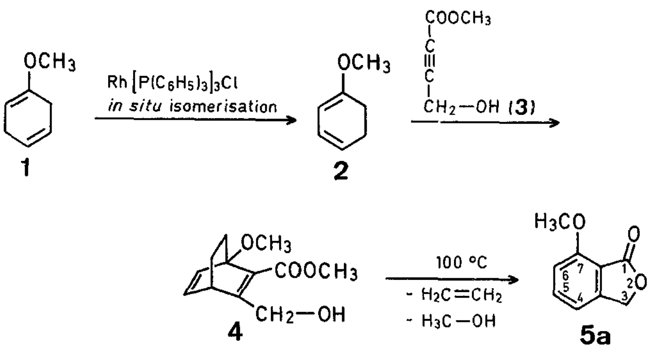
Synthesis of 3-Arylphthalides via Diels-Alder Reactions of Cyclohexa-1,3-dienes with Ethyl 4-Aryl-4-hydroxybut-2-ynoates

Philip A. HARLAND, Philip HODGE*

Department of Chemistry, University of Lancaster, Bailrigg, Lancaster, LA1 4YA, Great Britain

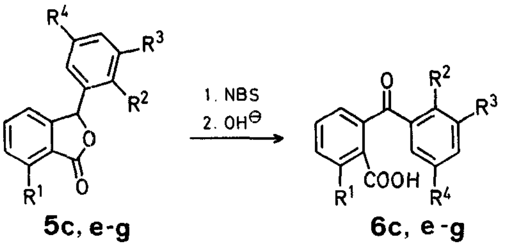
7-Methoxyphthalide (**5a**) can be prepared in one step by reacting diene (**1**) with acetylene (**3**) in the presence of tris[triphenylphosphine]chlororhodium (TCR) as catalyst at 100 °C[1] (Scheme **A**). We have successfully extended this method to the synthesis of 3-arylphthalides **5b-h** (Table), several of which are not readily available by Friedel-Crafts approaches involving either reaction of phthalic anhydrides with benzene derivatives[2] or reaction of 3-bromophthalides with reactive benzene derivatives[3]. 3-Arylphthalides are of interest as intermediates in the synthesis of anthraquinones[2,3].



Scheme **A**

The ethyl 4-aryl-4-hydroxybut-2-ynoates (used instead of **3**, above) were prepared from the appropriate aromatic aldehydes and lithiated ethyl propynoate in yields of 41–52% according to Ref.[4]. Cyclohexa-1,3-diene was obtained commercially; 1-methoxycyclohexa-1,4-diene and 1,4-dimethoxycyclohexa-1,4-diene were prepared by Birch reductions[1]. The phthalides were synthesised by heating the appropriate acetylenes and dienes at 100 °C in the absence of solvent. With the unconjugated dienes, tris[triphenylphosphine]chlororhodium was added to catalyse *in situ* conjugation[1,5] (Table).

It should be noted that phthalides **5d-g** were the only phthalides isolated from the respective reactions indicating that, as expected[1,5,6], the Diels-Alder reactions proceeded regiospecifically and in each case gave the product with a methoxy group adjacent to the carbonyl group.



Scheme **B**

Phthalides **5c** and **5g** were obtained as oils ~90% pure (¹H-N.M.R.). To obtain solid derivatives and confirm their structures they were successively treated with *N*-bromosuccinimide and alkali. This gave the benzoylbenzoic acids **6c** and **6g**. Similarly, phthalides **5e** and **5f** gave the acids **6e** and **6f**. Treatment of the latter two acids with sulphuric acid gave respectively 1,5-dihydroxyanthraquinone and, after demethylation, 1,4,5-trihydroxyanthraquinone in excellent yields from the phthalides. The following procedures are typical.

Ethyl 4-Aryl-4-hydroxybut-2-ynoates:

These are prepared by the procedure described[4] for the preparation of ethyl 4-hydroxy-4-phenylbut-2-ynoate (Table).

I.R. (film): $\nu = 3255, 2220, 1723\ cm^{-1}$.

7-Methoxy-3-phenylphthalide (5d):

A mixture of 2,5-dihydroanisole (2.18 g, 0.02 mol), ethyl 4-hydroxy-4-phenylbut-2-ynoate (4.08 g, 0.02 mol), and tris[triphenylphosphine]chlororhodium (40 mg) is stirred at 100 °C under nitrogen for 24 h. The cold mixture is dissolved in benzene (15 ml) and chromatographed on a silica gel column. Elution with chloroform/methanol (95:5) and evaporation of the solvents give the product as crystals. Recrystallisation from chloroform gives pure **5d**; yield: 2.0 g (44%); m.p. 139–141.5 °C.

$C_{15}H_{12}O_3$	calc.	C 74.98	H 5.04
(240.3)	found	74.65	5.11

I.R. (KBr): $\nu = 1760\ cm^{-1}$.

¹H-N.M.R. ($CDCl_3$): $\delta = 4.01$ (s, 3H); 6.44 (s, 1H); 6.9 (m, 2H); 7.5 (m, 4H); 7.6 ppm (m, 2H).

