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A general route to 2-arylbenzofurans, consisting of reaction of an *o*-halogenophenol ester with a cuprous arylacetylide, was employed to synthesize medicagol methoxybenzofuran. 2,4-Dimethoxyacetophenone was converted to 2,4-dimethoxyphenylacetylene in three steps and reaction of the cuprous salt with 2-iodo-4,5-methylenedioxyphenyl acetate gave the desired 2-(2',4'-dimethoxyphenyl)-5,6-methylenedioxybenzofuran.

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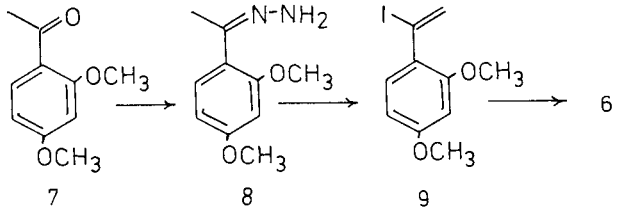
From *Sophora tomentosa* L., there have recently been isolated two arylbenzofurans (**1** and **2**), which were identified by methylation to 2-(2',4'-dimethoxyphenyl)-5,6-methylenedioxybenzofuran (**3**), known as medicagol methoxybenzofuran (**3**) and previously obtained by degradation of the alfalfa coumestan, medicagol (**4**) (2) and flemichapparin-C (**5**) (3). Reports of the occurrence of several other 2-(2',4'-dihydroxyphenyl)benzofurans and their methyl ethers (4-7), coupled with the recognition of some as phytoalexins (5,6) have stimulated interest in their synthesis and biosynthesis (8).

We report here a synthesis of the key transformation product, 2-(2',4'-dimethoxyphenyl)-5,6-methylenedioxybenzofuran (**3**), based upon earlier work (9) in which it was shown that a benzofuran could be directly produced by reaction of an *o*-halogenophenol ester with a cuprous acetylide.

For the preparation of the required 2,4-dimethoxyphenylacetylene (**6**) we have utilized a modification of an apparently rather neglected procedure, developed by Oliveto and coworkers (10) from observations of Barton, *et al.* (11), for conversion of a methyl ketone to an alkyne. The starting ketone, 2,4-dimethoxyacetophenone (**7**) was converted to the hydrazone (**8**) which on treatment with iodine in the presence of triethylamine yielded the vinyl iodide (**9**). Elimination of hydrogen iodide from **9** was smoothly effected by treatment with sodium hydride (12) to give the alkyne (**6**) from which the cuprous salt (**10**) was generated in a standard manner (13). Coupling of the cuprous salt (**10**) with 2-iodo-4,5-methylenedioxyphenyl acetate (**11**) was effected by heating in pyridine solution to give in 30% yield medicagol methoxybenzofuran (**3**) with empirical constants in excellent agreement with those reported by the Japanese workers (1) for the derivative



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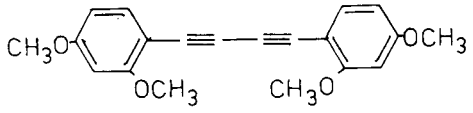

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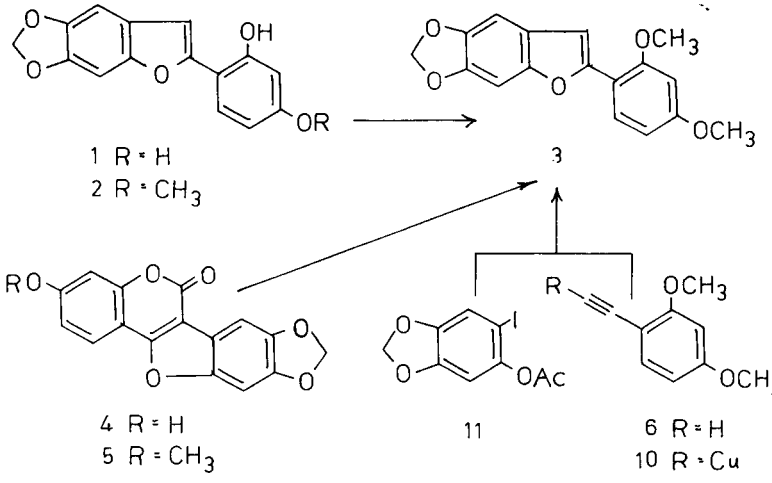

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from their natural products (**1**) and (**2**). The acetylene oxidation product, 1,4-bis(2',4'-dimethoxyphenyl)buta-1,4-diyne (**12**), was also isolated in 10% yield as a by-product of the coupling reaction.

