A Convenient Synthesis of 2-Arylindenes

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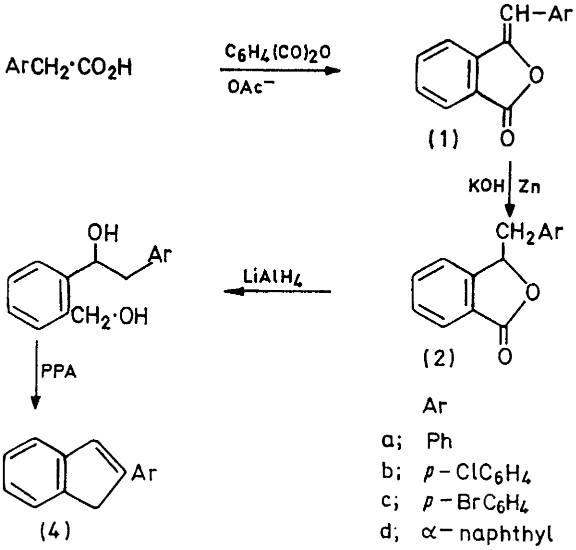
The syntheses of *o*-hydroxymethyl-*trans*-stilbenes, 2-aryl-1-(*o*-hydroxymethylphenyl)ethanols, and 1-aryl-2-(*o*-hydroxymethylphenyl)ethanols from readily available 3-substituted phthalides are described. Their reaction with polyphosphoric acid is a route, superior in convenience and yield, to 2-arylindenes.

In order to prepare 2-hydroxymethyl-*trans*-stilbene (5a), needed for another project, we attempted the acid-catalysed dehydration of 1-(*o*-hydroxymethylphenyl)-2-phenylethanol (3a). In dilute sulphuric acid, the stilbene alcohol (5a) was the major product, but in polyphosphoric acid (PPA) 2-phenylindene (4a) was obtained.

Previously reported routes[1] to 2-arylindenes are unsatisfactory since they give, at best, moderate yields and often require exotic starting materials. To illustrate the generality of our reaction, we have prepared three other 2-arylindenes by the route outlined (Scheme 1). The only obvious limitation is that easily reducible groups should be absent.

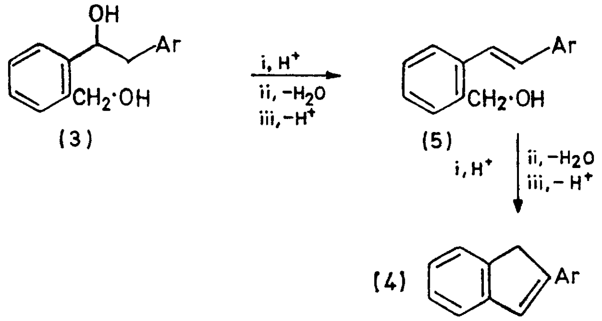


Scheme 1

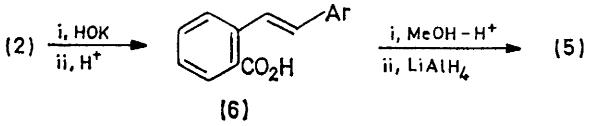
The syntheses of the saturated phthalides (2) follow modified standard procedures (see Experimental section), and reduction with lithium aluminium hydride gave the precursor diols (3) in high yields. The diols were warmed with PPA at steam-bath temperature and the water-insoluble material was chromatographed on alumina to give 2-arylindenes (4) as the only identified products. I.r. and n.m.r. examination suggested that the gummy by-products were hydrocarbons and/or ethers.

The yield of 2-phenylindene (4a) isolated was 50—55%; this may be a reflection of the heterogeneous nature of the reaction mixture, which remained a sludgy mass at all times. However, the use of thrice the quantity of PPA did not raise the yield and neither did the use of PPA containing other ratios of phosphorus pentoxide to phosphoric acid. A separate experiment showed that 2-phenylindene was stable in PPA. Raising the reaction temperature to 220° did raise the yield to 78%, and the chromatography became unnecessary. Yields of the other 2-arylindenes have been less satisfactory but still acceptable because the low yield occurs at this last step.

