Synthesis of Phthalates, Benzoates, and Phthalides via the *in situ* Generation of Methoxycyclohexa-1,3-dienes and their Subsequent Diels-Alder Reactions with Acetylenes

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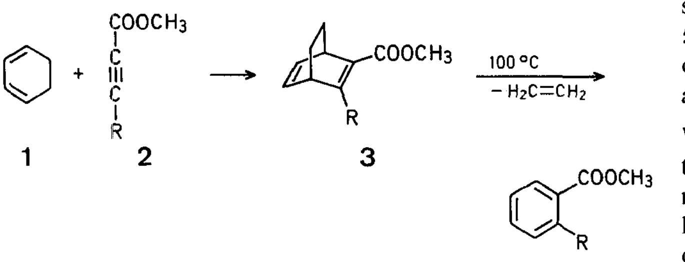
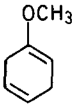
Reactions of cyclohexa-1,3-dienes (e.g. **1**) with acetylenes **2** at >100 °C provide short routes to certain aromatic compounds[1]. Above 100 °C, the initial Diels-Alder adducts **3** lose ethylene and give aromatic compounds **4** (Scheme A). We report convenient preparations of several phthalates, benzoates, and phthalides based on this approach. Such compounds are useful starting materials for many syntheses, especially those of anthraquinones[2] and anthracyclinones[3].



Scheme A

Dimethyl 3-methoxyphthalate (**7a**) was synthesised in three steps in the above manner[4]. First, anisole was reduced to 1-methoxycyclohexa-1,4-diene (**5**) with sodium and ethanol in liquid ammonia[5]. Then, the 1,4-diene **5** was equilibrated with the 1,3-diene **6** using potassium amide in liquid ammonia[6]. Finally, the 1,3-diene **6** was treated with dimethyl acetylene dicarboxylate at 100–140 °C. Three derivatives of **7a** were prepared similarly[4]. These syntheses could be improved if the 1,4-diene could be isomerised to the 1,3-diene *in situ*, i.e. in the presence of the dienophile[7,8], since then the total diene rather than just the equilibrium portion would be potentially capable of reaction and the syntheses would be reduced to just two practical steps.



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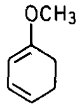

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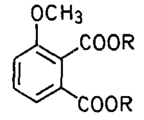
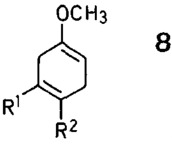


7a $R = CH_3$
b $R = C_2H_5$

In situ isomerisation can be achieved thermally[7,9]. Thus, phthalate **7a** was prepared in 91% yield by treating the Birch reduction product of anisole [mainly diene **5**] with dimethyl acetylenedicarboxylate for 36 h in a sealed tube at 170–180 °C[9]. Isomerisation of methoxycyclohexa-1,4-dienes can, however, generally be achieved under milder conditions using dichloromaleic anhydride (DCMA)[8] or tris[triphenylphosphine]chlororhodium (TCR) as catalyst[10]. A recent note[11] describing the preparation of phthalate **7b** by reaction of diene **5** with diethyl acetylenedicarboxylate in the presence of dichloromaleic anhydride prompts us to report our work in this area.

We have reacted dienes **5** and **8a–d**, prepared by Birch reduction of the corresponding aromatic compounds[12], with dimethyl acetylenedicarboxylate, ethyl propynoate, or methyl 4-hydroxybut-2-ynoate[13] at 100–140 °C in the presence of dichloromaleic anhydride or tris[triphenylphosphine]chlororhodium. The result are summarised in the Table.



8a $R^1 = H, R^2 = OCH_3$
b $R^1 = H, R^2 = CH_3$
c $R^1 = OCH_3, R^2 = H$
d $R^1 = CH_3, R^2 = H$

With dimethyl acetylenedicarboxylate as the dienophile, the corresponding phthalates were prepared and isolated in yields of 45–70%. Somewhat higher yields (75–80%) were obtained in some cases from larger scale reactions. In each case, the prod-

Table. Reactions of Various Cyclohexadienes with Dienophiles in the Presence of a Catalyst