EXPERIMENTAL

Nmr spectra were determined for solutions in deuteriochloroform with tetramethylsilane as internal standard.

2,4-Dimethoxyacetophenone Hydrazone (**8**).

Hydrazine (95%, 6 ml.) was added to a solution of 2,4-dimethoxyacetophenone (5.47 g.) in ethanol (100 ml.) and triethylamine (44 ml.), and the mixture heated under reflux for 4.5 hours and kept overnight at room temperature. It was then diluted with water (250 ml.), extracted with ether and the extract washed successively with water, brine and water. Evaporation of the dried (sodium sulfate) extract gave a yellow oil (3.86 g.) which crystallized from carbon tetrachloride to give the hydrazone (**8**) as prisms, m.p. 99-100°; nmr: δ 2.12 (s, Me), 3.83 (s, 2- and 4-OMe), 5.01 (br. s, $-NH_2$), 6.55-6.63 (m, H-3 and -5) and 7.07 (d, J = 9 Hz, H-6). A sample for analysis, recrystallized from ethanol, had m.p. 108-110°.

Anal. Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.84; H, 7.39; N, 14.31.

2,4-Dimethoxyphenylacetylene (**6**).

To a solution of the hydrazone (**8**) (3.86 g.) in tetrahydrofuran (350 ml.) and triethylamine (175 ml.) was added dropwise over 15 minutes under nitrogen a solution of iodine (12 g.) in tetrahydrofuran (35 ml.). The mixture was stirred for a further 60 minutes, then diluted with water (200 ml.). Extraction with ether (3 x 100 ml.) and successive washing of the extract with 1*N* hydrochloric acid, 10% sodium thiosulphate and brine and evaporation of solvents gave a residual black oil (5.20 g.) which was dissolved in ether and filtered through a short column of basic alumina. The vinyl iodide (**9**) was eluted as a dark oil (14); nmr: δ 3.78 (s, OMe), 3.84 (s, OMe), 6.08 (d, J = 1 Hz, vinyl H), 6.22 (d, J 1 Hz, vinyl H), 6.33-6.53 (m, H-3 and -5) and 7.21 (d, J = 10 Hz, H-6).

A solution of the vinyl iodide (**9**) (3.98 g.) in dry tetrahydrofuran (150 ml.) was added to excess sodium hydride (from a 50% oil dispersion washed several times with pentane) under nitrogen, and the mixture heated under reflux overnight. The reaction was quenched by addition of ethanol, dilution with water and extraction with ether. Evaporation of the washed and dried extract gave a residue which was dissolved in light petroleum and chromatographed on neutral alumina. Elution with carbon tetrachloride gave 2,4-dimethoxyphenylacetylene (**6**) as a colourless oil (1.01 g.), b.p. 98° (0.8 mm); nmr: δ 3.22 (s, alkyne-H), 3.76 (s, OMe), 3.83 (s, OMe), 6.36-6.48 (m, H-3 and -5) and 7.37 (d, J 8 Hz, H-6).

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 74.04; H, 6.57.

Cuprous 2,4-Dimethoxyphenylacetylide (**10**).

Hydroxylamine hydrochloride (870 mg.) was added portionwise with stirring over 5 minutes to a cooled (ice-bath) solution of cupric sulphate pentahydrate (1.56 g.) in concentrated ammonium hydroxide (6.6 ml.) and water (25 ml.) under nitrogen. The mixture was stirred for a further 10 minutes (fading of dark blue colour), then a solution of the alkyne (**6**) (1.01 g.) in ethanol (35 ml.) added in one portion. A voluminous yellow precipitate appeared immediately, and after further dilution with water (200 ml.) was collected by filtration. After washing with water, ethanol and ether, and drying (phosphorus pentoxide) under reduced pressure, the cuprous acetylide (**10**) was obtained as a bright yellow-orange solid (1.15 g.).