A rational pathway for this cyclisation is shown in Scheme 2. It follows from this Scheme that the stilbene alcohol (5) should also give the 2-arylindene (4) under the same conditions. Alcohols (5) were prepared as outlined in Scheme 3. Treatment of the alcohols with PPA at 100 and at 220° gave the 2-arylindenes (4) in yields similar to those from the diols (3). The reaction mixtures were again sludgy and dilution with more PPA did not raise the yield.



Scheme 2



Scheme 3

Another consequence of this pathway (Scheme 2) is that any precursor which can produce the alcohol (5) under these conditions should also give indenes with PPA. In particular, 2-(*o*-hydroxymethylphenyl)-1-phenylethanol (7a) should undergo a similar reaction.

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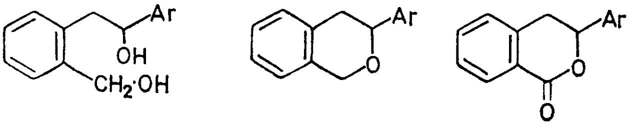
[1] (*a*) J. v. Braun and G. Mantz, *Ber.*, 1929, **62**, 1062; (*b*) F. Mayer, A. Sieglitz, and W. Ludwig, *ibid.*, 1921, **54**, 1400; (*c*) M. Tiffeneau and H. Dorlencourt, *Compt. rend.*, 1906, **143**, 1242; (*d*) P. A. Plattner, R. Sandrin, and J. Wyss, *Helv. Chim. Acta*, 1946, **29**, 1604, 1606; (*e*) D. G. Markees and A. Burger, *J. Amer. Chem. Soc.*, 1949, **71**, 2031; (*f*) T. S. Cantrell and H. Shechter, *ibid.*, 1967, **89**, 5868; (*g*) S. A. Galton, M. Kalafer, and F. M. Beringer, *J. Org. Chem.*, 1970, **35**, 1.

Others [2,3] have reported that this diol gave the cyclic ether (8) in acidic medium. However, one group [2] isolated the diol as a liquid and the ether as an air-sensitive solid, m.p. 114—115°. Later workers [3] obtained a solid diol, m.p. 88—89°, and an air-insensitive ether, m.p. 76—77°, in 14% yield.



(7) (8) (9)

SCHEME 4

We have repeated the synthesis of diol (7a) by the route described.[2] Treatment of the acid (6a) with concentrated sulphuric acid [4] gave the 3-phenylisochroman-1-one (9a), which was reduced to the diol (7a), m.p. 87—88°. It was necessary to subject compound (9a) to the reduction twice to get complete conversion; after one treatment the product was an oil which still showed carbonyl absorption.

Treatment of the diol (7a) with PPA gave 2-phenylindene in 88% yield and uncharacterised gummy tars. In acetic acid, containing phosphoric acid, a 9% yield of the ether (8) was obtained but no 2-phenylindene. The corresponding *p*-chloro-diol (7b) also gave a high yield (74%) of 2-*p*-chlorophenylindene (4b) with PPA at 220°.

The preparation of 2-phenylindene (4a) from the diol (3a) by this method is particularly convenient because this diol is obtained in high yield by reduction of the commercially available (Aldrich) 3-benzylphthalide (2a). The most useful alternative synthesis involves the reaction of phenylmagnesium halide with indan-2-one followed by the dehydration of the product alcohol.[1*a*] Indanone is about ten times more costly than 3-benzylphthalide, and the reported yields of about 50% compare unfavourably to the 78% obtained in this work.

EXPERIMENTAL

I.r. spectra were obtained for Nujol mulls with a Perkin-Elmer 237B or 700 spectrophotometer. N.m.r. measurements were made for solutions in [^{2}H]chloroform (tetramethylsilane as internal standard) with a Perkin-Elmer R12A spectrometer. Coupling constants for ABX systems were derived from measurements upon solutions to which the shift reagent [pivaloyl(perfluorobutyryl)methanato]-europium(III) had been added,[5] and values were confirmed by spectral simulation on a JEOL JRA1 computer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York. Polyphosphoric acid was prepared by dissolving phosphorus pentoxide (75 g) in 85% phosphoric acid (50 ml).

