Synthesis of Pterofuran and Vignafuran

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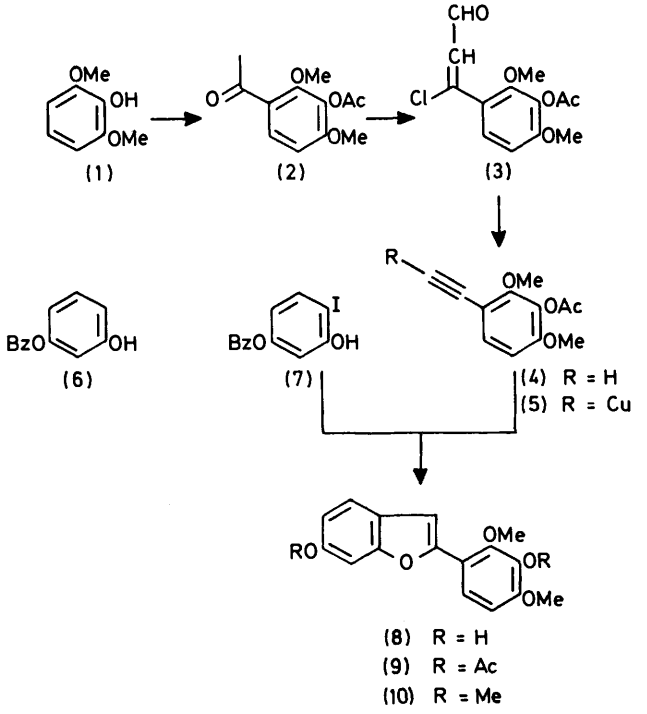
The naturally occurring 2-arylbenzofurans pterofuran (8) and vignafuran (19) have been synthesized by short procedures involving reactions of a copper(I) arylacetylide with an *ortho*-halogenophenol.

PTEROFURAN, isolated from the heartwood of *Pterocarpus indicus*, has been identified as 6-hydroxy-2-(3-hydroxy-2,4-dimethoxyphenyl)benzofuran (8).[1] Its synthesis and that of some derivatives were subsequently achieved [2] for



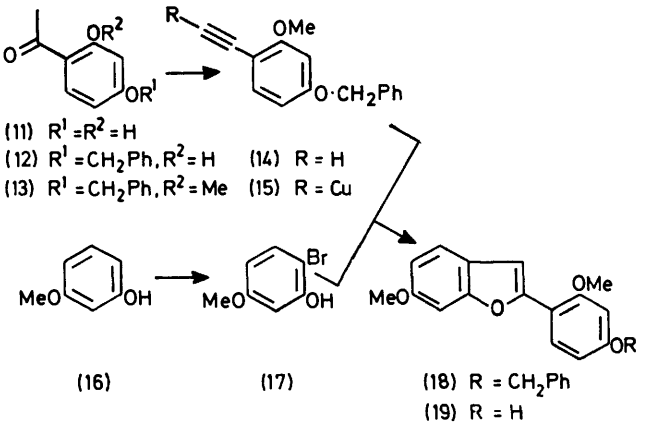
the purpose of structure confirmation, but the key step of heterocycle formation (copper-catalysed reaction of a diazoacetophenone with a resorcinol monoether) suffered from a low yield (2—9%) and/or lack of specificity in direction of ring closure. We report here a short improved synthesis in which the heterocycle is constructed by the reaction of a readily obtained *ortho*-iodophenol with the appropriate copper(I) arylacetylide. This is an adaptation of a procedure developed by Castro [3-6] and recently used in the synthesis of natural norlignans.[7]

The required acetylene (4) was readily obtained from 2,6-dimethoxyphenol (1). Acid-catalysed acylation of the phenol (1) gave the acetophenone (2), which by a Vilsmeier reaction gave the β-aryl-β-chloroacrylaldehyde (3). Without purification, this was treated with hot aqueous base to induce deformylation and dehydrochlorination,[8] and then reacetylated to give the acetylene (4) from which the copper(I) salt (5) was prepared by treatment with copper sulphate and hydroxylamine hydrochloride in ammonium hydroxide.

6-Iodoresorcinol 3-benzoate (7) was readily obtained by the action of iodine monochloride on resorcinol benzoate (6). Coupling of compounds (5) and (7) was effected by heating in pyridine, and basic hydrolysis of the product gave pterofuran (8) in 78% yield, characterized as the diacetate (9) and the dimethyl ether (10).

