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Preparation and Properties of Unsymmetrical Benzoins and Related Compounds

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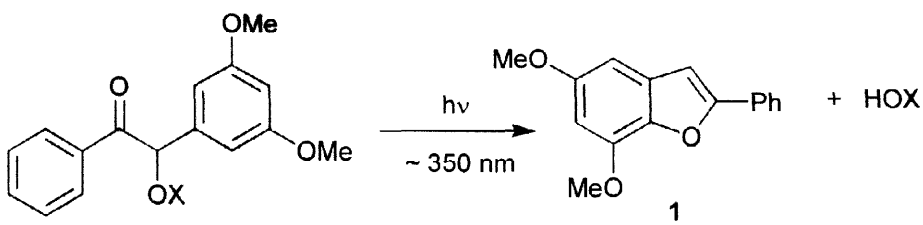
Abstract: Synthesis of unsymmetrical benzoins and their esters can be compromised by isomerisation via the enediol (or its anion). This could be avoided by suitable reaction conditions for the benzoins and their esters **2a/b** and **3a/b** but not for the 3-furyl compound **4a**. A convenient synthesis of 3,5-dimethoxy-2,4,6-trimethylbenzaldehyde **10** is described and the compound was converted to the hindered benzoin **5a**.

INTRODUCTION

The photocleavage of benzoin derivatives has been of interest to several groups in recent years. In particular carboxylate[1] and phosphate[2,3] esters, carbamates[4-6] and carbonates[7] of 3',5'-dimethoxybenzoin undergo clean photolysis to liberate the respective acid together with 5,7-dimethoxybenzo[*b*]furan **1** (Scheme 1). We have recently published preliminary results of an investigation into the photolytic mechanism which indicated that the primary photochemical event is heterolytic cleavage of the C–O bond α to the benzoyl carbonyl group, assisted by electronic interaction between the electron-rich dimethoxybenzene ring and the singlet n,π* excited ketone.[8] To extend this mechanistic study we required the acetate esters **2b-5b** of several new unsymmetrical benzoins or related compounds, and preparation of each of these compounds exposed some interesting results which are reported here. Details of photolytic studies with these compounds will be described elsewhere.



Scheme 1

RESULTS AND DISCUSSION

Unsymmetrical benzoins can be synthesised efficiently from trimethylsilyl (TMS) ethers of aryl cyanohydrins, either by addition of a Grignard reagent to the nitrile[9] or by metallation followed by addition of

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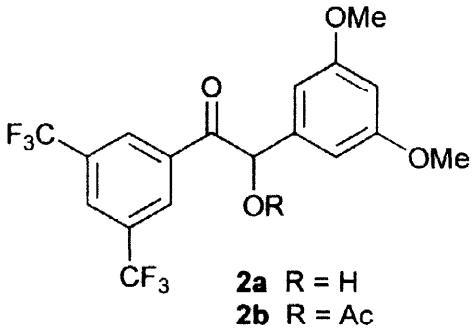
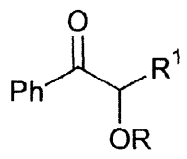
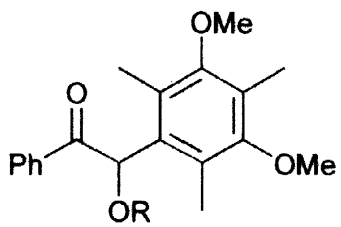
the cyanohydrin carbanion to an aromatic aldehyde.[10] Both methods have recently been used for this purpose by our group[2a] and others.[3a,11] Addition of 3,5-bis(trifluoromethyl)phenylmagnesium bromide[12] to the cyanohydrin TMS ether of 3,5-dimethoxybenzaldehyde gave a reaction mixture from which the expected benzoin **2a** could be isolated by chromatography. In the course of an attempt to obtain the acetate **2b** directly from the crude reaction mixture, the benzoin **2a** was treated with acetic anhydride–pyridine at room temperature. These conditions would normally yield the acetate **2b** and thus we were surprised to obtain instead the enediol diacetate **6**. Enediol diesters are well known products from acylation of benzoins under forcing conditions, such as heating with Ac_2O–KOAc,[13] or have been obtained under milder conditions when steric[14] or hydrogen bonding[15] effects favour the enediol rather than the hydroxyketone tautomer of the benzoin. In the present case, the ^1H NMR spectrum of the benzoin confirmed that it exists as the hydroxyketone (see Experimental section) and facile formation of the diacetate **6** must arise from unusually ready enolisation caused by the inductive effect of the trifluoromethyl groups. By contrast, treatment of the crude reaction product with acetyl chloride in the absence of added base readily gave the acetate **2b** and photolysis of this compound cleanly gave the expected benzofuran **7**.



