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AN EFFICIENT SYNTHESIS OF 4,6 DIMETHOXYAURONES

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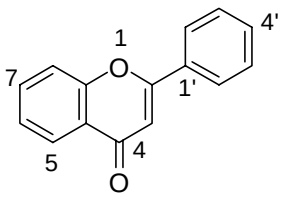
Abstract 4,6-Dimethoxybenzofuran-3(2*H*)-one was synthesized in two steps Starting from phloroglucinol and used as a useful starting block for the synthesis of aurones by condensation with benzaldehyde derivatives.

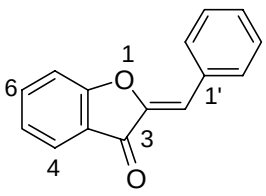
INTRODUCTION

Aurones are secondary metabolite pigments widely present in fruits and vegetables. These highly colored flavonoids derivatives are mostly found as their hydroxylated, methoxylated or glycosylated forms (Figure 1). Beside their contribution to plants color, aurones possess a wide range of biological activities.[1] Especially, they have been described as antifungal agents and as phytoalexins. Aureusidin (4,6,3',4'-tetrahydroxyaurone) was found to be a potent inhibitor of iodothyronine-deiodinase in rat liver microsomal membrane.[2] Recently, Kayser *et al.* reported the drug-potential of aurones for *Leishmania* infections.[3] Literature surveys have disclosed the frequent presence of a 4,6-dihydroxyl groups in these compounds (Figure 1).[4] In the flavone series, these hydroxyl groups (positions 5 and 7) are often required for the biological activities.[5,6] Our interest in the biological properties of variably substituted aurones prompted us to investigate the synthesis of 4,6-oxygenated aurones.

Aurones are synthesized by the oxidative cyclization of 2'-hydroxychalcones.[7] Joshi *et al*. have synthesized aurones by condensation of 2-bromo-2'-hydroxyacetophenone with salicylaldehyde.[8] Flavones are also oxidized to aurones using strong oxidizing agents.[9-11] Some sensitive substituents, like glycosyl and isoprenyl groups which are frequently present on flavones and aurones,[4] are incompatible with such reagents. In this Note, we describe the synthesis of 4,6-dimethoxybenzofuran-3(2*H*)-one as a convenient starting block and its use for the synthesis of aurones.



Flavone

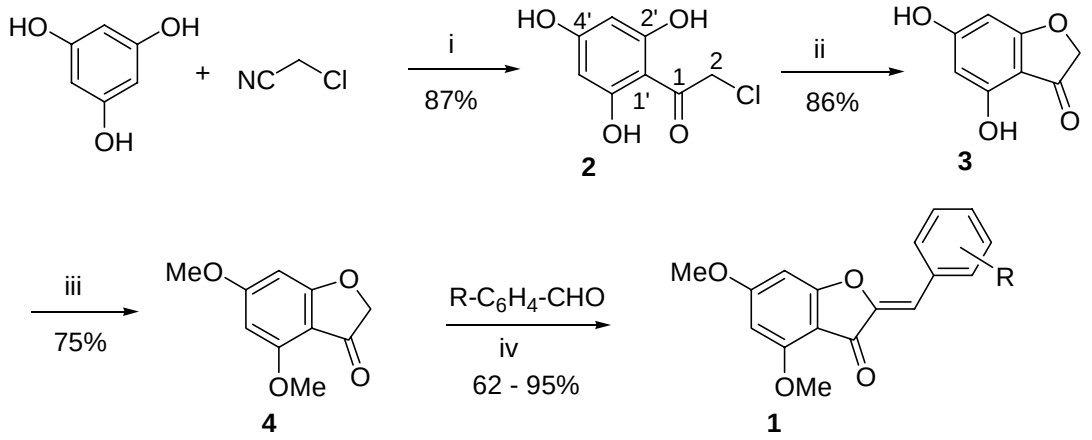


Aurone

Figure 1.

RESULTS AND DISCUSSION

The key intermediate, 4,6-dimethoxybenzofuran-3(2*H*)-one (**4**) was obtained in three steps starting from phloroglucinol.