A recent investigation [9] of the phytoalexins of cowpea, *Vigna unguiculata* (L.) Walp., infected with *Colletotrichum lindemuthianum*, revealed the presence of an antifungal arylbenzofuran, named vignafuran and identified as 2-(4-hydroxy-2-methoxyphenyl)-6-methoxybenzofuran (19). It was synthesized [9] in minute yield among a mixture of isomers by a Hoesch reaction. We now report a synthesis by the same general halogenophenol–arylacetylide coupling reaction as above.

The acetylene (14) was obtained from resacetophenone (11) by successive benzylation to give the 4-benzyl ether (12) and methylation to afford the 4-benzyl-2-methyl



ether (13), followed by conversion of the methyl ketone into the ethyne function by the Bodendorf procedure.[8] The known 2-bromo-5-methoxyphenol (17) [10] was obtained by treatment of resorcinol methyl ether (16) at −20 °C with dioxan dibromide. Coupling of the copper(I) acetylide (15) with (17) gave, in 34% yield,

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vignafuran benzyl ether (18), which on hydrogenolytic debenzylation gave vignafuran (19), with n.m.r. and u.v. spectra in excellent agreement with those reported.

EXPERIMENTAL

N.m.r. spectra were determined for solutions in [^{2}H]-chloroform (unless otherwise stated) with tetramethylsilane as internal standard.

3-*Acetyl*-2,6-*dimethoxyphenyl Acetate* (2).—Prepared from 2,6-dimethoxyphenol as described,[11] the ketone (2) had m.p. 108—109° (lit., 110°); δ 2.33 (s, OAc), 2.58 (s, CO·CH_3), 3.87 (s, 2- and 6-OMe), 6.77 (d, *J* 9 Hz, H-5), and 7.68 (d, *J* 9 Hz, H-4).

3-*Ethynyl*-2,6-*dimethoxyphenyl Acetate* (4).—(i) A solution of the ketone (2) (10 g) in dimethylformamide (5 ml), cooled to 0 °C, was added with stirring to the Vilsmeier reagent [from phosphoryl chloride (10 g) and dimethylformamide (10 ml)]. The mixture was then heated at 60 °C for 4 h, kept at room temperature overnight, then poured into saturated sodium acetate solution and stirred for 1 h. The mixture was extracted with ether (3 × 75 ml) and the extract washed with water, dried, and evaporated to leave 3-(1-chloro-2-formylvinyl)-2,6-dimethoxyphenyl acetate (3) as a dark oil, δ 2.35 (s, OAc), 3.98 (s, OMe), 4.05 (s, OMe), 6.75 (d, *J* 7 Hz, C=CH), 6.82 (d, *J* 9 Hz, H-5), 7.59 (d, *J* 9 Hz, H-4), and 10.28 (d, *J* 7 Hz, CHO).

(ii) A solution of the aldehyde (3) in dioxan (*ca.* 50 ml) was added dropwise to a boiling solution of sodium hydroxide (5 g) in water (100 ml). The mixture was heated under reflux for 1 h, then cooled, diluted with water (100 ml), acidified with acetic acid, and extracted with ether (3 × 75 ml). The extract was washed with sodium hydrogen carbonate solution and water, dried, and evaporated to give crude 3-ethynyl-2,6-dimethoxyphenol as a dark oil, δ 3.25 (s, C≡CH), 3.78 (s, OMe), 3.97 (s, OMe), 6.00br (s, OH), 6.53 (d, *J* 9 Hz, H-5), and 6.95 (d, *J* 9 Hz, H-4).

(iii) The phenolic acetylene was heated on a steam-bath for 1 h with pyridine–acetic anhydride (3 : 1) and the product worked up with ether. The resulting orange oil (4) showed δ 2.45 (s, OAc), 3.30 (s, C≡CH), 3.73 (s, OMe), 3.87 (s, OMe), 6.62 (d, *J* 9 Hz, H-5), and 7.20 (d, *J* 9 Hz, H-4).

Copper(I) 3-*Acetoxy*-2,4-*dimethoxyphenylacetylide* (5).—Hydroxylamine hydrochloride (900 mg) was added in batches to a stirred solution of copper sulphate pentahydrate (1.6 g) in concentrated ammonium hydroxide (7 ml) and water (25 ml) under nitrogen. The solution was cooled in an ice-bath for 15 min, then a solution of the acetylene (4) (1.39 g) in ethanol (50 ml) was added with stirring while a yellow precipitate developed. The solution was further diluted with water (250 ml), and the product (5) filtered off, washed with water (5 × 20 ml), ethanol, and ether, and vacuum-dried (yield 1.20 g).