Coupling of Cuprous 2,4-Dimethoxyphenylacetylide (**10**) with 2-Iodo-4,5-methylenedioxyphenyl Acetate (**11**).

A solution of the iodosesamol acetate (**11**) (9) (1.58 g.) in pyridine (10 ml.) was added to the cuprous acetylide (**10**) (1.15 g.) in the same solvent (30 ml.) and the mixture refluxed under nitrogen for 16 hours. It was then cooled, diluted with ether (700 ml.), stored overnight at 0°, then filtered. The filtrate was washed with water (3 x 150 ml.), brine (3 x 50 ml.), decolourized with charcoal and dried (sodium sulfate). Evaporation under reduced pressure gave a residual tan solid (1.17 g.), which was boiled with methanol and filtered. On cooling, the filtrate deposited colourless needles (0.47 g.) determined to be a mixture of two products by tlc. This mixture was dissolved in carbon tetrachloride and chromatographed on a column (10 x 2.5 cm diameter) of silica gel (Merck, 230-400 mesh). Elution with the same solvent yielded 2-(2',4'-dimethoxyphenyl)-5,6-methylenedioxybenzofuran (**3**) as needles (331 mg) from methanol, m.p. 171-172° [lit. m.p. 166-167° (2), 168-169° (1)]; ir (potassium bromide): 1610, 1580, 1500, 1040 and 950 cm^{-1}, δ 3.84 (s, C-4' OMe), 3.94 (s, C-2' OMe), 5.96 (s, $-OCH_2O-$), 6.54-6.65 (m, H-3' and 5'), 6.93 (br. s., H-4), 6.99 (overlapping dd, J = 1 Hz, H-7), 7.07 (d, J = 1 Hz, H-3) and 7.88 (dd, J = 8 and 2 Hz, H-6'). Elution with benzene then yielded 1,4-bis(2',4'-dimethoxyphenyl)buta-1,4-diyne (**12**) as needles (74 mg.), m.p. 176-176.5°; ir (potassium bromide): 2137 (C≡C), 1606, 1303, 1215, 1163 and 832 cm^{-1}; nmr: δ 3.83 (s, OMe), 3.87 (s, OMe), 6.43-6.53 (m, H-3' and 6') and 7.42 (d, J = 10 Hz, H-5').

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.50; H, 5.87.

Further quantities of the benzofuran (**3**) (102 mg.) and diacetylene (**12**) (17 mg.) were obtained by similar chromatography of the methanol extract filtrate.

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REFERENCES AND NOTES

(1) M. Komatsu, I. Yokoe and Y. Shirataki, *Chem. Pharm. Bull.*, **26**, 1274 (1978).

(2) A. L. Livingston, S. C. Witt, R. E. Lundin and E. M. Bickoff, *J. Org. Chem.*, **30**, 2353 (1965).

(3) N. Adityachaudhury and P. K. Gupta, *Phytochemistry*, **12**, 425 (1973).

(4) A. J. Brink, G. J. H. Rall and J. P. Engelbrecht, *Tetrahedron*, **30**, 311 (1974).

(5) N. W. Preston, K. Chamberlain and R. A. Skipp, *Phytochemistry*, **14**, 1843 (1975).

(6) J. L. Ingham and P. M. Dewick, *ibid.*, **17**, 535 (1978).

(7) A. B. deOliveira, M. Iracema, L. M. Madruga and O. R. Gottlieb, *ibid.*, **17**, 593 (1978).

(8) M. Martin and P. M. Dewick, *ibid.*, **18**, 1309 (1979).

(9) F. G. Schreiber and R. Stevenson, *Org. Prep. Proc. Int.*, **10**, 137 (1978).

(10) A. K. Krubimer, N. Gottfried and E. P. Oliveto, *J. Org. Chem.*, **34**, 3502 (1969).

(11) D. H. R. Barton, R. W. O'Brien and S. Sternhell, *J. Chem. Soc.*, 470 (1962).

(12) In preparation of other alkynes, we had found this reagent preferable to potassium hydroxide in methanol, which caused partial hydrolysis to the starting ketone.

(13) R. D. Stephens and C. E. Castro, *J. Org. Chem.*, **28**, 3313 (1963).

(14) Attempted further purification by chromatography on silica gel and elution with carbon tetrachloride gave a yellow oily solid which rapidly darkened with decomposition.