Unsaturated Phthalides (1) (cf. *ref.* 6).—Phthalic anhydride (40 mmol), the arylacetic acid (40 mmol) and anhydrous sodium acetate (0·3 g) were intimately mixed and heated by boiling diethylene glycol for 2—3 h. The internal temperature of the mixture rose to 243°.[*] Recrystallisation of the cooled mixture from ethanol gave the products: (1b) (63%), m.p. 150° (lit.,[7] 152—153°), τ 2·36 (8H, m) and 3·67 (1H, s); (1c) (59%), m.p. 169—170° (lit.,[8] 162°), τ 2·31 (8H, m) and 3·68 (1H, s) (Found: C, 59·5; H, 3·0. Calc. for $C_{15}H_9BrO_2$: C, 59·8; H, 3·1%); and (1d) (45%), m.p. 179—180° (lit.,[8] 179°), τ 2·2 (11H, m) and 2·86 (1H, s).

Saturated Phthalides (2).—These were obtained by the reduction of compounds (1) with zinc in potassium hydroxide solution: [9] (2b) (94%), m.p. 147° (lit.,[7] 148·5—149°), τ 2·50 (8H, m), 4·1 (1H, t), and 6·78 (2H, dd); 3-p-*bromobenzylphthalide* (2c) (97%), m.p. 138—140° (Found: C, 59·4; H, 3·4. $C_{15}H_{11}BrO_2$ requires C, 59·5; H, 3·7%), τ 2·18—2·96 (8H, m), 4·36 (1H, t), and 6·80 (2H, dd); and 3-α-*naphthylmethylphthalide* (2d) (88%), m.p. 119—120° (Found: C, 83·0; H, 5·3. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%), τ 2·47 (11H, m), 4·18 (1H, t), and 6·39 (2H, sept). The septuplet and triplet were treated as an ABX system: [10] J_{AB} 13·7, J_{AX} 6·9, J_{BX} 6·2 Hz.

Saponification of Saturated Phthalides (2).—Phthalide (2) and potassium hydroxide (2 equiv.) were heated in diethylene glycol for 1—2 h under reflux. The hot solution was poured into a large excess of ice–water and acidified with concentrated hydrochloric acid. The precipitate was collected, washed with water, and recrystallised from aqueous ethanol to give compound (6a) (73%), m.p. 159—160° (lit.,[9] 158—160°), $\nu_{max.}$ 1690 and 965 cm^{-1}; compound (6b) (76%), m.p. 153—154° (lit.,[7] 152—153°), $\nu_{max.}$ 1680 and 970 cm^{-1}; 4′-*bromo*-trans-*stilbene*-2-*carboxylic acid* (6c) (89%), m.p. 179°, $\nu_{max.}$ 1690 and 965 cm^{-1} (Found: C, 59·6; H, 3·6%. $C_{15}H_{11}BrO_2$ requires C, 59·5; H, 3·7%); and *o*-(2-α-*naphthylmethylvinyl*)*benzoic acid* (6d) (96%), m.p. 160—161°, $\nu_{max.}$ 1685 and 965 cm^{-1} (Found: C, 82·9; H, 5·1. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%).

Esterification of the Acids (6).—The acid (6), excess of methanol, and sulphuric acid catalyst were heated under reflux and then worked up as usual to give methyl *trans*-stilbene-2-carboxylate (86%), b.p. 146° at 0·05 mmHg, (lit.,[11] 168—170° at 0·5 mmHg); *methyl* 4′-*chloro*-trans-*stilbene*-2-*carboxylate* (94%), m.p. 92° (from petroleum) (Found: C, 70·6; H, 5·0. $C_{16}H_{13}ClO_2$ requires C, 70·5; H, 4·8%); or *methyl* 4-*bromo*-trans-*stilbene*-2-*carboxylate* (95%), m.p. 102° (from aq. ethanol) (Found: C, 60·5; H, 4·1. $C_{16}H_{13}BrO_2$ requires C, 60·6; H, 4·1%). The methyl ester of (6d) was obtained as an oil which was used without further purification.