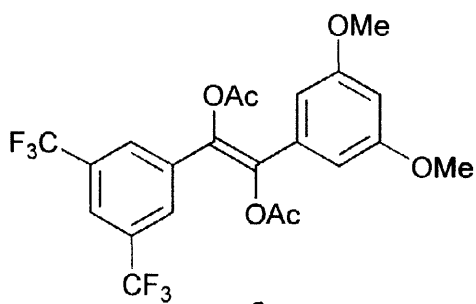
2a R = H
2b R = Ac



3a R = H, R^1 = 2-furyl
3b R = Ac, R^1 = 2 furyl
4a R = H, R^1 = 3-furyl
4b R = Ac, R^1 = 3-furyl



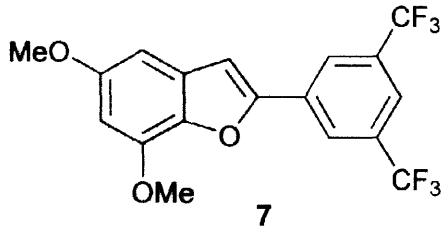
5a R = H
5b R = Ac



6

We also required the two benzofuroin acetates **3b** and **4b** to compare their reactivity with that of the poorly photolabile furoin esters reported by Peach *et al.*[16] The 2-furyl compound **3a** has been reported previously[17] but the 3-furyl compound **4a** was unknown. Synthesis of each alcohol was achieved by reaction of the anion of benzaldehyde cyanohydrin TMS ether with the appropriate furaldehyde but in each case isolation of the product was complicated by facile equilibration with the respective furobenzoins **8** and **9**. For the 2-furyl compound, deprotection of the initial cyanohydrin TMS ether product was performed with TBAF

to avoid exposure of the furan to the strongly acidic conditions previously used.[2a] However the TBAF procedure gave a mixture of the compounds **3a** and **8** (ratio ~4:1), which were conveniently distinguished by the ^{1}H NMR signals of their methine protons at δ 6.02 and 5.76 respectively. Addition of one equivalent of acetic acid to the deprotection solution to buffer the basicity of the fluoride ion[18] reduced the proportion of the unwanted isomer **8**, and three equivalents of acetic acid (with respect to TBAF) suppressed it completely, thereby enabling isolation of the pure benzofuroin **3a**. Cameron *et al.*[11] have reported that 3,5-dimethoxybenzoin was completely isomerised during analogous TBAF deprotection of its TMS cyanohydrin precursor.



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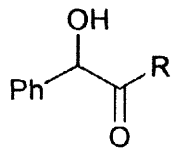


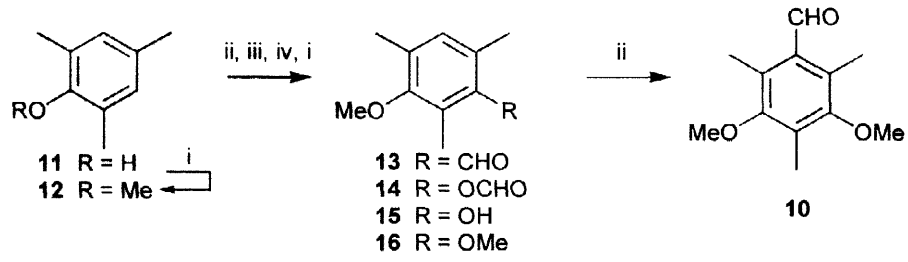
8 R = 2-furyl
9 R = 3-furyl

An authentic sample of the 2-furobenzoin **8** which aided the spectroscopic assignments was obtained by a published procedure[19] in which benzoin, 2-furaldehyde and KCN were heated together. Contrary to the published data, in our hands the reaction generated a mixture of benzoin, furoin and the furobenzoin **8** (characterised by ^{1}H NMR signals of the methine protons for each at δ 5.94, 5.79 and 5.74 respectively) in a ratio of ~2:1:3.5, but the required compound **8** could be isolated by chromatography.