6-*Iodoresorcinol* 3-*Benzoate* (7).—Prepared as described [12] from resorcinol benzoate [13] (6) by treatment with iodine monochloride in acetic acid, this had m.p. 154—155° (lit.,[12] 153—155°).

6-*Hydroxy*-2-(3-*hydroxy*-2,4-*dimethoxyphenyl*)*benzofuran* (*Pterofuran*) (8).—A mixture of the salt (5) (2.51 g) and the iodophenol (7) (3.04 g) in pyridine (50 ml) was heated under reflux (nitrogen atmosphere) for 23 h, then cooled, and stirred with concentrated ammonium hydroxide solution (50 ml). It was then extracted with ether (3 × 100 ml) and the extract washed successively with water, 10% potassium carbonate solution, water, and 10% hydrochloric acid, dried, and evaporated to leave a brown syrup. This was heated on a steam-bath for 1 h with potassium hydroxide (3 g) in water (100 ml). The mixture was poured onto ice containing concentrated hydrochloric acid (20 ml) and worked up with ether to give an oil which crystallized from benzene–ethanol yielding pterofuran (8) as fine needles (1.99 g), m.p. 206° (lit.,[1] 208—208.5°), with u.v. absorption in agreement with that reported; δ [$(CD_3)_2SO$] 3.87 (s, OMe), 3.92 (s, OMe), 6.40 (s, OH), 6.83 (dd, *J* 2.5 and 8.5 Hz, H-5), 7.01 (d, 8.5 Hz, H-4), 7.22 (s, H-3), 7.41 (d, *J* 9 Hz, H-5′ or -6′), and 7.47 (d, *J* 9 Hz, H-6′ or -5′). The diacetate, prepared with pyridine–acetic anhydride, had m.p. 135—135.5° (lit.,[1] 135.5—136.5°), with concordant u.v. spectrum; δ 2.32 (s, OAc), 2.38 (s, OAc), 3.87 (s, 2′- and 4′-OMe), 6.83 (d, *J* 9 Hz, H-5′), 6.98 (dd, *J* 8.5 and 2.5 Hz, H-5), 7.20 (s, H-3), 7.30 (d, *J* 2.5 Hz, H-7), 7.56 (d, *J* 8.5 Hz, H-4), and 7.83 (d, *J* 9 Hz, H-6′). The dimethyl ether (10), prepared with dimethyl sulphate, showed δ 3.85, 3.88, 3.93, and 3.97 (s, 4 OMe), 6.76 (d, *J* 9 Hz, H-5′), 6.85 (dd, *J* 8.5 and 2.5 Hz, H-5), 7.07 (d, *J* 2.5 Hz, H-7), 7.17 (s, H-3), 7.46 (d, *J* 8.5 Hz, H-4), and 7.66 (d, *J* 9 Hz, H-6′).

4-*Benzyloxy*-2-*hydroxyphenyl Methyl Ketone* (12).—Prepared from resacetophenone (11) as described,[14] the ketone (12) had m.p. 102—103° (lit.,[14] 103°; lit.,[15] 111°), δ [$CDCl_3$–$(CD_3)_2CO$] 2.50 (s, $COCH_3$), 5.05 (s, PhCH_2), 6.49 (dd, *J* 9 and 2.5 Hz, H-5), 6.50 (d, *J* 2.5 Hz, H-3), 7.40 (s, Ph), 7.63 (d, *J* 9 Hz, H-6), and 12.78 (s, OH).

4-*Benzyloxy*-2-*methoxyphenyl Methyl Ketone* (13).—A mixture of the ketone (12) (15.5 g), anhydrous potassium carbonate (13.8 g), and methyl iodide (14.1 g) was stirred at room temperature for 72 h in dimethyl sulphoxide (100 ml), then poured into saturated brine and extracted with ether. Evaporation of the washed and dried extract gave a syrup which was extracted with light petroleum (b.p. 40—60 °C). Concentration of the extract gave the *methyl ether* (13) as pale yellow plates (9.70 g), m.p. 64—65° (Found: C, 74.9; H, 6.25. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%); δ 2.56 (s, $COCH_3$), 3.84 (s, OCH_3), 5.08 (s, PhCH_2), 6.52 (d, *J* 2.5 Hz, H-3), 6.60 (dd, *J* 9 and 2.5 Hz, H-5), 7.40 (s, Ph), and 7.83 (d, *J* 9 Hz, H-6).