Scheme 1. (**i**) a. $ZnCl_2$, HCl, Et_2O, 0°C ; b. 1N HCl, 100°C. (**ii**). MeONa, MeOH, reflux, 2 h. (**iii**). MeI, K_2CO_3, DMF, 80°C, 1 h. (**iv**). KOH, MeOH/H_2O, rt, 1 h.

Condensation of phloroglucinol with chloroacetonitrile catalyzed by $ZnCl_2$ gave the imine intermediate which was hydrolyzed *in situ* with aqueous 1N HCl to provide the corresponding ketone (**2**) in 87 % yield.[12,13] Using chloroacetyl choride as the acylating agent furnished **2** in very low yield. Treatment of **2** with sodium methoxide in MeOH gave benzofuranone (**3**) in 86% yield. The overall yield for this process was about 74 % and we have found it can be easily accomplished on multigram scale.

The acidic 6-hydroxyl group and the chelated 4-hydroxyl group were protected with MeI using K_2CO_3 in DMF to give (**4**) in 75 % yield. Condensation of (**4**) with benzaldehyde derivatives in the presence of an excess of KOH in H_2O/MeOH gave the expected aurone (**1**) in high yields. The configuration of the double bond is exclusively Z as can be assigned on the basis of the chemical shift of the olefinic proton δ 6.70 (δ 7.01 for the *E* isomer) as previously reported.[7]

Table 1. 4,6-Dimethoxyaurones (**1**) prepared according to Scheme 1.

Entry	R	Yield (%) of 1 from 4
1a	H	62
1b	4'-F	77
1c	4'-Cl	94
1d	4'-Br	80
1e	2',4',5'-$(OMe)_3$	95
1f	4'-$N(Me)_2$	71

If appropriately substituted benzaldehydes are selected, our synthetic approach constitutes a simple and high yield procedure for the synthesis of diverse aurones. The 4,6-methoxy groups can be partialy or totally hydrolyzed to yield 4-hydroxy-6-methoxy aurones or 4,6-dihydroxyaurones respectively.[14] This methodology may aid in studying the structure-activity relationship of aurones.

EXPERIMENTAL

General : Melting points were measured on a Fisher micromelting point apparatus and are uncorrected. MS spectra were determined on a JEOL HX-110 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on Bruker AC-200 spectrometer and were referenced to internal standards, TMS (δ_H = 0.00, δ_C = 0.0); $CDCl_3$ (δ_H = 7.27, δ_C = 77.0); CD_3OD (δ_H = 4.87, δ_C = 49.2), or DMSO-*d*$_6$ (δ_H = 2.49, δ_C = 39.4).

2',4',6'-Trihydroxy-2-chloroacetophenone (2). To a mixture of phloroglucinol (5 g, 39.7 mmol) and chloroacetonitrile (2.5 mL, 39.7 mmol) in ether (100 mL) was added anhydrous $ZnCl_2$ (0.54 g, 3.96 mmol). The solution was cooled to 0°C and HCl was bubbled through the reaction for 15 min. The solution was left in the cold-room overnight and HCl was bubbled again for 15 min. The precipitated imine was filtered off and washed three times with ether. The imine was dissolved in 100 mL of 1N HCl and heated at 100°C for 1 h. The solid was filtered off, washed three times with water and dried under vacum to yield pure acetophenone (**2**) as a pale white solid which was used without further purification. Yield 6.97 g (87%) ; mp 185-187 °C (Et_2O); ^{1}H NMR (DMSO-*d*$_6$, 200 MHz) δ 4.20 (2H, s), 6.15 (2H, s), 11.23 (1H, br s), 12.76 (2H, br s); ^{13}C NMR (DMSO-*d*$_6$, 50 MHz) δ 50.8 (C-2), 94.8 (C-3', C-5'), 102.6 (C-1'), 164.0 (C-2', C-6'), 165.6 (C-4'), 194.7 (C-1); HRMS calcd for $C_8H_7O_4Cl$: 202.1951; found: 202.1948. Anal. Calcd for $C_8H_7O_4Cl$: C, 47.43; H, 3.48; Cl, 17.50. Found: C, 47.36; H, 3.47; Cl, 17.41.