Synthesis of the 3-furyl compound **4a** was as described for **3a**, except for the use of 3-furaldehyde. In this case the presence of acetic acid during TBAF deprotection did not prevent substantial isomerisation and the crude reaction product contained the isomers **4a** and **9** in a ratio of ~3:2. Fortunately the required ester **4b** was readily isolated by crystallisation after acetylation, and then saponification of the mother liquor gave the free isomeric alcohol **9**. The remarkably ready isomerisation of **4a** to **9** is probably driven by favourable resonance interaction of the carbonyl group with the oxygen of the 3-furyl ring in **9**, where the structure can be regarded as a vinylogous ester.

The dimethoxytrimethylbenzoin **5a**, which on illumination should be unable to cyclise as in Scheme 1, was also of interest to us and its synthesis required the unknown 3,5-dimethoxy-2,4,6-trimethylbenzaldehyde **10**. A previous route to derivatives of trimethylresorcinol, which began from dinitromesitylene, involved laborious stepwise reduction, diazotisation etc.[20] and proceeded in poor overall yield. We therefore developed the much easier procedure shown in Scheme 2, starting from readily available mesitol **11**. Despite numerous literature reports, methylation with dimethyl sulfate was always incomplete in our hands, but the pure ether **12** could be obtained after extraction of unreacted mesitol with Claisen's alkali.[21] Formylation of **12** with dichloromethyl methyl ether–$TiCl_4$[22] readily gave the aldehyde **13**, which was smoothly oxidised to the formate **14** with H_2O_2–SeO_2.[23] Alkaline hydrolysis gave the phenol **15** which was methylated to give diether

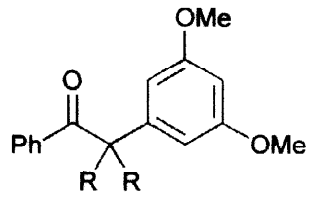
16 (again using Claisen's alkali extraction to remove any unreacted phenol). Formylation of **16** gave the aldehyde **10** in an overall yield of 26 % for the six steps from mesitol. The aldehyde **10** reacted smoothly with the anion of benzaldehyde cyanohydrin TMS ether to give the benzoin **5a** after deprotection with TBAF–HOAc, and Ac_2O–pyridine then gave the expected acetate **5b**.



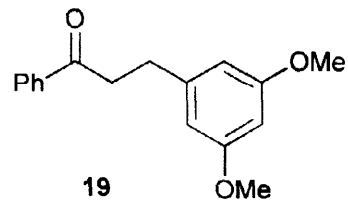
Scheme 2

Reagents: (i) Me_2SO_4-aq. NaOH; (ii) Cl_2CHOMe-$TiCl_4$; (iii) H_2O_2-SeO_2; (iv) KOH-aq. MeOH;

Three additional compounds were required for our photochemical investigation and are reported here for conciseness. They were the deoxybenzoin **17**, its α,α-dimethyl analogue **18** and the homodeoxybenzoin **19**. In each case they were prepared by standard methods reported in the Experimental section.



17 R = H
18 R = Me



19

The results described here highlight the well-known propensity of unsymmetric benzoins for structural isomerisation, which in part has stimulated continued interest in mild methods for synthesis of these compounds.[17,24] Recent data from this laboratory on the unexpectedly easy regioisomerisation of carbamates derived from 3',5'-dimethoxybenzoin[6] indicate that positional integrity should never be assumed, whether for the parent benzoins or their *O*-acyl derivatives.

ACKNOWLEDGEMENTS

We are grateful to the MRC Biomedical NMR Centre for access to facilities and to Dr V. R. N. Munasinghe for recording NMR spectra.

EXPERIMENTAL

Analyses were carried out by MEDAC Ltd., Brunel University, Uxbridge. NMR spectra were determined on JEOL FX90Q or Bruker WM400 spectrometers for solutions in deuteriochloroform and with tetramethylsilane as internal standard; *J* values are given in Hz. Infrared spectra were determined for Nujol mulls and ultraviolet spectra for solutions in ethanol. Merck 9385 silica gel was used for flash chromatography. Light petroleum was the fraction boiling between 40-60 °C. Organic extracts were dried over anhydrous Na_2SO_4 and solvents were evaporated under reduced pressure.