4-*Benzyloxy*-2-*methoxyphenylacetylene* (14).—(i) A solution of the ketone (13) (3.60 g) in dimethylformamide (10 ml) was added dropwise to the reagent prepared by addition of phosphoryl chloride (4 g) with stirring to dimethylformamide (4 ml) at 0 °C. The mixture was heated at 60 °C for 4 h, left at room temperature overnight, then poured into cold concentrated sodium acetate solution (200 ml) and stirred for 30 min. The precipitated orange oil was extracted with methylene chloride, and the washed and dried extract evaporated to give crude 3-(4-benzyloxy-2-methoxyphenyl)-3-chloroprop-2-enal as a red-brown oil, δ 3.73 (s, OMe), 5.05 (s, PhCH_2), 6.55 (d, *J* 2.5 Hz, H-3′), 6.58 (dd, *J* 9 and 2.5 Hz, H-5′), 6.86 (d, *J* 7 Hz, C=CH), 7.40 (s, Ph), 7.66 (d, *J* 9 Hz, H-6′), and 10.24 (d, *J* 7 Hz, CHO).

(ii) The crude aldehyde was dissolved in dioxan (30 ml) and added dropwise to a hot solution of sodium hydroxide (15 g) in water (100 ml). The mixture was heated under

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reflux for 1 h, concentrated to half bulk, diluted with water (100 ml), and extracted with ether. The washed and dried extract was evaporated to give a residual oil which was dissolved in benzene and filtered through a short column of silica gel. This gave the acetylene (14) as an oil (446 mg, 16%), δ 3.20 (s, C≡CH), 3.77 (s, OMe), 4.98 (s, PhCH_2), 6.44 (dd, *J* 9 and 2.5 Hz, H-5′), 6.47 (d, *J* 2.5 Hz, H-3′), 7.34 (s, Ph), and 7.34 (d, *J* 9 Hz, H-6′).

Copper(I) *4-Benzyloxy-2-methoxyphenylacetylide* (15).—This was prepared as for (5) as a yellow solid in 88% yield.

2-Bromo-5-methoxyphenol (17).—This was prepared by a procedure [16] introduced for one-step monobromination of resorcinol ethers. To a solution of *m*-methoxyphenol [17] (16) (5 g) in ether (100 ml) at −20 °C was added with stirring dioxan dibromide (10 g) in ether (25 ml). The mixture was allowed to warm to room temperature, washed with water, and aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was distilled through a Vigreux column to yield the bromophenol in 83% yield as an oil, b.p. 104—105° at 3 cmHg (lit.,[10] 152° at 25 cmHg), δ 3.73 (s, OMe), 3.54br (s, OH), 6.39 (dd, *J* 8 and 2.5 Hz, H-2), 6.63 (d, *J* 2.5 Hz, H-4), and 7.30 (d, *J* 8 Hz, H-3).

Vignafuran Benzyl Ether (18).—A mixture of the salt (15) (504 mg) and the bromophenol (17) (340 mg) in pyridine (25 ml) was heated under reflux (nitrogen atomosphere) for 24 h. The product was worked up as for pterofuran (8). Crystallization from ethanol gave 2-(4-benzyloxy-2-methoxyphenyl)-6-methoxybenzofuran (18) (204 mg, 34%), m.p. 111—116° (Found: M^+, 360.136 59. $C_{23}H_{20}O_4$ requires *M*, 360.136 16); δ 3.83 (s, OMe), 3.91 (s, OMe), 5.10 (s, PhCH_2), 6.6—7.1 (m, 4 aryl H and H-3), 7.38 (s, Ph and 1 aryl H), and 7.95 (d, *J* 9 Hz, H-6′).

Vignafuran (19).—A solution of the benzyl ether (18) (149 mg) in acetic acid (50 ml) was stirred with palladium–charcoal (10%; 50 mg) under hydrogen for 30 min (rapid uptake ceased). It was then filtered, diluted with water, and extracted with ether (3 × 50 ml). The extract was washed with saturated hydrogen carbonate solution and then 10% sodium hydroxide (3 × 25 ml). The latter washings were acidified and re-extracted with ether, and the washed and dried extract was evaporated. The residual oil was chromatographed on a silica gel plate [developed by chloroform–ethanol (97 : 3)], and the major zone was eluted with acetone to give vignafuran (19) as a clear oil (38 mg, 40%), δ 3.84 (s, OMe), 3.90 (s, OMe), 6.53 (m, H-3′ and -5′), 6.85 (dd, *J* 9 and 2 Hz, H-5), 7.05 (m, H-3 and -7), 7.43 (d, *J* 9 Hz, H-4), 7.85 (d, *J* 9 Hz, H-6′); $\lambda_{max.}$ (EtOH) 210 (log ε 4.50), 224sh (4.16), 245sh (4.02), 283 (4.32), 308sh (4.47), 320 (4.59), and 336 nm (4.57).

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