Cyclisation of Acids (6a *and* b) *to Isochromanones*.—The acids (6) were treated with concentrated sulphuric acid

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[*] Fresh diethylene glycol was used for every run. Used material tended to darken and its b.p. was lowered.

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[3] R. C. Vaulx, F. N. Jones, and C. R. Hauser, *J. Org. Chem.*, 1964, **29**, 1387.

[4] E. Leupold, *Ber.*, 1901, **34**, 2832.

[5] C. S. Springer, jun., D. W. Meek, and R. E. Sievers, *Inorg. Chem.*, 1967, **6**, 1105.

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[9] D. F. DeTar and L. A. Carpino, *J. Amer. Chem. Soc.*, 1956, **78**, 475.

[10] J. A. Pople, W. G. Schneider, and H. J. Bernstein, ' High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959, p. 132.

[11] G. Berti and F. Bottari, *Gazzetta*, 1959, **89**, 2380.

at room temperature[4] (it is important not to warm the acid mixture as much lower yields result). The products were 3-phenylisochroman-1-one (9a) (94%), m.p. 87° (from ethanol) (lit.,[4] 88—89°), τ 2·32 (9H, m), 4·57 (1H, q), and 6·84 (2H, d), J_{AB} 16·2, J_{AX} 11·8, J_{BX} 3·0 Hz; and 3-p-*chlorophenylisochroman*-1-*one* (9b) (63%), m.p. 92° (from ethanol) (Found: C, 69·5; H, 4·2. $C_{15}H_{11}ClO_2$ requires C, 69·6; H, 4·3%), τ 2·40 (8H, m), 4·59 (1H, q), and 6·87 (2H, d), J_{AB} 16·4, J_{AX} 12·1, J_{BX} 3·1 Hz.

Reductions to Alcohols.—The precursor (phthalide, ester, or isochromanone) was reduced with excess of lithium aluminium hydride in ether. The crude alcohols were recrystallised from 1-chlorobutane.

From the appropriate methyl esters were obtained 2-hydroxymethyl-*trans*-stilbene (5a) (99%), m.p. 92° (lit.,[12] 92—93°); 4′-*chloro*-2-*hydroxymethyl*-trans-*stilbene* (5b) (91%), m.p. 122—123° (Found: C, 73·3; H, 5·7. $C_{15}H_{13}ClO$ requires C, 74·6; H, 5·4%); 4′-*bromo*-2-*hydroxymethyl*-trans-*stilbene* (5c) (94%), m.p. 102° (Found: C, 62·5; H, 4·4. $C_{15}H_{13}BrO$ requires C, 62·3; H, 4·5%); and o-(2-α-*naphthylvinyl*)*benzyl alcohol* (5d) (84%), m.p. 128—129° (Found: C, 87·8; H, 6·3. $C_{19}H_{16}O$ requires C, 87·7; H, 6·2%).

From the saturated phthalides (2) were obtained 1-(o-*hydroxymethylphenyl*)-2-*phenylethanol* (3a) (99%), m.p. 106° (Found: C, 78·7; H, 7·1. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%), τ 2·8 (9H, m), 5·5 (2H, s), 5·0 (1H, t), and 7·0 (4H, d); 2-p-*chlorophenyl*-2-(o-*hydroxymethylphenyl*)-*ethanol* (3b) (65%), m.p. 88° (Found: C, 68·9; H, 6·1. $C_{15}H_{15}ClO_2$ requires C, 68·6; H, 5·8%), τ 2·60 (8H, m), 5·5 (2H, s), 4·95 (1H, t), and 6·98 (4H, d); 2-p-*bromophenyl*-1-(o-*hydroxymethylphenyl*)*ethanol* (3c) (79%), m.p. 95° (Found: C, 59·0; H, 4·8. $C_{15}H_{15}BrO_2$ requires C, 58·7; H, 4·9%), τ 2·77 (8H, m), 5·53 (2H, s), 4·97 (1H, t), and 7·04 (4H, d); and 1-(o-*hydroxymethylphenyl*)-2-α-*naphthylethanol* (3d) (86%), m.p. 116—117° (Found: C, 82·0; H, 6·4. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%), τ 2·43 (11H, m), 4·79 (1H, t), 5·63 (2H, s), 6·51 (2H, d), and 7·21 (2H, s).

