An Efficient Synthesis of 3,5-Dimethoxyhomophthalic Acid, A key Intermediate for Synthesis of Natural Isocoumarins

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3,5-Dimethoxyhomophthalic acid was prepared efficiently in three steps, from 3,5-dimethoxybenzyl bromide *via* rhodium-catalyzed direct carbonylation to 3,5-dimethoxyphenylacetic acid followed by successive *o*-formylation and oxidation. Isocoumarins related to agrimonolide and achlisocoumarin 1 were prepared in single step by condensation of the homophthalic acid with appropriate acid chlorides.

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Introduction.

Isocoumarins and dihydroisocoumarins are the secondary metabolites of a wide variety of plants, fungi, bacteria, marine organisms, and also among insect venoms and pheromones; exhibiting a wide variety of structural diversity and biological activities [1-3].

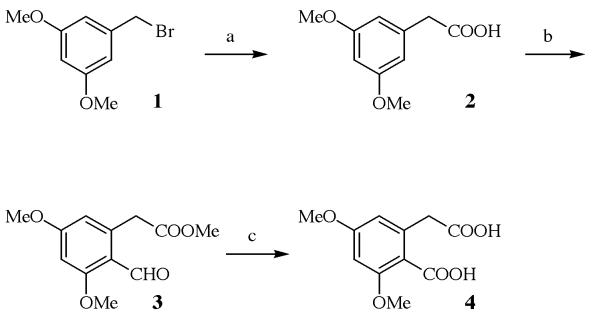
The majority of the natural isocoumarins are derived biogenetically from acetate *via* the acetate-polymalonate pathway, hence most of them possess C-6 and C-8 dioxygenation [2,4]. Some well known examples being the 6-methoxymellein [5], diaporthin [6], fusamarin [7], asperentin derivatives [8], agrimonolide [9], canescin A and B [10], sclerotiorin A and B [11], LL-1640-6, 7, 8 [12], feralolide [13], achlisocoumarin [14], dihydroisocoumarins from *Ononis natrix* [15], and various chlorinated isocoumarins from *Swartzia* and *Periconia* spp. [16]. A number of other natural products like actinobolin, bactinobolin A, B, C, botrallin, semi-vioxanthin, altenuene, alternariol, altenuisol, zearalanone, parasperone A, ascoquinone A, emodin, ascochitin, and citrinin posses a similar oxygenation pattern on benzene ring.

3,5-Dimethyoxyphenylacetic acid has extensively been used as a key starting substance towards the synthesis of a number of naturally occurring 3,4-dihydroisocoumarins *e.g.*, dihydroisocoumarins of *Ononis natrix*, peniolactol, 6-methoxymellein [17] and fusamarin [7]. Direct condensation of acid chlorides with homophthalic acids has recently been proved to be an authentic route for the construction of 3-substituted isocoumarin skeleton [18], therefore synthesis of phenylacetic acid on one hand and that of homophthalic acid on the other is of enormous practical importance.

A number of synthetic routes for the homophthalic acids have been reported. These include the cleavage of indandiones with various oxidizing agents [19], *ortho*-carboxylation of phenylacetic acids [20], carboxylation of dilithium *ortho*-toluates with dimethylcarbonate [16,21], and cuprous catalyzed reaction of benzoic acids with ethyl acetate [22].

In conjunction with our previous work on the synthesis of natural isocoumarins and dihydroisocoumarins we needed a short and reliable synthetic route to the title homophthalic acid. The recent report of rhodium-catalyzed direct carbonylation of benzyl bromides to the corresponding phenylacetic acids [23] prompted us to extend this procedure to 3,5-dimethoxyphenylacetic acid.

Scheme 1



Reagents and conditions (a) $[RhCl(COD)]_2$, CO (1 atm) KI, HCO_2H, (b) (i) MeOH/H+ (ii) $POCl_3$, DMF (c) (i) $NaClO_2/NaH_2PO_4$ (ii) 5% KOH, MeOH

Results and Discussion.