1-[3,5-Bis(trifluoromethyl)phenyl]-2-(3,5-dimethoxyphenyl)ethene-1,2-diyl diacetate **6** *and 2-[3,5-bis-(trifluoromethyl)phenyl]-1-(3,5-dimethoxyphenyl)-2-oxoethyl acetate* **2b**

A mixture of 3,5-bis(trifluoromethyl)bromobenzene (3.91 g), magnesium turnings (1.14 g) and a crystal of iodine in dry ether (9 ml) was warmed gently until reaction began and a solution of 3,5-bis(trifluoromethyl)bromobenzene (10 g; total 47.4 mmol) in dry ether (50 ml) was added slowly to maintain a gentle reflux. After complete addition, the mixture was heated at reflux for 30 min, and cooled in an ice bath. A solution of α-(3,5-dimethoxyphenyl)-α-(trimethylsilyloxy)acetonitrile (12.2 g, 46 mmol) in dry ether (30 ml) was added dropwise and the mixture was stirred at rt for 1 h, then poured onto a mixture of ice and solid NH_4Cl and extracted with EtOAc. The organic extract was washed with water, dried and evaporated and the residue was dissolved in a mixture of methanol (80 ml) and 2 M hydrochloric acid (25 ml) and heated at reflux for 2 h. The solution was cooled to rt, most of the methanol was removed under reduced pressure and the residue was diluted with water and extracted with EtOAc. The extract was washed with water, dried and evaporated and a portion (0.6 g) of the residue (total 17.2 g) was flash chromatographed [EtOAc–light petroleum (20:80)] to give the benzoin **2a** as a gum, δ_H (90 MHz) 8.40 [2 H, br s, Ar(1) 2,6-H], 8.04 [Ar(1) 4-H], 6.48 [2 H, d, *J* 2.2, Ar(2) 2,6-H], 6.37 [1 H, t, Ar(2) 4-H], 5.87 (1 H, s, C*H*OH) and 3.73 (6 H, s, OMe). This compound was acetylated with acetic anhydride–pyridine overnight at rt and after work up was flash chromatographed [EtOAc–light petroleum (12.5:87.5)]. The material recovered was crystallised from Et_2O–light petroleum to give the diacetate **6** as prisms (162 mg), mp 131-132 °C. (Found: C, 53.6; H, 3.9. $C_{22}H_{18}F_6O_8$ requires C, 53.7; H, 3.7 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 285 (16 200); ν_{max}/cm^{-1} 1780, 1760; δ_H (90 MHz) 8.00 [2 H, br s, Ar(1) 2,6-H], 7.83 (1 H, br s, Ar(1) 4-H], 6.72 (2 H, d, *J* = 2.2, Ar(2) 2,6-H], 6.48 (1 H, t, Ar(2)H-4), 3.80 (6 H, s, OMe), 2.16 (3 H, s, Me) and 2.10 (3 H, s, Me).

The remaining crude reaction mixture (16 g) was dissolved in acetyl chloride (64 ml) and kept overnight at rt. Unreacted acetyl chloride was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic extract was washed with water, aq. $NaHCO_3$ and brine, dried and evaporated, and the residue was flash chromatographed [EtOAc–light petroleum (10:90)]. The main fraction was crystallised from light petroleum to give the acetate **2b** as colourless needles (3.15 g), mp 81-82 °C (Found: C, 53.4; H, 3.6. $C_{20}H_{16}F_6O_5$ requires C, 53.3; H, 3.6 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 225 (15 500) and 267 (3200); ν_{max}/cm^{-1} 1730, 1710; δ_H (90 MHz) 8.38 (2 H, br s, Ar(2)H-2,6), 8.01 [1 H, br s, Ar(2) 4-H], 6.69 (1 H, s, C*H*OAc), 6.59 [2 H, d, *J* = 2.2, Ar(1) 2,6-H], 6.45 [1 H, t, Ar(1) 4-H], 3.77 (6 H, s, OMe) and 2.23 (3 H, s, Me).