From the isochromanone (9a) was obtained 2-(*o*-hydroxymethylphenyl)-1-phenylethanol (7a) (99%), m.p. 88° (lit.,[3] 88—89°), τ 2·82 (9H, m), 5·60 (3H, sext), 6·07 (2H, s), and 7·01 (2H, d). From compound (9b) was recovered 1-p-*chlorophenyl*-2-(o-*hydroxymethylphenyl*)*ethanol* (7b), m.p. 109° (Found: C, 68·5; H, 5·6. $C_{15}H_{15}ClO_2$ requires C, 68·6; H, 5·8%), τ 2·76 (8H, m), 5·42 (3H, sext), 5·65 (2H, s), and 6·99 (2H, d).

2-*Arylindenes.*—The alcohol (3), (5), or (7) (1·00 g) was added to PPA (10 ml) and the mixture was heated on a steam-bath (100°) for 30 min or in an oil-bath maintained at 220° for 1 h. The mixture was poured into ice–water (200 ml) and the precipitate extracted into ether. The extracts were washed with saturated solutions of sodium hydrogen carbonate and sodium chloride. Evaporation left a residue which was chromatographed on alumina (50 g) with petroleum (b.p. 30—60°)–benzene (4 : 1 v/v) as eluant. The 2-arylindenes were recrystallised from ethanol. Elution with more polar solvents gave gums and oils which were rejected. The results are displayed in the Table.

Yields of 2-arylindenes by cyclisation with PPA

Alcohol	Product	% Yield [reaction temp. (°C)]
(3a)	2-Phenylindene[a]	56 (100)
		78 (220)
(5a)	2-Phenylindene	54 (100)
		78 (220)
(7a)	2-Phenylindene	68 (100)
		88 (220)
(3b)	2-*p*-Chlorophenylindene[b]	31 (100)
(5b)	2-*p*-Chlorophenylindene	21 (100)
(7b)	2-*p*-Chlorophenylindene	74 (220)
(3c)	2-*p*-Bromophenylindene[c]	18 (100)
(5c)	2-*p*-Bromophenylindene	16 (100)
(3d)	2-α-Naphthylindene[d]	12 (100)
(5d)	2-α-Naphthylindene	26 (100)

[a] M.p. 165° (lit.,[16] 165—166°). [b] M.p. 175° (lit., 177—178°) (P. M. G. Bavin, C. R. Ganellin, J. M. Loynes, and R. G. W. Spickett, *J. Medicin. Chem.*, 1969, **12**, 513). [c] M.p. 185° (Found: C, 66·7; H, 4·3. $C_{15}H_{11}Br$ requires C, 66·5; H, 4·1%). [d] M.p. 80° (Found: C, 94·1; H, 5·9. $C_{19}H_{14}$ requires C, 94·2; H, 5·8%).

3-*Phenylisochroman* (8a).—The diol (7a) (2·00 g) was dissolved in glacial acetic acid (15 ml) containing phosphoric acid (0·5 ml) and the solution was warmed on a steam-bath for 20 min. Ice was added and the resulting thick oil was collected and chromatographed on alumina (50 g). Elution with petroleum–benzene (2 : 3) gave the product (8a) (0·162 g, 9%), m.p. 76° (from ethanol) (lit.,[3] 75—77°), τ 2·73 (9H, m), 5·00 (2H, s), 5·26 (1H, q), and 6·98 (2H, d). No 2-phenylindene was obtained.

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