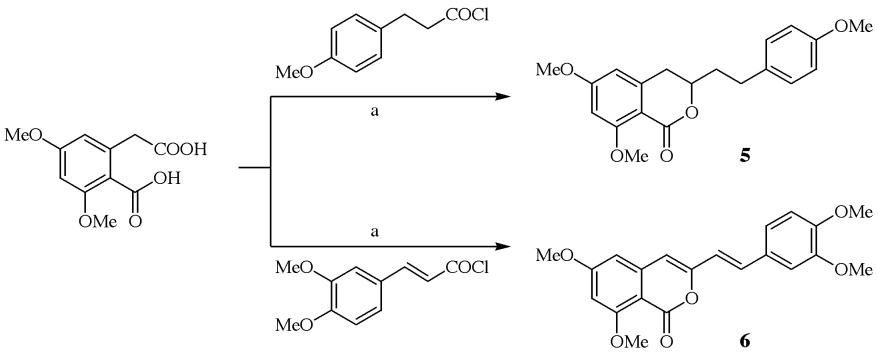
Commercially available 3,5-dimethoxybenzyl bromide **1** was treated with carbon monoxide and potassium iodide (5 mol %) in formic acid under catalysis of the dimer of chloro (1,5-cyclooctadiene) rhodium (I), (10 mol %) to afford 3,5-dimethoxyphenylacetic acid **2** in 78 % yield. The phenylacetic acid was characterized by the 2H singlet for $ArCH_2$ at δ 3.58 and a broad singlet at δ 11.23 for the carboxylic proton in ^{1}H-NMR and at δ 42.3 (CH_2) and 179.15 (COOH) in ^{13}C-NMR. IR spectrum showed the carboxyl absorptions at 1722 and at 3400 cm^{-1} and EIMS showed the molecular ion peak at m/z 196 and that at m/z 151 for benzylic cation or tropyllium ion. The methyl ester of acid was subjected to Vilsmier Haack formylation to afford methyl 2-formyl-3,5-dimethoxyphenyl acetate **3**. The latter exhibited peak for CHO at δ 10.41 and at δ 189.8 in ^{1}H-NMR and ^{13}C-NMR respectively. Mild oxidation of aldehydic function was achieved using sodium chlorite, sodium dihydrogen phosphate in presence of t-amylene as chlorine scavenger [24] to afford the corresponding carboxy ester in 85% yield.

Saponification of the carboxy ester finally furnished the title homophthalic acid **4** in 80% yield. EIMS showed the M^+-

18 at m/z 222 in addition to other characteristic changes in NMR and IR spectra.

Isocoumarins related to agrimonolide (**5**) isolated from *Agrimonia pilosa* [9] and achlisocoumarin I from *Achylis triphylla* (**6**) [14] were prepared in good yields by condensation of homophthalic acid **4** with acid chlorides derived from commercial 4-methoxyphenylpropionic and 3,4-dimethoxycinnamic acid respectively. (Scheme 2). The isocoumarins **5** and **6** showed the characteristic singlets (H4) at δ 7.20 and δ 6.56 respectively.

Scheme 2



Reagents and conditions: a: 200 °C, 4 h

Thus a short and efficient synthesis of 3,5-dimethoxyhomophthalic acid has been achieved involving rhodium catalyzed direct carbonylation as the key step and its use in the synthesis of natural isocoumarins has been demonstrated.

EXPERIMENTAL

3,5-Dimethoxybenzyl bromide and bis-(1,5-cyclooctadiene)-dirhodium (I)-dichloride were the commercial products from Aldrich and Fluka, respectively. ^{1}H NMR and the ^{13}C NMR spectra were recorded at 400 MHz (Bruker AM-400) and 100 MHz (Bruker AM-100) respectively as deuteriochloroform solutions. IR spectra were recorded on a Bruker Vector 22 and Mass Spectra (70eV, electron impact) on a MAT 312 instrument and elemental analyses with CHN-Rapid Heräus. Flash Column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh).