2-(2′-Methoxybenzoyl)-6-methoxybenzoic Acid (6e) and its Cyclisation:

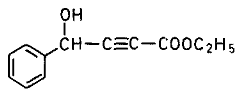
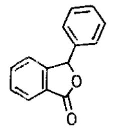
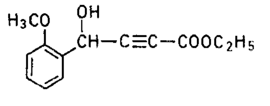
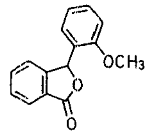
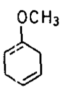
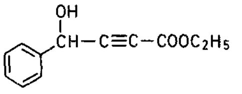
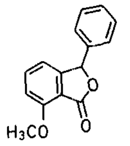
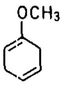
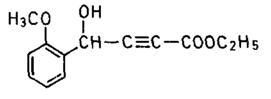
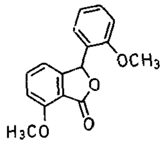
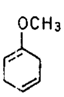
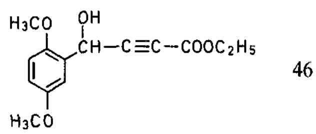
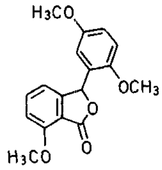
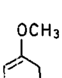
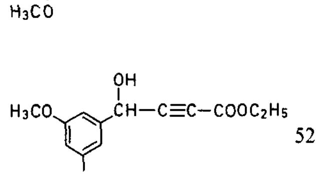
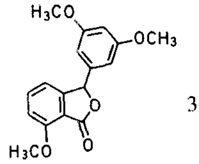
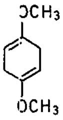
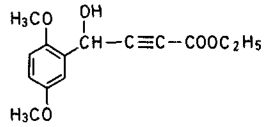
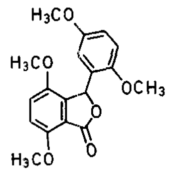
A mixture of phthalide **5e** (540 mg, 2.0 mmol), *N*-bromosuccinimide (356 mg, 2.0 mmol), and benzoyl peroxide (10 mg) in carbon tetrachloride (10 ml) is heated to reflux and stirred for 2 h in the presence of a 500 W tungsten lamp. The reaction mixture is cooled, filtered, and the solvent evaporated from the filtrate. The residue is treated for 1 h at 20 °C with 5% aqueous sodium hydroxide (10 ml). The mixture is washed with ether (25 ml), acidified with dilute hydrochloric acid (25 ml), and extracted with ether (3 × 50 ml). Evaporation of the magnesium sulphate dried extracts gives the acid **6e** in the lactol form; yield: 510 mg (81%); m.p. 169–169.5 °C (from chloroform).

$C_{16}H_{14}O_5$	calc.	C 67.12	H 4.93
(286.3)	found	67.39	5.01

I.R. (KBr): $\nu = 3420, 1745\ cm^{-1}$.

The above lactol (72 mg) is treated with concentrated sulphuric acid (5 ml) at 100 °C for 6 h. The mixture is poured on to ice (10 g). The preci-

Table. 3-Arylphthalides **5b-h** prepared[a]

Diene	Ethyl 4-Aryl-4-hydroxybut-2-ynoate				3-Arylphthalide				
		Yield [%]	m.p. or b.p./ torr [°C]	Molecular formula[b] or Lit. data			Yield [%]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]
		49	140-141°/ 0.75	95-98°/ $4 \cdot 10^{-4}$[9]	**5b**		42	115-116°	115-117°[8]
		41	180-185°/ 6	$C_{13}H_{14}O_4$ (234.2)	**5c**		31[c]	oil	—[d]
					**5d**		44	139-141.5°	$C_{15}H_{12}O_3$ (240.3)
					**5e**		41[c]	189-190.5°	$C_{16}H_{14}O_4$ (270.3)
		46	200-205°/ 6	$C_{14}H_{16}O_5$ (264.3)	**5f**		47[f]	156-158.5°	$C_{17}H_{16}O_5$ (300.3)
		52	178-183°/ 3	$C_{14}H_{16}O_5$ (264.3)	**5g**		36[c]	oil	—[g]
					**5h**		36	157-158°	$C_{18}H_{18}O_6$ (330.3)

[a] Reaction of equimolar amounts of diene and acetylene (except for **5b** and **5c** where 2 equivalents of diene are used) at 100 °C for 24 h in the presence of tris[triphenylphosphine]chlororhodium (except for **5b** and **5c**, reaction for 48 h in the absence of catalyst).

[b] Satisfactory microanalyses obtained: C ±0.33, H ±0.30.

[c] Overall yield of derived benzoylbenzoic acid **6**.

[d] Converted to acid **6c**; yield: 37%; m.p. 138-140 °C (Ref.[10], m.p. 142-144 °C).

[e] Converted to acid **6e**; see experimental, and subsequently to *1,5-dihydroxyanthra-9,10-quinone*.

[f] Converted to acid **6f**; yield: 87%; m.p. 164-165 °C; $C_{17}H_{16}O_6$ (306.3); and subsequently to *1,4,5-trihydroxyanthraquinone*; yield: 77%; m.p. 268-271 °C (Ref.[7], m.p. 270-271 °C).

[g] Converted to acid **6g**; yield: 85%; m.p. 195-197 °C; $C_{17}H_{16}O_6$ (306.3).

pitate is filtered off and dried. Recrystallisation from aqueous methanol (1:1, v:v) gives *1,5-dihydroxyanthra-9,10-quinone*; yield: 50 mg (85%); m.p. 279 °C (Ref.[7], m.p. 280 °C); diacetate m.p. 242° (dec) (Ref.[7], m.p. of diacetate 245 °C).

I.R. (KBr): ν=3400, 1625 cm^{-1}.

U.V. (C_2H_5OH): λ=225 (log ε=4.57); 253 (4.25); 287 (3.98); 418 (3.98); 432 nm (3.95).

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