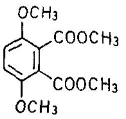
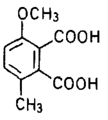
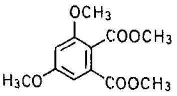
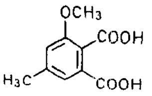
Product	Diene	Catalyst	Reaction conditions time[a]/temperature[b]	Yield[c] [%]	m.p. [°C] or b.p. [°C]/torr	
					found	reported
A: Dimethyl acetylenedicarboxylate as dienophile:						
7a	**5**	DCMA	1 h/130 °C	70	75–77°	77–77.5°[14]
7a	**5**	TCR	1 h/130 °C	<15[d]	—	—
	**8a**	DCMA	1 h/140 °C	67	99–100°	102–103°[14]
	**8b** **8b**	DCMA TCR	10 h/140 °C 17 h/140 °C	45[f] 15[f]	195–196.5°	—[e]
	**8c**	DCMA	1 h/140 °C	63	92–93°	92–94°[14]
	**8d** **8d**	DCMA TCR	18 h/140 °C 18 h/140 °C	~ 1[f] 45[f]	200–204° (dec)	202°[14] (dec)

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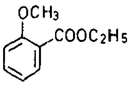
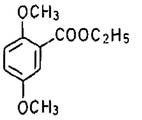
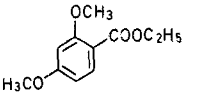
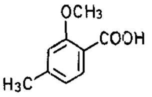
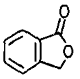
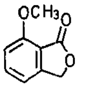
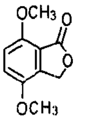
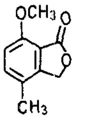
Table. (Continued)

Product	Diene	Catalyst	Reaction conditions time[a]/temperature[b]	Yield[c] [%]	m.p. [°C] or b.p. [°C]/torr	
					found	reported
B: Ethyl propynoate as dienophile:						
	**5**	DCMA	4 h/100 °C	56	229–235°/745	246–248°/ 732[14]
	**8a**	DCMA	4 h/100 °C	63	276–280°/760	285°/760[14]
	**8c**	DCMA	4 h/100 °C	55	241–245°/755	170°/13[14]
	**8d**	TCR	4 h/100 °C	15[f]	70–71°	74°[14]
C: Methyl 4-hydroxybut-2-ynoate as dienophile:						
	**1**	none	4.5 h/100 °C	61	73–74°	75°[14]
	**5**	TCR	15 h/100 °C	55	109–110°	107–109°[15]
	**8a**	DCMA	20 h/140 °C	0		
	8a	TCR	5 h/100 °C	39	174–174.5°	–[g]
	**8b**	TCR	15 h/100 °C	45	oil	–[h]

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[a] Reactions were carried out until gas evolution ceased, or until I.R. or ^{1}H-N.M.R. analysis of the reaction mixture showed that one or both of the starting materials had reacted.

[b] Oil bath temperatures.

[c] Yields of isolated material.

[d] A mixture of hexamethyl mellitate and octamethoxycarbonylcyclooctatetraene was obtained in 85% yield.

[e] New compound; crystallised from aqueous ethanol:

$C_{10}H_{10}O_5$	calc.	C 57.14	H 4.80
(210.2)	found	56.90	4.45

I.R. (Nujol): $\nu = 1690$ cm^{-1}.
^{1}H-N.M.R. (acetone-d_6): $\delta = 2.59$ (s, 3H); 4.04 (s, 3H); 7.56 (d, 1H, $J = 9$ Hz); 7.72 ppm (d, 1H, $J = 9$ Hz).

[f] The reaction mixture was hydrolysed (alcoholic KOH) and the acid isolated.

[g] See experimental section.

[h] New compound; 97% pure by ^{1}H-N.M.R. analysis.
I.R. (film): $\nu = 1765$ cm^{-1}.
^{1}H-N.M.R. (CDCl$_3$): $\delta = 2.44$ (s, 3H); 4.02 (s, 3H); 5.28 (s, 2H); 7.05 (d, 1H, $J = 9$ Hz); 7.56 ppm (d, 1H, $J = 9$ Hz).

uct was that which had a methoxy group adjacent to a methoxycarbonyl group and where a methyl or second methoxy group present in the original diene was retained. This indicates that in each reaction the conjugated diene that reacted with dimethyl acetylenedicarboxylate was that obtained by 'pivoting' the enol ether double bond. The preferred catalyst for the synthesis of phthalates was generally dichloromaleic anhydride, principally because tris[triphenylphosphine]chlororhodium also catalysed the cyclo-oligomerisation of dimethyl acetylenedicarboxylate[16]. Despite this, however, tris[triphenylphosphine]chlororhodium proved to be much the better catalyst for the synthesis of dimethyl 3-methoxy-5-methylphthalate.

Several benzoates were prepared using the above procedure, but with ethyl propynoate in place of dimethyl acetylenedicarboxylate. The main point of interest was to determine which of the several possible products were obtained. In each case only one product was isolated and, as expected[8], it was that with a methoxy group adjacent to the ethoxycarbonyl group.