3,5-Dimethoxyphenylacetic Acid (**2**).

A stirred solution of 3,5-dimethoxybenzyl bromide (**1**) 5 g (21.63 mmol), 0.18 g KI (1.08 mol), and 0.18 g (1.08 mol) $[RhCl(COD)]_2$ in formic acid (50 ml) was flushed with Ar, and CO at 1 atm. pressure was introduced. The reaction mixture was stirred at 60 °C for 24 h, cooled to room temperature, concentrated and then diluted with ethyl acetate. The organic phase was washed successively with 1 *N* hydrochloric acid, and brine, dried over magnesium sulphate and the solvent rotary evaporated. Flash column chromatography of the residue using petroleum ether:ethyl acetate (8:3) afforded white solid which on recrystallization from methanol gave the acid (**2**) as colourless scales 3.30 g (78%). ^{1}H nmr: δ 3.57 (s, 2H, $ArCH_2$), 3.87 (s, 6H, MeO x2), 6.34 (s, 1H, H-4), 6.44 (s, 2H, H2, H6); ^{13}C nmr: δ 179.15 (COOH), 163.81 (C3/C5), 139.30 (C1), 109.47 (C2/C6), 99.72 (C4), 56.40 (MeO-3/5), 42.13 ($ArCH_2$); ir (potassium bromide): 2913, 2849, 1734, 1694, 1598, 1572, 1471, 1151, 832 cm^{-1}; ms *m/z* (%): 196 (M^+,100), 151 (61.1), 137 (3.2), 121 (30.4).

Anal. Cacld. for $C_{10}H_{12}O_4$: C 61.22, H 6.16. Found: C 61.19, H 6.18.

Methyl 3,5-Dimethoxyphenylacetate.

A stirred solution of 3,5-dimethoxyphenylacetic acid (**2**) 3 g (15.3 mmol) in absolute methanol (75 ml) and conc. sulfuric acid (3 drops) was heated under reflux for 4 h. The reaction mixture was cooled and sodium carbonate was added with stirring until the acid was neutralized. The reaction mixture was filtered and the solvent evaporated to leave methyl ester 3.2 g (100 %) as light yellow oil. ^{1}H nmr: δ 3.61 (s, 2H, $ArCH_2$), 3.87 (s, 6H, MeO x2), 3.70 (s, 3H, COOMe) 6.34 (s, 1H, H-4), 6.44 (s, 2H, H2, H6); ^{13}C nmr: δ 173.25 (CO), 163.81 (C3/C5), 139.30 (C1), 109.47 (C2/C6), 99.72 (C4), 56.34 (MeO-3/5), 51.77 (COOMe), 40.12 ($ArCH_2$); ir (film): 2908, 2849, 1722, 1694, 1587, 1572, 1471, 1151, 832 cm^{-1}; ms: *m/z* (%): 210 (M^+,100), 179 (23.6), 151 (61.1), 137 (5.7), 121 (24.6), 109 (2.7), 91 (7.3).

Anal. Calcd. for $C_{11}H_{14}O_4$: C 62.85, H 6.71. Found: C 62.79, H 6.78

Methyl 2-formyl-3,5-dimethoxyphenylacetate (**3**).

Phosphorus oxychloride (2.68 g, 1.6 ml, 17.1 mmol) was added dropwise to a stirred solution of the above methyl ester (3 g, 14.3 mmol) in freshly distilled dry DMF (25 ml) at 55 °C. The solution was then heated at 100 °C for 10 minutes and then stirred overnight. The mixture was poured into aqueous sodium acetate (10%, 100 ml) with stirring when the solid precipitated, which was collected by filtration and recrystallized from ethanol to yield 2.65 g of **3** (11.15 mmol, 78%) as yellow needles. ^{1}H nmr: δ 3.71 (s, 3H, COOMe), 3.87 (s, 3H, MeO), 3.89 (s, 3H, MeO), 3.94 (s, 2H, $ArCH_2$), 6.33 (d, 1H, *J*=2.76 Hz, H-4), 6.43 (d, 1H, *J*=2.76 Hz, H6), 10.41 (s, 1H, CHO); ^{13}C nmr: δ 189.8 (CHO), 173.30 (CO), 164.81 (C5), 164.81 (C3), 139.30 (C1), 117.7 (C2),