2-[3,5-Bis(trifluoromethyl)phenyl]-5,7-dimethoxybenzo[b]furan **7**

A solution of the acetate **2b** (170 mg) in toluene (30 ml) in a Pyrex tube was irradiated under nitrogen for 1 h with a 100 W mercury arc lamp. The solvent was removed under reduced pressure and the residue was

dissolved in MeOH (15 ml) and 2 M aq. NaOH (0.5 ml) to saponify residual ester **2b**. After 5 min, the solution was neutralised with glacial acetic acid and worked up. Flash chromatography [EtOAc–light petroleum (2:98)] gave the benzofuran **7** as colourless needles (50 mg) after crystallisation (MeOH), mp 125-126 °C (Found: C, 55.3; H, 3.2. $C_{18}H_{12}F_6O_3$ requires C, 55.4; H, 3.1 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 312 (24 300); δ_H 8.23 (2 H, br s, Ar 2,6-H), 7.79 (1 H, br s, Ar 4-H), 7.12 (1 H, s, 3-H), 6.63 and 6.51 (2 × 1 H, 2 × d, J = 2.2, 4,6-H), 4.02 (3 H, s , OMe) and 3.86 (3 H, s, OMe).

1-(2-Furyl)-2-oxo-2-phenylethanol **3a**

A stirred solution of dry diisopropylamine (4.78 g, 47.8 mmol) in dry dimethoxyethane (45 ml) was cooled to -70 °C under nitrogen and treated with *n*-butyl lithium (2.5 M in hexane, 19.1 ml, 47.8 mmol), keeping the temperature below -60 °C. The mixture was stirred for 10 min and a solution of α-(trimethylsilyloxy)phenylacetonitrile (8.91 g, 43.5 mmol) in dry dimethoxyethane (18 ml) was added over 10 min. The solution was stirred for 30 min at -70 °C and a solution of redistilled furfural (4.18 g, 43.5 mmol) in dry dimethoxyethane (18 ml) was added dropwise, keeping the temperature below -60 °C. The mixture was allowed to warm to rt over 4 h, then mixed with saturated aq. NH_4Cl (90 ml), stirred for 10 min and extracted with ether. The organic extract was washed with aq. NH_4Cl (2 × 75 ml), dried and evaporated to leave a pale oil (12.1 g). This material was dissolved in CH_2Cl_2 (105 ml) and a portion (95 ml) of the solution was mixed with glacial acetic acid (7.45 ml) and TBAF (1 M in THF; 43.6 ml). After 0.5 h, the solution was concentrated approx. 2-fold under reduced pressure, diluted with ether and washed with water and aq. $NaHCO_3$, dried and evaporated. The residue was crystallised (EtOAc–light petroleum) to give the benzofuroin **3a** (3.38 g), mp 118-120 °C (lit.[17] 119 °C). The ^{1}H NMR spectrum was identical to that reported.[17]

2-(2-furyl)-2-oxo-1-phenylethanol **8**

An aqueous ethanolic solution of benzoin, furfural and KCN was heated as described[19] and the solid which crystallised on cooling was filtered, washed well with water and dried. Tlc [EtOAc–light petroleum (35:65)] showed two spots, R_f 0.63 and 0.46. The more polar material was isolated by flash chromatography and the furobenzoin **8** was crystallised (EtOAc–light petroleum), mp 145.5-146.5 °C (lit.[24] 147-148 °C). The ^{1}H NMR spectrum was identical to that published.[24]

1-(2-Furyl)-2-oxo-2-phenylethyl acetate **3b**

The 2-benzofuroin **3a** was acetylated with Ac_2O–pyridine overnight at rt and the product was crystallised from EtOAc–light petroleum to give the acetate **3b**, mp 126.5-127.5 °C (Found: C, 68.8; H, 4.9. $C_{14}H_{12}O_4$ requires C, 68.8; H, 4.95 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 245 (12 200); ν_{max}/cm^{-1} 1735, 1685; δ_H (400 MHz) 7.92 (2 H, dd, J 8.4 and 1.4, Ph 2,6-H), 7.55 (1 H, t, J 8.4, Ph 4-H), 7.44 (1 H, d, J 1.8, furan 5-H), 7.42 (2 H, t, Ph 3,5-H), 6.96 (1 H, s, C*H*OAc), 6.46 (1 H, d, J 3.3, furan 3-H), 6.37 (1 H, dd, furan 4-H) and 2.21 (3 H, s, Me).