4,6-Dihydroxybenzofuran-3(2*H*)-one (3). To a solution of (**2**) (4.3 g, 21.2 mmol) in methanol (50 mL) was added sodium methoxide (4.19 g, 77.6 mmol) and the mixture was refluxed for 2 h. After cooling, the solution was acidified with 1N HCl and evaporated. The residue was extracted with ethyl acetate and the extract was washed with water, brine, dried over Na_2SO_4 and evaporated. Column chromatography using CH_2Cl_2 as eluent gave 3.02 g (86%) of **3** as a brown solid. mp 210-212 °C (CH_2Cl_2); ^{1}H NMR (CD_3OD, 200 MHz) δ 4.56 (2H, s), 5.88 (1H, d, *J* = 1.8 Hz), 5.94 (1H, d, *J* = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 76.48 (C-2), 91.6 (C-7), 95.5 (C-5), 104.1 (C-9), 159.2 (C-8), 170.4 (C-6), 177.8 (C-4), 198.1 (C-3); HRMS calcd for $C_8H_6O_4$: 165.7342; found: 165.7342. Anal. Calcd for $C_8H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.80; H, 3.61.

4,6-Dimethoxybenzofuran-3(2*H*)-one (4). To a solution of **3** (1 g, 6.02 mmol) in DMF (15 mL) was added K_2CO_3 (1.66 g, 12.04 mmol) and MeI (1.12 mL, 18.06 mmol). The solution was heated at 80°C for 1 h, poured into water and extracted with EtOAc. The EtOAc was dried with anhydrous Na_2SO_4, filtered and removed by rotary evaporation to yield a brown, viscous oil. The oil was subjected to column chromatography using 1:1 hexane:EtOAc to yield 876 mg (75%) of pure **4** as a yellow solid. mp 132-133 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.74 (3H, s), 3.78 (3H, s), 4.45 (2H, s), 5.88 (1H, d, *J* = 1.7 Hz), 6.02 (1H, d, *J* = 1.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.03 (OCH_3), 56.05 (OCH_3), 75.5 (C-2), 88.9 (C-7), 93.0 (C-5), 104.8 (C-9), 158.9 (C-8), 169.8 (C-6), 177.2 (C-4), 194.9 (C-3), HRMS calcd for $C_{10}H_{10}O_4$: 193.7883; found: 193.7883. Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.78; H, 5.15.

Aurones 1(a-f), general procedure: To a solution of **4** (100 mg, 0.51 mmol) in MeOH (5 mL) was added benzaldehyde (0.76 mmol) followed by the addition of KOH (500 mg, 8.92 mmol in 1 mL of H_2O). The solution was stirred at rt for 30 min, hydrolyzed by adding water and extracted three times with EtOAc. The EtOAc was dried with anhydrous Na_2SO_4, filtered and removed by evaporation to yield crude **1** which was purified by column chromatography using hexane:ethyl acetate 3:1.

(*Z*)-Benzylidene-4,6-dimethoxybenzofuran-3(*2H*)-one (1a): Yellow powder; mp 154-156 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.90 (3H, s), 3.94 (3H, s), 6.12 (1H, d, *J* = 1.8 Hz), 6.37 (1H, d, *J* = 1.7 Hz), 6.76 (1H, s), 7.40-7.37 (3H, m), 7.85 (2H, dd, J_1 = 1.7 Hz, J_2 = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.1 (OCH_3), 56.2 (OCH_3), 89.3 (C-7), 94.1 (C-5), 106.6 (C-9), 110.7 (Ph-**C**H=), 128.7 (C-2', C-6'), 129.3 (C-4'), 131.1 (C-3', C-5'), 132.6 (C-1'), 147.9 (C-2), 159.5 (C-8), 169.0 (C-4', C-6'), 180.6 (C-3) ; HRMS calcd for $C_{17}H_{14}O_4$: 281.8978; found: 281.8978. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.26; H : 4.98.