99.72 (C4), 56.30 (MeO), 55.71 (MeO), 51.77 (COOMe), 40.12 ($ArCH_2$) ppm; ir (film): 2896, 2849, 1722, 1680, 1593, 1572, 1471, 1151, 899 cm^{-1}; ms: *m/z* (%): 238 (M^+, 60.3), 210 (67.3), 151 (59.4), 137 (4.7), 121 (23.9).

Anal. Calcd. for $C_{12}H_{14}O_5$: C 60.50, H 5.92. Found: C 60.49, H 6.01.

Methyl 2-Carboxy-3,5-dimethoxyphenylacetate.

A solution of sodium chlorite 9.1 g (100 mmol) and 9.1 g (76 mmol) sodium dihydrogen phosphate (76 mmol) in 90 ml of water was added dropwise to a stirred solution of formyl ester (**3**) (2.6 g, 11 mmol), *t*-butyl alcohol (210 ml) and 2-methyl-2-butene (50 ml). The resulting pale yellow reaction mixture was stirred at room temperature overnight. Volatiles were removed on rotary and the residue dissolved in water (100 ml) and extracted with petroleum ether. The aqueous phase on acidification with hydrochloric acid directly gave the carboxy ester 2.36 g (9.3 mmol, 85%). ^{1}H nmr: δ 3.71 (s, 3H, COOMe), 3.89 (s, 3H, MeO), 3.91 (s, 3H, MeO), 4.02 (s, 2H, $ArCH_2$), 6.48 (d, 1H, *J*=2.14, H-4), 6.52 (d, 1H, *J*=2.20, H6), 11.21 (br, 1H, COOH); ^{13}C nmr: δ 172.57 (ArCOOH), 174.30 (CO), 164.81 (C5), 164.81 (C3), 139.30 (C1), 110.30 (C2), 99.72 (C4), 56.30 (MeO), 55.71 (MeO), 51.77 (COOMe), 40.29 ($ArCH_2$) ppm; ir (potassium bromide): 3000-2500, 1730, 1685, 1598, 1572, 1471, 1151, 832 cm^{-1}; ms: *m/z* (%): 254 (M^+, 43.7), 210 (45.1), 179 (45.9), 151(61.1), 137 (5.9), 121 (32.7).

Anal. Calcd. for $C_{12}H_{14}O_5$: C 60.50, H 5.92. Found: C 60.49, H 6.01.

3,5-Dimethoxyhomophthalic Acid (**4**).

Aqueous sodium hydroxide (5%, 85 ml) was added to a stirred solution of above carboxy ester 2 g (7.8 mmol), in methanol (25 ml) and the reaction mixture refluxed for 3 h. After cooling, the methanol was rotary evaporated and the aqueous phase acidified with dilute hydrochloric acid when the white solid precipitated. The solid was recrystallized from ethyl acetate petroleum ether to afford **4** 1.5 g (6.3 mmol, 80%), as colourless scales. ^{1}H nmr: δ 4.15 (s, 2H, $ArCH_2$), 3.89 (s, 3H, MeO), 3.91 (s, 3H, MeO), 6.48 (d, 1H, *J*=2.14, H-4), 6.72 (d, 1H, H6), 10.41 (s, 1H, COOH); ^{13}C nmr: δ 179.86 (COOH), 172.57 (ArCOOH), 164.0 (C5), 164.81 (C3), 139.40 (C1), 111.20 (C2), 99.81 (C4), 56.30 (MeO), 55.71 (MeO), 39.01 ($ArCH_2$) ppm; ir (potassium bromide): 3000-2500, 1700, 1685, 1580, 1572, 1471, 1151, 832 cm^{-1}; ms: *m/z*(%): 240 (M^+, 41.3), 222 (61.1), 194 (23.6), 182 (23.4).

