An efficient synthesis of dimethoxyphthalides

Madhusudan V. Paradkar[a]* Sanjeev A. Kulkarni[ab], Augustine R. Joseph[a] and Anup A. Ranade[a]

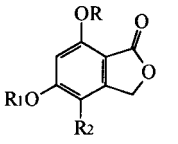
[a]*Department of Chemistry, PostGraduate and Research Centre, A.G. College, Karve Road, Pune 411 004, India*

[b]*Present address: Department of Medicinal Chemistry, Virginia Biotechnology Centre, Richmond-VA-23219–1534, USA*

J. Chem. Research (S), 2000, 364–366
J. Chem. Research (M), 2000, 0944–0956

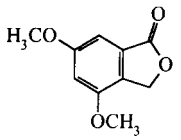
This communication describes a convenient route for the synthesis of naturally occurring dimethoxyphthalides using a Vilsmeier-Haack formylation.

The phthalide nucleus is present in a large number of natural products. A few dihydroxyphthalides and their derivatives have also been reported from natural sources. 5,7-Dimethoxyphthalide **1a**, for example, has been isolated from *Helichrysum italicum*,[1] while its demethoxy analogues **1c** and **1d** occur in an Indian species, *Anaphalis contorta*[2] and 5,7-dihydroxy-4-methylphthalide **1f** has been isolated from *Aspergillus flavus*.[3] Another dimethoxyphthalide **2** has been reported from *Albizzia jubrissin*.[4] These phthalides are valuable as they possess significant biological properties[5,6] and also are widely accepted synthons for the construction of various types of polycyclic systems[7] including isocoumarins,[8] anthraquinones,[9] anthracycline antibiotics,[10] lignans,[11] *etc*. The phthalides **1b** and **1e**, for example, are potential precursors of mycophenolic acid (MPA) **3**, an important antiparasitic,[12] antineoplastic[13] and antiviral[14] agent, in a synthesis involving a stereospecific orthoester Claisen rearrangement.[15] Although a variety of approaches for the synthesis of phthalides **1a**,[16] **1b**[17] and **2**[16h] have been reported involving mostly use of organometallics,[16d,h] considerable attention to new approaches for building these systems is still being paid because of their impressive biological properties and versatility as synthetic intermediates. As a part of our ongoing program directed towards the synthesis of naturally occurring and biologically active phthalides followed by their transformation to highly active anthraquinones and other polycyclic systems, our first goal was to develop an efficient, high yielding and simple route to these phthalides. The present approach developed for the synthesis of 5,7-dimethoxyphthalide, **1a** and its demethoxy analogues **1c** and **1d** is depicted in Scheme 1. The ester, ethyl 3,5-dimethoxy benzoate **4a** was reduced to the alcohol **6a** using lithium aluminium hydride. The alcohol **6a** which was obtained, was masked using acetic anhydride-pyridine and the resultant acetate **7a** was then formylated using DMF and $POCl_3$ to afford the aldehyde **8a**, which was subsequently oxidized using potassium permanganate to the phthalide **1a** in 65% yield. Furthermore, **1a** was found to undergo partial as well as complete demethylation to afford **1c** and **1d** respectively in presence of anhydrous aluminium chloride and dichloromethane as the solvent. Maintaining the basic theme the approach which was developed for the synthesis of **1b** is also depicted in Scheme 1. The introduction of a methyl group was effected via the reduction of the corresponding formyl group. Ethyl 3,5-dimethoxybenzoate **4a** was subjected to a Vilsmeier–Haack formylation using DMF-$POCl_3$ to give ethyl 3,5-dimethoxy-2-formylbenzoate **5** in 80% yield. The formyl ester **5** on Clemmenson reduction using Zn–Hg/HCl in presence of toluene, provided ethyl 3,5-dimethoxy-2-methylbenzoate **4b**, which was reduced to the corresponding alcohol **6b**. The hydroxyl group was protected using acetic anhydride-pyridine to afford the acetate **7b**. Formylation of this using DMF-$POCl_3$ provided the required aldehyde **8b**, which was oxidized using potassium permanganate to the desired 5,7-dimethoxy-4-methylphthalide **1b**. The synthesis of 4,6-dimethoxyphthalide **2** has also been achieved as shown in Scheme 1. Ethyl 3,5-dimethoxy-2-formylbenzoate **5** was reduced using sodium borohydride in methanol. Hydrolysis of the resultant reduced product provided the phthalide **2** in 90% yield