(*Z*)-4,6-Dimethoxy-(4'-fluorobenzylidene)benzofuran-3(*2H*)-one (1b): White powder; mp 173-174 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.92 (3H, s), 3.96 (3H, s), 6.14 (1H, d, *J* = 1.7 Hz), 6.38 (1H, d, *J* = 1.7 Hz), 6.73 (1H, s), 7.16 (2H, t, *J* = 8.7 Hz), 7.85 (2H, dd, J_1 = 5.5 Hz, J_2 = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.2 (OCH_3), 56.3 (OCH_3), 89.4 (C-7), 94.2 (C-5), 105.0 (C-9), 109.7 (Ph-**C**H=), 116.1 (d, *J* = 22.4 Hz, C-3', C-5'), 129.0 (C-1'), 133.1 (d, *J* = 8.5 Hz, C-2', C-6'), 147.6 (C-2), 159.6 (C-8), 163.2 (d, *J* = 250 Hz, C-4'), 169.1 (C-4, C-6), 180.7 (C-3) ; HRMS calcd for $C_{17}H_{13}O_4F$: 299.8883; found: 299.8880. Anal. Calcd for $C_{17}H_{13}O_4F$: C, 68.00; H, 4.36; F, 6.33. Found: C, 67.95; H, 4.35; F, 6.02.

(*Z*)-(4'-Chlorobenzylidene)-4,6-dimethoxybenzofuran-3(*2H*)-one (1c): White powder; mp 173-174 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.92 (3H, s), 3.96 (3H, s), 6.14 (1H, d, *J* = 1.7 Hz), 6.38 (1H, d, *J* = 1.7 Hz), 6.70 (1H, s), 7.39 (2H, d, *J* = 8.6 Hz), 7.79 (2H, d, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.1 (OCH_3), 56.2 (OCH_3), 89.3 (C-7), 94.2 (C-5), 105.0 (C-9), 109.3 (Ph-**C**H=), 129.0 (C-3', C-5'), 131.1 (C-1'), 132.2 (C-2', C-6'), 135.2 (C-4'), 148.0 (C-2), 159.5 (C-8), 169.0, 169.1 (C-4, C-6), 180.4 (C-3) ; HRMS calcd for $C_{17}H_{13}O_4Cl$: 316.3427; found: 316.3418. Anal. Calcd for $C_{17}H_{13}O_4Cl$: C, 64.46; H, 4.14; Cl, 11.19. Found: C, 64.42; H. 4.11; Cl, 11.08.

(Z)-4'-Bromobenzylidene-4,6-dimethoxybenzofuran-3(*2H*)-one (1d): Yellow powder; mp 171-172 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.92 (3H, s), 3.96 (3H, s), 6.14 (1H, d, *J* = 1.7 Hz), 6.38 (1H, d, *J* = 1.7 Hz), 6.68 (1H, s), 7.54 (2H, d, *J* = 8.6 Hz), 7.72 (2H, d, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.1 (OCH_3), 56.2 (OCH_3); 89.3 (C-7), 94.1 (C-5), 105.1 (C-9), 109.2 (Ph-**C**H=), 123.5 (C-4'), 131.5 (C-1'), 131.9 (C-2', C-6'), 132.3 (C-3', C-5'), 148.1 (C-2), 159.5 (C-8), 169.0, 169.1 (C-4, C-6), 180.4 (C-3) ; HRMS calcd for $C_{17}H_{13}O_4Br$: 360.7935; found: 360.7930. Anal. Calcd for $C_{17}H_{13}O_4Br$: C, 56.53; H, 3.63; Br, 22.12. Found: C, 56,49; H, 3.60; Br, 22.00.

