered, dried and recrystallised from alcohol–water to obtain the desired 2-chloro-3,5-dimethoxyphenylacetic acid (**11**) as white crystals.

Yield: 82%; m.p. 161°C. IR: 2400–3000, 1710 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz); data δ 3.83 (s, 6H), 3.88 (s, 2H), 6.49 (bs, 1H), 6.65 (bs, 1H); Anal. calcd. for $C_{10}H_{11}ClO_4$: C, 52.07; H, 4.81. Found: C, 52.27; H, 4.84.

Ethyl 2-chloro-3,5-dimethoxyphenylacetate (**12**): 2-Chloro-3,5-dimethoxyphenylacetic acid (**11**) (21.69 mmol) was dissolved in dry ethanol (50 ml). To this solution, conc. H_2SO_4 (0.5 ml) was added and refluxed on a water bath for 2 h. Excess ethanol was removed under reduced pressure and the residue poured over crushed ice. An oily product separated out, which was extracted with (20 ml × 3) portions of ether. The ether layer was washed with water, 10% $NaHCO_3$ and again with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield an oily residue that was purified by column chromatography over silica gel using hexane as eluent to obtain (**12**) as white crystals.

Yield: 90%; m.p. 61°C. IR 1745 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz); data δ 1.26 (t, J = 6 Hz, 3H), 3.74(s, 2H), 3.79 (s, 3H), 3.87 (s, 3H), 4.18 (q, J = 6 Hz, 2H), 6.45 (bs, 2H). Anal. calcd. for $C_{12}H_{15}ClO_4$: C, 55.71; H, 5.84. Found: C, 55.73; H, 5.85.

Ethyl 2-chloro-3,5-dimethoxy-2-formyl-phenylacetate (**13**): DMF (1.8 ml, 23.22 mmol) was cooled in an ice-bath and $POCl_3$ (2.16 ml, 23.22 mmol) was added with stirring while maintaining the reaction temperature below 5°C. Dimethoxyphenyl acetate (**12** or **14**) (19.34 mmols) was added to the Vilsmeier–Haack complex at 0–5°C. The reaction mixture was allowed to attain room temperature and then it was heated at 80°C for 3 h. The resulting dark red mixture was cooled and decomposed over saturated solution of sodium acetate under stirring. Workup provided the aldehydes (**13** or **15**) as cream coloured solids which were purified by column chromatography over silica gel using hexane–ethylacetate as eluent and recrystallised from hexane-acetone to obtain (**13** or **15**) as white crystals.

Aldehyde (**13**): Yield: 83%; m.p. 121°C. IR 1700, 1745 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz); data δ 1.25 (t, J = 6 Hz, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 4.17 (q, J = 6 Hz, 2H), 4.32 (s, 2H), 6.49 (s, 1H), 10.43 (s, 1H). Anal. calcd. for $C_{13}H_{15}ClO_5$: C, 54.46; H, 5.27. Found: C, 54.50; H, 5.30.

Aldehyde (**15**): Yield: 80%; m.p. 110°C, (lit[10]. m.p. 108–110°C). IR 1705, 1735 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz); data δ 1.25 (t, J = 6 Hz, 3H), 3.94 (s, 3H) 3.98 (s, 3H), 4.17 (q, J = 6 Hz, 2H), 4.32 (s, 2H), 6.49 (s, 2H) 10.35 (s, 1H), Anal. calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.35. Found: C, 61.93; H, 6.38

6-Chloro-3,5-dimethoxyhomophthalic acid (**6**): A mixture of ethyl 2-chloro-3,5-dimethoxy-2-formyl-phenylacetate (**13**) (1.5 g, 5.24 mmol), 1,4-dioxan (20 ml) and water (5 ml) was heated to 80°C and treated with a solution of $KMnO_4$ (1.16 g, 7.33 mmol) dissolved in water (15 ml). After completion of the addition, stirring was continued at 80°C for 45 min. The reaction mixture was then basified with NaOH (5%) and immediately filtered hot. The filtrate was acidified with conc. H_2SO_4 to provide a cream coloured solid, which was purified by recrystallisation from dichloromethane (CH_2Cl_2) to furnish the desired 6-chloro-3,5-dimethoxyhomophthalic acid **(6)** as colourless crystals.

Yield: 66%; m.p. 222°C, (lit[7]. m.p. 215–225°C). IR 2500–3000, 1700 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz); data δ 3.89 (s, 3H), 3.90 (s, 2H), 3.96 (s, 3H), 6.81 (s, 1H) Anal. calcd. for $C_{11}H_{11}ClO_6$: C, 48.10; H, 4.04. Found: C, 48.12; H, 4.08.

4,6-dichloro-3,5-dimethoxyhomophthalic acid (**7**): Ethyl 3,5-dimethoxy-2-formyl-phenylacetate (**15**) (1 g, 3.97 mmol) was dissolved in 1,4-dioxan (15 ml). To this solution sulfuryl chloride (SO_2Cl_2) (1.3 ml, 16.17 mmol) was added and the resultant mixture was refluxed in an oil bath for 1 h. The reaction mixture was then cooled to room temperature and poured into ice-cold water. It was extracted with three 10 ml portions of dichloromethane. The combined

organic extract was washed with water, 10% $NaHCO_3$ solution, again with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain a light brown sticky mass. To this mass, 5% aq. NaOH solution (20 ml) was added and the mixture heated, with stirring, on a steam bath for 30 min. The reaction mixture was then filtered hot. The filtrate was cooled to room temperature and acidified with 1 : 1 HCl to obtain crude (**7**) as a light brown solid which was recrystallised from alcoho–water to obtain 4,6-dichloro-3,5-dimethoxyhomophthalic acid (**7**) as colourless crystals.

Yield: 60%; m.p. 151°C, (lit[8]. m.p. 151°C). IR 2500–3000, 1702 cm^{-1}; ^1H NMR: ($CDCl_3$, 300 MHz); data δ 3.85 (s, 6H), 4.05 (s, 2H), Anal. calcd. for $C_{11}H_{10}Cl_2O_6$: C, 42.74; H, 3.26. Found: C, 42.76; H, 3.29.

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