Anal. Calcd. for $C_{11}H_{12}O_6$: C 55.00, H 5.04. Found: C 54.92, H 5.11.

Syntheses of Isocoumarins.

General Procedure.

Commercial 4-Methoxyphenylpropionic and 3,4-dimethoxycinnamic acid (8 mmol) were converted to corresponding acid chlorides on heating with thionyl chloride (9.6 mmol) for 30 min under reflux, in the presence of a drop of DMF. A mixture of homophthalic acid **4** (2.0 mmol) and the appropriate acid chloride was heated at 200 °C for four hours when the tlc analysis showed completion of the reaction. The residue was dissolved in ethyl acetate and washed with a 5% aqueous solution of sodium carbonate to remove the unreacted homophthalic acid. The organic phase was separated, dried and concentrated. Flash Column chromatography of residue using silica gel and pet ether (40-80 °C) as eluent afforded the isocoumarins.

6,8-Dimethoxy-3-[(2'-ethyl-(4''-methoxyphenyl)]isocoumarin (**5**).

This compound was obtained as an oil (55%); ir (ν_{max}, neat): 1734,1257, 1031 cm^{-1}; ^{1}H nmr: δ 7.20 (1H, s), 6.90 (1H, d, J= 2.4 Hz), 6.78 (1H, d J=1.5 Hz), 2.88 (1H, t, J=7.7 Hz), 2.57 (1H,t, J=7.9 Hz), 7.15 (2H, dd, J=8.9,1.2, Hz), 7.05 (2H, dd, J=8.2,1.7 Hz), 3.79 (3H, -OCH_3, s), 3.77 (3H, -OCH_3, s) ppm; ms: *m/z* (%): 340 (31, M^+), 205 (45.0), 163 (11.6), 149 (12.8), 135 (9.5), 121 (100), 91 (13.6).

Anal. Cacld. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C 70.03, H 6.07.

6,8-Dimethoxy-3-[(3',4'-Dimethoxyphenylethenyl)]isocoumarin (**6**).

This compound was obtained as a yellow semi solid (61%) ir (potassium bromide): 1680, 1602, 1584, 1080 cm^{-1}. ^{1}H nmr: δ 3.80 (3H, s, OMe), 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 6.47 (1H, d, J=2.2 Hz, H-5), 6.51 (1H, d, J=2.2 Hz, H-7), 6.56 (1H, s, H-4), 6.75 (1H, d, J=16.5 Hz, H-7), 6.90 (1H, d, J=7.5 Hz, H-5), 7.1 (1H, dd, J=2.5 Hz, J_2= 9 Hz, H-6), 7.21 (H, d, J=2.1,Hz, H-2), 7.25 (1H, d, J=16 Hz), s) ppm. ms: *m/z* (%): = 368 (45, M^+), 205 (45), 177 (11.9), 163 (11.6), 149 (12.8), 135 (14.5), 121 (100), 91 (15.9), 76 (8.2), 65 (12.1).

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.39; H, 5.53.