1-(3-Furyl)-2-oxo-2-phenylethyl acetate **4b** *and 2-(3-furyl)-2-oxo-1-phenylethanol* **9**

3-Furaldehyde (4.26 g, 44.4 mmol) was used instead of furfural in the procedure as given above for preparation of the benzofuroin **3a**. The crude material (7.8 g) obtained after HOAc–TBAF treatment was acetylated with acetic anhydride–pyridine at rt overnight, and after work-up the recovered material was crystallised from MeOH to give a colourless solid (2.13 g), ~95% pure by ^{1}H NMR (see Discussion). A second crystallisation (MeOH) gave the pure acetate **4b** (2.05 g), mp 120-121 °C (Found: C, 68.8; H, 4.95.

$C_{14}H_{12}O_4$ requires C, 68.9; H, 4.9 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 244 (12 100); ν_{max}/cm^{-1} 1730, 1685; δ_H (90 MHz) 7.90-8.02 (2 H, m, Ph 2,6-H), 7.34-7.58 (5 H, m, Ph 3,4,5-H and furan 2,5-H), 6.84 (1 H, s, C*H*OAc), 6.43 (1 H, dd, *J* 0.8 and 1.7, furan 4-H) and 2.18 (3 H, s, Me).

The mother liquor from the first crystallisation was concentrated under reduced pressure and redissolved in MeOH (50 ml) and 1 M aq. NaOH (6 ml). After 5 min at rt, the solution was neutralised with glacial acetic acid, concentrated under reduced pressure, diluted with ether and washed with water and aq. $NaHCO_3$, dried and evaporated. The residue crystallised from ether–light petroleum to give the 3-furobenzoin **9** (1.1 g), mp 135-136 °C (Found: C, 71.1; H, 5.0. $C_{12}H_{10}O_3$ requires C, 71.3; H, 5.0 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 258 (3600) and 316 (260); ν_{max}/cm^{-1} 3450, 1665; δ_H (400 MHz) 7.81 (1 H, m, furan 2-H), 7.33-7.37 (6 H, m, Ph-H and furan 5-H), 6.71 (1 H, m, furan 4-H), 5.49 (1 H, d, *J* 5, singlet after D_2O exchange, C*H*OH) and 4.45 (1 H, d, OH).

3-Methoxy-2,4,6-trimethylbenzaldehyde **13**

2,4,6-Trimethylphenol **11** (34 g, 0.25 mol) was added to a solution of NaOH (10.4 g) in water (170 ml) and the mixture was stirred in an ice-bath while dimethyl sulfate (26 ml) was added over 20 min. The mixture was heated at 100 °C for 2 h and cooled in ice. NaOH (5.7 g) was added, followed by dimethyl sulfate (13 ml) over 15 min. The mixture was heated at 100 °C for a further 2 h, cooled and extracted with light petroleum (350 ml). The organic extract was washed with Claisen's alkali[21] (2 × 50 ml) and water, dried and evaporated. The residue was distilled to give 2,4,6-trimethylanisole **12** (26.2 g, 70 %), bp 98-100 °C (25 mmHg) [lit.[25] 105 °C (36 mmHg)].

A stirred solution of 2,4,6-trimethylanisole **12** (39.3 g, 0.26 mol) in dry CH_2Cl_2 (170 ml) was cooled in an ice-bath and $TiCl_4$ (83 g, 0.44 mol) was added over 5 min, followed by dichloromethyl methyl ether (25.1 g, 0.22 mol) over 30 min. The mixture was stirred for a further 10 min in the ice-bath, and at rt for 30 min, then poured onto crushed ice (250 g). The lower layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, 1 M aq. HCl, 1 M aq. NaOH and brine, dried and evaporated. The residue was distilled to give forerun of the ether **12**, followed by the aldehyde **13** (31 g, 67 %), bp 106-108 °C (1.1 mmHg); δ_H (90 MHz) 10.52 (1 H, s, CHO), 6.90 (1 H, br s, 5-H), 3.68 (3 H, s, OMe) 2.52 (6 H, s, Me) and 2.30 (3 H, s, Me). The 2,4-dinitrophenylhydrazone had mp 195.5-197 °C (from glacial acetic acid) (lit.[26] 189-190 °C).