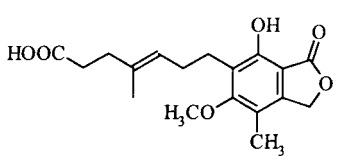


1

a; R = R1 = CH_3, R2 = H
b; R = R1 = R2 = CH_3
c; R = R2 = H, R1 = CH_3
d; R = R1 = R2 = H
e; R = H, R1 = R2 = CH_3
f; R = R1 = H, R2 = CH_3



2



3

In conclusion the present paper describes a convenient method and involving a use of Vilsmeier-Haack formylation offering several distinct advantages for the synthesis of 5,7-dimethoxyphthalide **1a**, its demethoxy analogues **1c** and **1d**, 5,7-dimethoxy-4-methylphthalide **1b**, which is a useful intermediate for mycophenolic acid and 4,6-dimethoxyphthalide **2**.

Experimental

All melting points are uncorrected. IR spectra were recorded on Perkin Elmer and ^{1}H-NMR spectra on a Jeol FX 90Q instrument. Chemical shifts are expressed in PPM downfield from TMS as an internal standard and coupling constants in Hertz. Elemental analysis was obtained on a HOSLI semi-automatic C, H analyzer.

General procedure for reduction: A solution of the ester **4a** or **4b** (47.62 mmol) in anhydrous ether (50 ml) was added dropwise to a slurry of lithium aluminium hydride (2.42 g, 63.80 mmol) and anhydrous ether (100 ml) under efficient stirring and nitrogen atmosphere. The reaction mixture was refluxed for 3 h. It was decomposed sequentially with moist ether (50 ml), water (50 ml) and saturated ammonium chloride solution (aq. 100 ml). The ether layer was separated, washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give benzyalcohol **6a** as colourless needles and **6b** as colourless oil. M.P.: **6a** (45 °C, lit[18]. m.p. 45 °C), **6b** (oil, lit[19]. oil). Yield: **6a** (84%), **6b** (90%). IR cm^{-1} (nujol): **6a** (3452), **6b** (3455) ^{1}H-NMR δ ($CDCl_3$): **6a** [3.87, s, 6H; 4.22, bs, 1H (D_2O exchangeable); 4.75, s, 2H; 6.50, t(*J*=2Hz), 1H; 6.62, d(*J*=2Hz), 2H]. **6b** [2.14, s, 3H; 3.83, s, 6H; 4.04, bs, 1H (D_2O exchangeable); 4.69, s, 2H; 6.44, d(*J*=2Hz), 1H; 6.61, d (*J*=2Hz), 1H]. Anal. calcd. for $C_9H_{12}O_3$: **6a** (C, 64.26; H, 7.19). Found: **6a** (C, 64.28; H, 7.22). Anal. calcd. for $C_{10}H_{14}O_3$: **6b** (C, 65.91; H, 7.74). Found: **6b** (C, 65.94; H, 7.76).

General procedure for acetylation: Dimethoxybenzyl alcohol **6a** or **6b** (29.76 mmol) was added to a solution of dry pyridine (25 ml) and acetic anhydride (25 ml). The reaction mixture was kept at room temperature with occasional shaking for 3 hours. It was then decomposed over crushed ice with stirring and then extracted with chloroform. The organic layer was successively washed with water, dilute HCl, saturated sodium carbonate, and again water. It was dried over

* To receive any correspondence.

anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography on silica gel using hexane as the eluent to provide the resultant acetates **7a** as pale yellow oil and **7b** as white crystals. M.P. : **7a** (oil), **7b** (71 °C): Yield: **7a** (86%), **7b** (88%): IR cm^{-1} (nujol: **7a** (1740), **7b** (1744). ^{1}H-NMR δ ($CDCl_3$): **7a**[2.00, s, 3H; 3.84, s, 6H; 5.14, s, 2H; 6.48, t (*J*=2Hz), 1H; 6.57, d, (*J*=2Hz), 2H]/ **7b** [2.07, s, 6H; 3.71, s, 6H; 5.03, s, 2H; 6.4, bs, 2H]. Anal. calcd. for $C_{11}H_{14}O_4$: **7a** (C, 62.85; H, 6.71). Found: **7a** (C, 62.68; H, 6.75). Anal. calcd. for $C_{12}H_{16}O_4$: **7b** (C, 64.27; H, 7.19). Found: **7b** (C, 64.28; H, 7.22).

General procedure for Vilsmeier Haack formylation: Ethyl 3,5-dimethoxybenzoate (**4a**) or dimethoxybenzyl acetate (**7a** or **7b**) (23.81 mmol) were added dropwise to a complex prepared from DMF (1.74 g, 1.85 ml, 23.81 mmol) and $POCl_3$ (3.65g, 2.3 ml, 23.81 mmol) at 5 °C. The reaction mixture was allowed to attain room temperature and then it was heated at 80 °C for 3 hours. The resulting dark red mixture was cooled and decomposed with saturated solution of sodium acetate with stirring The aldehydes **5, 8a** and **8b** separated out as pale yellow solids which were filtered, washed with water, dried and then crystallized from hexane-ethyl acetate. M.P.: **5** (132 °C), **8a** (110–112 °C), **8b** (175 °C). Yield: **5** (80%), **8a** (78%), **8b** (85%). IR cm^{-1} (nujol): **5** (1725, 1708), **8a** (1740, 1715), **8b** (1744, 1712). ^{1}H-NMR δ ($CDCl_3$): **5** [1.39, t (*J*=8Hz), 3H; 3.91, s, 3H; 3.97, s, 3H; 4.46, q (*J*-8Hz), 2H; 6.63, bs, 1H; 6.70 bs, 1H; 10.50, s, 1H]. **8a** [2.02, s, 3H; 3.91, bs, 6H; 5.69, s, 2H; 6.66, bs, 1H; 6.89, bs, 1H; 10.44, s, 1H]. **8b** [2.17, s, 6H; 3.86, s, 6H; 5.11, s, 2H; 6.36, s, 1H; 10.50, s, 1H]. Anal. calcd. for $C_{12}H_{14}O_5$: **5** (C, 60.49; H, 5.92). Found: **5** (C, 60.18; H, 5.96). Anal. calcd. for $C_{12}H_{14}O_5$: **8a** (C, 60.49; H, 5.92). Found: **8a** (C, 60.02; H, 5.98). Anal. calcd. for $C_{13}H_{16}O_5$: **8b** (C, 61.89; H, 6.39). Found: **8b** (C, 61.89; H, 6.41).

General procedure for oxidation using $KMnO_4$: Formyl benzyl acetate **8a** or **8b** (21.0 mmol) was added portionwise to a mixture of water (50 ml) and 1,4-dioxane (20 ml) and heated at 80 °C. A solution of $KMnO_4$ (3.32 g, 21.0 mmol) was added to this mixture within 10 minutes under mechanical stirring. After completion of the addition, stirring was continued at 80 °C for 45 minutes. The reaction mixture was then basified with NaOH (5%) and immediately filtered hot. The filtrate was acidified with conc. H_2SO_4 when a pink solid precipitated out. The contents were further heated on water bath for 30 minutes and then cooled to room temperature. The pink solid was filtered, washed with water and dried. When crystallized from acetone-ether the phthalides **1a** and **1b** were obtained as off white crystals. M.p.: **1a** (149 °C, lit[2]. m.p. 149–150 °C), **1b** (200–202 °C, lit[17a]. m.p. 202 °C). Yield: **1a** (68%); **1b** (70%). IR cm^{-1} (nujol): **1a** (1760); **1b** (1765). 1H-NMR δ ($CDCl_3$): **1a** [3.91, s, 3H; 4.00, s, 3H; 5.23, s, 2H; 6.50, bs, 1H; 6.57, bs, 1H]. **1b** [2.01, s, 3H; 3.88, s, 3H; 3.94, s, 3H; 5.06, s, 2H; 6.36, s, 1H]. Anal. calcd. for $C_{10}H_{10}O_4$: **1a** (C, 61.85; H, 5.19). Found: **1a** (C, 62.15; H, 5.01). Anal. calcd. for $C_{11}H_{12}O_4$: **1b** (C, 63.45; H, 5.81). Found: **1b** (C, 63.46; H, 5.84).