(*Z*)-Benzylidene-4,6,2',4',5'-pentamethoxybenzylidenebenzofuran-3(*2H*)-one (1e): Yellow powder ; mp > 260 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.84 (3H, s), 3.85 (3H, s), 3.80 (3H, s), 3.91 (3H, s), 3.95 (3H, s), 6.12 (1H, d, *J* = 1.7 Hz), 6.32 (1H, d, *J* = 1.7 Hz), 6.51 (1H, s), 7.29 (1H, s), 7.83 (1H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.2 (OCH_3), 55.3 (OCH_3), 55.4 (OCH_3), 55.6 (OCH_3), 55.9 (OCH_3), 88.3 (C-7), 93.1 (C-5), 95.7 (C-3'), 104.6 (C-9), 112.6 (Ph-**C**H=), 113.9 (C-6'), 142.3 (C-5'), 145.8 (C-2), 151 (C-4'), 153.9 (C-2'), 158.5 (C-8), 167.6 (C-4, C-6), 179.6 (C-3); HRMS calcd for $C_{20}H_{20}O_7$: 371.6772 ; found: 371.6772. Anal. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found : 64.45; H, 5.37.

(Z)-4,6-Dimethoxy-(4'-dimethylaminobenzylidene)benzofuran-3(*2H*)-one 1f: Orange powder; mp 188-189 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.04 (6H, s), 3.89 (3H, s), 3.94 (3H, s), 6.11 (1H, d, *J* = 1.7 Hz), 6.36 (1H, d, *J* = 1.7 Hz), 6.70 (1H, s), 6.75 (2H, d, *J* = 8.8 Hz), 7.77 (2H, d, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.2 (N-$(Me)_2$), 56.1 (O CH_3), 56.3 (OCH_3), 89.2 (C-7), 93.8 (C-5), 105 (C-9), 112.1 (C-3', C-5'), 112.7 (Ph-**C**H=), 120.5 (C-1'), 133.1 (C2', C-6'), 146.0 (C-2), 151.1 (C-4'), 159.3 (C-8), 168.3, 168.5 (C-4, C-6), 180 (C-3) ; HRMS calcd for $C_{19}H_{19}NO_4$: 324.9666; found: 324.9661. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.64; H, 5.90; N, 4.33.

REFERENCES AND NOTES

1. J. R. Harborne, The Flavonoids: Advances in Research Since 1986, Chapman and Hall, London, 1994, pp. 399-341.
2. M. Aufmkolk, J. Koerhle, R. D. Hesch, and V. Cody, *J. Biol. Chem*., 1986, **261**, 11623.
3. O. Kayser, A. F. Kiderlen, U. Folkens, and H. Kolodziej, *Planta Medica*, 1999, **65**, 316.
4. J. B. Harborne, H. Baxter, and G. P. Moss, *Phytochemical Directory : A Handbook of Bioactive Compounds from Plants*, Taylor & Francis LTD, London, 1999, pp. 362-374.
5. W. F. De Azevedo, H. J. Mueller-Dieckmann, U. Schulze-Gahnem, P. J. Worland, E. Saysville, and S. H. Kim, *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 2735.
6. F. Sicheri, I. Moarefi, and J. Kuriyan, *Nature*, 1997, **385**, 602.
7. K. Thakkar and M. Cushman, *J. Org. Chem*., 1995, **60**, 6499.
8. U. Kjoshi and M. V. Paradkar, *Indian. J. Chem., Sect.,* 1988, **27B**, 378.
9. B. Cummins, D. M. X. Donnely, J. F. Eades, H. Fletcher, F. O'Cinneide, E. M. Philbin, J. Swirski, T. S. Wheeler, and R. K. Wilson, *Tetrahedron*, 1963, **19**, 499.
10. T. R. Gormley and W. I. O'Sullvian, *Tetrahedron*, 1973, **29**, 369.
11. C. J. Adams and L. Main, *Tetrahedron*, 1991, **47**, 4979.
12. K. Wähälä and T. A. Hase, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3005.
13. Y. C. Chang, M. G. Nair, R. C. Santell, and W. G. Helferich, *J. Agric. Food. Chem*., 1994, **42**, 1869.
14. In a typical procedure : A solution of aurone (**1)** in CH_2Cl_2 was treated with BBr_3 (1M in CH_2Cl_2, 2 eq) at rt for 24 h to yield 4-hydroxy-6-methoxyaurones and 4,6-dihydroxyaurones which can be separated by chromatography. In the same conditions, aurone (**1e)** gave a complex mixture of several compounds.