3-Methoxy-2,4,6-trimethylphenol **15**

To a stirred solution of the aldehyde **13** (13 g, 73 mmol) in *t*-butanol (40 ml) was added SeO_2 (200 mg) followed dropwise by 30 % aq. hydrogen peroxide (15.3 ml), maintaining the temperature below 35 °C without external cooling (~1 h). The mixture was kept overnight at rt, then diluted with ether and washed with water and aq. $NaHCO_3$, dried and evaporated to leave the crude formate **14** as a pale oil (12.4 g, 87 %); δ_H (90 MHz) 8.28 (1 H, s, OCHO), 6.89 (1 H, br s, ArH), 3.69 (3 H, s, OMe), 2.25 (3 H, s, Me) and 2.10 (6 H, s, Me).

A solution of the crude formate **14** (39.3 g, 0.20 mol) in MeOH (400 ml) was mixed with a solution of KOH (23 g) in water (200 ml) and kept for 1 h at rt, then neutralised with 2 M aq. HCl and concentrated to *ca.* 200 ml under reduced pressure. The residue was extracted with ether, and the extract was washed with water, dried and evaporated. The crude solid crystallised from light petroleum to give the phenol **15** as needles (28.9 g, 86 %), mp 67-68 °C (lit.[27] 67-68 °C). The ^1H NMR spectrum was identical with that reported.[27]

1,3-Dimethoxy-2,4,6-trimethylbenzene **16**

The phenol **15** was methylated with dimethyl sulfate–aq. NaOH as for 2,4,6-trimethylphenol, including the work-up with Claisen's alkali, to give the diether **16** (86 %), bp 76-77 °C (0.9 mmHg) [lit.[28] 80 °C (1.5 mmHg)]; δ_H (90 MHz) 6.81 (1 H, br s, 5-H), 3.69 (6 H, s, OMe) and 2.22 (9 H, s, Me).

3,5-Dimethoxy-2,4,6-trimethylbenzaldehyde **10**

A solution of the diether **16** (25.1 g, 0.14 mol) in dry CH_2Cl_2 (110 ml) was cooled in an ice-bath and $TiCl_4$ (53.3 g, 0.28 mol) was added over 5 min, followed by dichloromethyl methyl ether (15.4 g, 0.14 mol) over 20 min. The mixture was stirred in the ice-bath for a further 15 min, then at rt for 30 min and at 35 °C for 15 min, cooled and poured onto crushed ice (150 g). The mixture was extracted with ether and the extract was washed with water, 1 M aq. HCl, 1 M aq. NaOH and water, dried and evaporated, and the residue was crystallised from light petroleum to give the aldehyde **10** as colourless needles (25.5 g, 87 %), mp 64-65 °C (Found: C, 69.1; H, 7.75. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7 %), λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 268 (11 600) and 314 (2400); ν_{max}/cm^{-1} 1685; δ_H (90 MHz) 10.54 (1 H, s, CHO), 3.69 (6 H, s, OMe), 2.48 (6 H, s, Me) and 2.29 (3 H, s, Me).

1-(3,5-Dimethoxy-2,4,6-trimethylphenyl)-2-oxo-2-phenylethanol **5a**

Prepared from α-(trimethylsilyloxy)phenylacetonitrile and the aldehyde **10** as described for benzofuroin **3a** to give benzoin **5a** as prisms (56 %), mp 118-120 °C (from MeOH) (Found: C, 72.6; H, 7.0. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 244 (11 700), 280sh (2050); ν_{max}/cm^{-1} 3465, 1675; δ_H (90 MHz) 7.66-7.79 (2 H, m, Ph 2,6-H), 7.23-7.7.47 (3 H, m, Ph 3,4,5-H), 5.93 (1 H, d, *J* 2, singlet after D_2O exchange, C*H*OH), 4.60 (1 H, d, OH), 3.61 (6 H, s, OMe), 2.24 (6 H, s, Me) and 2.21 (3 H, s Me).

1-(3,5-Dimethoxy-2,4,6-trimethylphenyl)-2-oxo-2-phenylethyl acetate **5b**

Benzoin **5a** was acetylated with Ac_2O–pyridine overnight at rt and worked up to give the acetate **5b**, mp 147-149 °C (after 2 crystallisations from MeOH) (Found: C, 70.6; H, 6.7. $C_{21}H_{24}O_5$ requires C, 70.8; H, 6.8 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 242 (12 000), 280 (2300); ν_{max}/cm^{-1} 1740, 1690; δ_H (90 MHz) 7.61-7.75 (2 H, m, Ph 2,6-H), 7.30-7.48 (3 H, m, Ph 3,4,5-H), 7.17 (1 H, s, C*H*OAc), 3.63 (6 H, s, OMe), 2.28 (6 H, s, Me), 2.24 (3 H, s, Me) and 2.22 (3 H, s, Me).