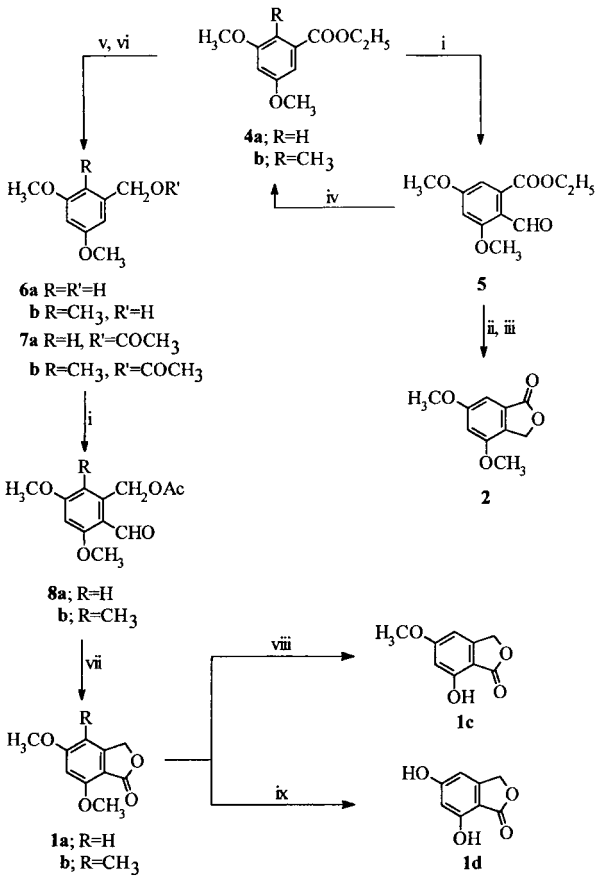
3,5-Dimethoxy-2-methyl-ethyl benzoate (**4b**): To an amalgam of zinc prepared from activated zinc powder (25 g), mercuric chloride (0.75 g) and HCl (50 ml, 5%) was added a solution of ethyl 3,5-dimethoxy-2-formyl benzoate, **5** (23.81 mmol) in toluene (50 ml) and conc. HCl (100 ml). After the initial vigorous reaction had subsided, the reaction mixture was refluxed for 1 hour and then allowed to cool to room temperature. The organic layer was separated and the aqueous layer was extracted with ether (3 × 50 ml). The combined organic extracts were washed with cold water, dried over anhydrous sodium sulphate and evaporated *in vacuo* to yield the desired reduced ester as pale yellow oil. Column chromatography over silica gel using hexane as eluent afforded **4b** as colourless viscous oil. M.p.: oil. Yield: 85%. IR cm^{-1} (nujol): 1726. ^{1}H-NMR δ ($CDCl_3$): 1.37, t (*J*=6.5Hz), 3H; 2.29, s, 3H; 3.76, s, 6H; 4.33 q (*J*=6.5Hz), 2H; 6.49, d (*J*=2Hz), 1H; 6.81, d (*J*=2Hz), 1H. Anal. calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.22.