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REFERENCES AND NOTES

[1] R. D. Barry, *Chem. Rev.*, **64**, 229 (1964).
[2] R. A. Hill, *Prog. Chem. Nat. Prod*., **49**, 1 (1986).
[3] E. Napolitano, *Org. Prep. Proced. Int*. **29**, 631 (1997).
[4] U. Sankawa in Comprehensive Natural Products Chemistry, **1**, p.17, 415-419, Elsevier Science Publishers Ltd., Amsterdam (1999).
[5] J. Mercier and J. Kuc, *J. Sci. Food Agric*., **73**, 60 (1997).
[6] M. Ichihara, T. Hashimoto, I. Hira, Y. Takeda, S. Sasamura, S. Sakaura, R. Sato and A. Tajimai, *Chem. Lett.*, 1495 (1989).
[7] S. M. Afzal, R. Pike, N. H. Rama, L. R. Smith, E. S. Turner and W. B. Whalley, *J. Chem. Soc. Perkin Trans. I*, 81(1978).
[8] G. F. Grove and M. Pople, *J. Chem. Soc. Perkin Trans. I*, 337 (1979).
[9] M. Yamato and K. Hashigaki, *Chem Pharm Bull.*, **24**, 200 (1976).
[10] C. N. Lewis, J. Staunton and D. C. Sunter, *J. Chem. Soc Perkin Trans. I*, 747 (1976).
[11] T. Sassa, H. Aoki, and K. Munakata, *Tetrahedron Lett.*, 5703 (1968); K. Tanaka , A. Kobayashi, and K. Yamashita, *Agric. Biol. Chem.*, **37**, 669 (1973).
[12] G.A. Elestad, F. M. Lovell, N. A. Perkinson, R. T. Haragreaves and W. J. McGahren, *J. Org. Chem*., **43**, 2339 (1978).
[13] G. Speranza, P. Manitto, P. Cassara and D. Monti, *Phytochemistry*, **33**, 175 (1993).
[14] M. Mizuno, S. Yoshida, M. Inuma, T. Tanaka, F. A. Long and K. Goto, *Chem. Pharm. Bull.*, **38**, 2075 (1990).
[15] A. S. Feliciano, J. M. Miguel del Corral, L. M Canedo, and M. Medarde, *Phytochemistry*, **29**, 945 (1990).
[16] G. B. Henderson and R. A. Hill, *J. Chem. Soc. Perkin Trans. I*, 111 (1982).
[17] N. H. Rama, A. Saeed and C. W. Bird, *Liebigs Ann. Chem.*, **4**, 711 (1995) *ibid.*, **12**, 1331 (1993); A. Saeed N. H. Rama, *J. Chem. Soc. Pak.*, **15**, 140 (1993).
[18] K. Nozawa, M. Yamada, Y. Tsuda, K. I. Kawai and

S. Nakajima, *Chem Pham Bull.*, **29**, 2491, 3486 (1981); H. Kaji, M. Yamada, K. Nozawa, K. I. Kawai and S. Nakajima, *Org. Prep. Proceed. Int.*, **18**, 253 (1986); A. Saeed, *Monat. Chemie*, **134**, 457 (2003); A. Saeed, *Helvetica Chim. Acta*, **86**, 377 (2003).

[19] K. Nozawa, S. Nakajima and K. I. Kawai, *Chem. Pharm. Bull.*, **28**, 1112 (1980); R. H. Carter, R. M. Colyer, R. A. Hill and J. Staunton, *J. Chem. Soc. Perkin Trans. I*, 1432 (1982); H. L. Slates, S. Weber and N. L. Wendler *Chimia*, **21**, 468 (1967); J. Mukherjee, J. N. Chatterjea, and S. C. Sengupta, *Indian J. Chem.*, **13**, 859 (1975); R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38**, 610 (1973).

[20] P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **82**, 45753 (1960); *Org. Syn. Coll. Vol.* **5**, 612, 1051 (1960); D. S. Breslow, E. Baumgarten and C. R. Hauser, *J. Am. Chem. Soc.*, **66**,1286 (1944).

[21] F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.*, **99**, 4533, (1977); F. M. Hauser and R. P. Rhee, *Synthesis*, 245 (1977).

[22] A. Bruggink and McKillop, *Tetrahedron*, **31**, 2601 (1975).

[23] A. Giroux, C. Nadeau and Y. Han, *Tetrahedron Lett.*, **41**, 7601 (2000).

[24] H. W. Pinnick, W. E. Childers and B. S. Bal, *Tetrahedron*, **37**, 2091 (1981).