2-(3,5-Dimethoxyphenyl)-1-phenylethanone **17**

The ketone **17** was previously described[29] as an oil. Here the crude product (4.1 g) was dissolved in 95 % EtOH (40 ml) with Girard's reagent T (4.1 g) and glacial acetic acid (4.1 ml). The solution was heated under reflux for 0.5 h then diluted with brine and washed well with ether. The aqueous layer was acidified to pH 1 with conc. HCl and heated under reflux for 2.5 h. The cooled solution was extracted with ether and the recovered material was flash chromatographed [EtOAc–light petroleum (15:85)] and crystallised from MeOH to give the ketone **17** as needles (1.65 g), mp 61-62 °C (Found: C, 74.7; H, 6.1. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3 %); λ_{max}/nm (ε $M^{-1}cm^{-1}$) 240 (14 900) and 275 (3100); ν_{max}/cm^{-1} 1685; δ_H (90 MHz) 7.94-8.05 [2 H, m, Ar(1) 2,6-H], 7.30-7.56 (3 H, m, ArH), 6.42 [2 H, d, *J* 2.2, Ar(2) 2,6-H], 6.34 [1 H, t, Ar(2) 4-H], 4.20 (2 H, s, CH_2) and 3.75 (6 H, s, OMe).

2-(3,5-Dimethoxyphenyl)-2-methyl-1-phenyl-1-propanone **18**

A stirred solution of α,α-dimethyl-3,5-dimethoxyphenylacetonitrile[30] (3.28 g) in dry benzene (60 ml) was cooled under nitrogen in an ice-bath and phenyl lithium (1.8 M in cyclohexane–Et_2O; 25 ml) was added dropwise. The solution was stirred in the ice-bath for 3 h and a further 3 h at rt, then treated dropwise with MeOH (4.5 ml) and water (15 ml). After 1 h at rt the mixture was extracted with ether and the organic layer was washed with 0.25 M aq. HCl (3 × 30 ml). The aqueous washings were further acidified to 0.5 M acid concentration and warmed on a steam bath for 15 min, cooled and extracted with Et_2O. The ether extract was washed with aq. $NaHCO_3$, dried and evaporated and the residue was crystallised (MeOH) to give the ketone **18** (3.53 g, 62 %), mp 65-66 °C (Found: C, 75.8; H, 7.1. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 230 (13 500) and 275 (2900); ν_{max}/cm^{-1} 1675; δ_H (90 MHz) 7.14-7.65 (5 H, m, Ph-H), 6.47 [2 H, d, *J* 2.2, Ar(2) 2,6-H], 6.36 [1 H, t, Ar(2) 4-H], 3.75 (6 H, s, OMe) and 1.56 (6 H, s, Me).

3-(3,5-Dimethoxyphenyl)-1-phenyl-1-propanone **19**

3,5-Dimethoxychalcone[31] (2.0 g) in EtOAc (80 ml) was stirred with 5 % Pd–C 0.2 g) under hydrogen at atmospheric pressure until gas uptake almost ceased. The solution was filtered and evaporated, and a solution of the residue in acetone (25 ml) was oxidised at 10 °C with Jones' reagent (2 ml). The solution was diluted with ether and washed with aq. $Na_2S_2O_3$ and $NaHCO_3$, dried and evaporated. The residue was flash chromatographed [EtOAc–light petroleum (10:90)] and crystallised from MeOH at -20 °C to give the ketone **19** (1.45 g), mp 33.5-35 °C (Found: C, 75.8; H, 6.7. $C_{17}H_{18}O_3$ requires C, 75.5; H, 6.7 %); λ_{max}/nm (ε/$M^{-1}cm^{-1}$) 238 (14 650), 275 (1820) and 280 (1830); ν_{max}/cm^{-1} 1690, 1680; δ_H (90 MHz) 7.91-8.07 [2 H, m, Ar(1) 2,6-H)], 7.33-7.61 [3 H, m, Ar(1) 3,4,5-H], 6.41 [2 H, d, *J* 2.2, Ar(3) 2,6-H], 6.31 [1 H, t, Ar(3) 4-H], 3.77 (6 H, s, OMe) and 2.89-3.40 (4 H, m, CH_2).

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