7-Hydroxy-5-methoxy phthalide (**1c**): 5,7-Dimethoxyphthalide **1a** (0.5 g, 2.58 mmol) was dissolved in dry CH_2Cl_2 (10 ml) and the solution was added dropwise to a well-stirred complex prepared from anhydrous $A1Cl_3$ (1.02 g, 7.73 mmol) and dry CH_2Cl_2. (20 ml) under stirring. The reaction mixture was stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure and the dry residue was decomposed by 1:1 HCl (100 ml). The solid obtained was filtered out, dried and triturated with dry ether, which provided the phthalide **1c** as a yellow solid. It was crystallized from hexane-chloroform. M.p.: 180 °C (lit[2]. m.p. 180 °C). Yield: 0.350 g (76%); IR cm^{-1} (nujol): 3280, 1720. ^{1}H-NMR δ ($CDCl_3$): 3.89, s, 3H; 5.29, s, 2H; 6.54, bs, 2H; 11.50, s, 1H. Anal. calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.91; H, 4.45.

5-7-Dihydroxy phthalide (**1d**): 5,7-Dimethoxyphthalide **1a** (1.0 g, 5.15 mmol) was subjected to demethylation by using anhydrous $A1Cl_3$ (3.45 g, 2.58 mmol) and dry dichloromethane (50 ml) as per the above procedure. The reaction was complete after 6 hours. Similar work up followed by trituration with ethanol provided the phthalide **1d** as a white solid.

M.p.: 239–240 °C (lit[2]. m.p. 240 °C). Yield: 0.640 g (75%). IR cm^{-1} (nujol): 3340, 3285, 1715. ^{1}H-NMR δ (DMSO-d_6): 5.16, s, 2H; 6.42, bs, 2H; 9.1, bs, 1H; 10.2, s, 1H. Anal. calcd. for $C_8H_6O_4$: C, 57.84; H, 3.64. Found : C, 57.88; H, 3.62.

4,6-Dimethoxy phthalide (**2**): Ethyl 3,5-dimethoxy-2-formyl benzoate **5** (1.0 g, 4.2 mmol) was dissolved in distilled methanol (75 ml) under stirring. To this solution was added sodium borohydride (1.0 g, 26.32 mmol) in portions, under stirring. The mixture was stirred further for 30 minutes. After completion of the reaction, excess methanol was evaporated *in vacuo* and the residue was acidified using 1: HCl (25 ml). The resultant solid obtained was filtered, washed with water, dried and crystallized from hexane-ethylacetate to furnish the phthalide **2** as colourless crystals. M.P.: 167 °C (lit[16h]. m.p. 169 °C). Yield: 0.74 g (90%). IR cm^{-1} (nujol): 1760. ^{1}H-NMR δ ($CDCl_3$): 3.80, s, 6H; 5.11, s, 2H; 6.60, d (*J*=2.6Hz), 1H; 6.83, d (*J*=2.6Hz), 1H. Anal. calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.88; H, 5.13.



Scheme 1

Reagents and conditions
(i) DMF-$POCl_3$, 80 °C, 4h; (ii) $NaBH_4$-CH_3OH, stir, room temp. 1h; (iii) H_3O^+, 80 °C, 30 min; (iv) Zn–Hg, HCl, toluene, reflux, 1h; (v) $LiAlH_4$, dry Et_2O, stir, R.T., 3h; (vi) Ac_2O-pyridine, stir R.T., 3h; (vii) $KMnO_4$-dioxane, stir, 80 °C 1h; (viii) 3 eq. $AlCl_3$-CH_2Cl_2, stir, R.T., 30 mins, (ix) 5 eq. $AlCl_3$-CH_2Cl_2, stir, R.T., 6h.

We are grateful to Dr. A.S. Inamdar, Principal, A.G. College, Pune for providing the necessary facilities and University of Pune for the spectral and elemental analyses. S.A. Kulkarni (SRF), A.R. Joseph (SRF) and A.A. Ranade (SRF) thank CSIR for financial assistance.

Received 9 May 2000; accepted 5 June 2000.
Paper 00/316.