Phthalides do not appear to have been prepared previously using the approach outlined in Scheme **A**. As a trial of the method, methyl 4-hydroxybut-2-ynoate, prepared by the literature method from propargyl alcohol[13], was treated with cyclohexa-1,3-diene at 100 °C. This gave the phthalide in 61% yield: the initial Diels-Alder adduct and/or the initial aromatic product having cyclised with the loss of methanol. In view of this success, methyl 4-hydroxy-but-2-ynoate was treated with dienes **5** and **8a–d** in the presence of dichloromaleic anhydride or tris[triphenylphosphine]chlororhodium. For these reactions the latter proved to be the better catalyst and from dienes **5, 8a,** and **8b,** the corresponding phthalides were obtained and isolated in yields of 39-55%. Again the products were those with a methoxy group adjacent to the carbonyl group. Not all the reactions were successful however: those with dienes **8c** and **8d** gave complex mixtures (reaction conditions: 18-24 h/100 °C).

Dienes **5** and **8a–d** were prepared by the lithium/ethanol/liquid ammonia reduction of the corresponding aromatic compounds[12]. The products (55-76% yields) distilled at the expected temperatures and ^{1}H-N.M.R. analyses indicated that they each contained more than 80% of the required diene.

Methyl 4-hydroxybut-2-ynoate was prepared via carboxylation of the Grignard reagent from propargyl alcohol tetrahydropyranyl ether[13]; b.p. 120 °C/6 torr (Ref.[14], b.p. 114-118 °C/3 torr).

I.R. (film): $\nu = 3400$, 2240, 1720 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.29$ (s, 1H); 3.80 (s, 3H); 4.30 ppm (s, 2H).

Dimethyl 3,5-Dimethoxyphthalate:

2,5-Dihydroresorcinol dimethyl ether (1.90 g, the crude product from the reduction of resorcinol dimethyl ether), dimethyl acetylenedicarboxylate (2.98 g), and dichloromaleic anhydride (40 mg) are heated together at 140 °C under nitrogen for 1 h by which time evolution of ethylene ceases. The reaction mixture is cooled, dissolved in ether, and chromatographed over silica gel. Elution with ether/hexane (40:60) gives dimethyl 3,5-dimethoxyphthalate which crystallizes from petroleum ether (b.p. 60-80 °C) as colourless crystals; yield: 2.21 g (63%); m.p. 92-93 °C (Ref.[14], m.p. 92-94 °C).

I.R. (Nujol): $\nu = 1725$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.80$ (s, 3H); 3.88 (s, 3H); 3.95 (s, 3H); 4.10 (s, 3H); 7.56 (d, 1H, $J = 2$ Hz); 7.95 ppm (d, 1H, $J = 2$ Hz).

Ethyl 2,5-Dimethoxybenzoate:

A mixture of 1,4-dimethoxy-2,5-dihydrobenzene (6.89 g), ethyl propynoate (4.92 g), and dichloromaleic anhydride (40 mg) is heated at 100 °C under nitrogen for 4 h. Distillation of the reaction mixture gives ethyl 2,5-dimethoxybenzoate; yield: 6.40 g (63%); b.p. 276-280 °C/760 torr (Ref.[14], b.p. 285 °C/760 torr).

I.R. (film): $\nu = 1720$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.34$ (t, 3H, $J = 7.5$ Hz); 3.72 (s, 3H); 3.75 (s, 3H); 4.28 (q, 2H, $J = 7.5$ Hz); 6.87 (m, 2H); 7.19 ppm (m, 1H).

4,7-Dimethoxyphthalide:

A mixture of 1,4-dimethoxy-2,5-dihydrobenzene (1.40 g), methyl 4-hydroxybut-2-ynoate (1.20 g), and tris[triphenylphosphine]chlororhodium (40 mg) is heated at 100 °C for 5 h. The cold mixture is dissolved in chloroform/benzene (1:1) and chromatographed over silica gel. Elution with chloroform/methanol (95:5) gives 4,7-dimethoxyphthalide which crystallises from carbon tetrachloride as white crystals; yield: 0.78 g (39%); m.p. 174-174.5 °C.

$C_{10}H_{10}O_4$	calc.	C 61.85	H 5.19
(194.2)	found	61.90	5.20

I.R. (Nujol): $\nu = 1765$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.76$ (s, 3H); 3.87 (s, 3H); 5.30 (br s, 2H); 6.80 ppm (q, 2H).

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