References

1 L. Opitz and R. Haensel, *Arch. Pharm. (Weinham)*, 1971, **304(3)**, 228.
2 B. Talpatra, M.K. Roy and S.K. Talpatra, *Indian J. Chem*., 1980, **19(B)**, 927.
3 J.F. Grove, *J. Chem Soc.*, *Perkin 1*, 1972, **19**, 2406.
4 Y. Nakano and T. Takashima, *Mokuzai Gakkaishi*, 1975, **21**, 577.
5 S. Osada and T. Inouye, *Kitanippon Byogaichu Kenkyukaiho*, 1981, **32**, 102 CA: **98**:174686s 1983.
6 J.P. Paupelin and G. Narcisse, *Fr. Demande*, 1979, 241561. CA:, **92**: 110834g 1980.
7 T.M. Harris, C.M. Harris, P.C. Kuzma, J.Y.C Lee, S. Mahalingam and S.G. Gilbreath, *J. Am. Chem. Soc*., 1988, **110(8)**, 6186.
8 R.S. Mali, P.G. Jagtap, S.R. Patil and P.N. Pawar, *J. Chem. Soc. Chem. Commun*., 1992, 883.
9 J.E. Baldwin and K.W. Bair, *Tetrahedron Lett*., 1978, 2559.
10 T. Li and Y. Wu, *J. Am. Chem. Soc*., 1981, **103**, 7007.
11 M. Iwao, H. Inoue and T. Karaishi, *Chem. Lett*., 1984, 1263.
12 R. Verham, T.D. Meek, L. Hedstrom and C.C. Wang, *Mol. Biochem. Parasitol*., 1987, **24**, 1.
13 E.H. Stet, R.A. Deabrau, J.P. Bokkerink, L.H.J. Lambooy, T.M. Vogelsmentik and F.J.M. Trijbels, *Ann. Clin. Biochem*., 1994, **31**, 174.
14 C. Alfieri, A.C. Allison and E. Kieff, *Antimicrob. Agents Chemother*., 1994, **38**, 126.
15 J.W. Patterson and G.T. Huang, *JCS. Chem. Commun*., 1991, 1579.
16 (a) A.J. Birch and J.J. Wright, *Aust. J. Chem*., 1969, **22**, 2635; (b) N.M. Rana, M.V. Sargent and J.A. Elix, *JCS. Perkin 1*, 1975, 1992; (c) B.M. Trost, G.T. Rivers and J.M. Gold, *J. Org. Chem*., 1980, 1835; (d) P.D. Noire and R.W. Franck, *Synthesis*, 1980, **11**, 882; (e) B. Talpatra, M.K. Roy and S. Talpatra, *J. Ind. Chem. Soc*., 1983, **60(12)**, 1169; (f) M.V. Sargent, *JCS.*, *Perkin 1*, 1987, 231; (g) G.H. Kulkarni and G. Kumaran, *Indian J. Chem*., 1995, **34B(5)**, 436; (h) R.S. Mali, P.G. Jagtap and S.G. Tilve, *Synth. Commun*., 1990, **20(17)**, 2641.
17 (a) L. Canonica, B. Rindone, E. Santaniello and C. Scolastico, *Tetrahedron*, 1972, **28**, 4395; (b) L. Colombo, C. Gennari, D. Potenza and C. Scolastico, *JCS. Chem. Commun*., 1979, 1021; (c) S. Aurrichio, A. Ricca and O.V. de Pava, *J. Org. Chem*., 1983, **48**, 602; (d) M. Watanabe, M. Tsukazaki, Y. Hamada, M. Owao and S. Furukawa, *Chem. Pharm. Bull*., 1989, **37**, 2948; (e) K. Kobayashi, H. Shimizu, M. Itoh and H. Suginome, *Bull. Chem. Soc. Jpn*., 1990, **63**, 2435; (f) J. Lee and W.K Anderson, *Synth. Commun*., 1992, **22**, 369; (g) J.W. Patterson, *Tetrahedron*, 1993, **22**, 4789; (h) J.W. Patterson, *J. Org. Chem*., 1995, **60**, 4542; (i) G.M. Makara and W.K. Anderson, *J. Org. Chem*., 1995, **60**, 5717; (j) G.M. Makara and W.K. Anderson, *Synth. Commun*., 1996, **26(10)**, 1935.
18 N. Koohei, N. Shoichi and K. Ken-ichi, *Chem. Pharm. Bull*., 1980, **28**, 1112.
19 C.H. Hassall and B.A. Morgan, *JCS. Perkin 1*, 1973, **23**, 2853.