Alkyl Isobenzofurans from Phthalides; Inter and Intramolecular Diels-Alder Reactions

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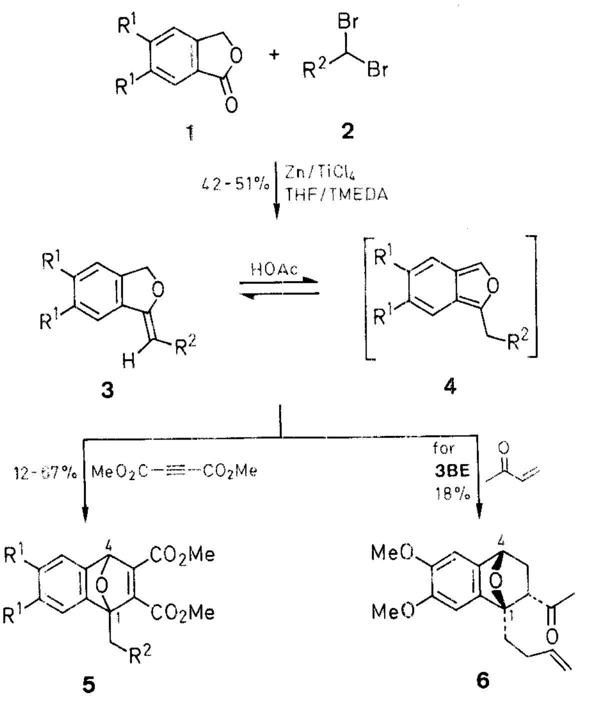
A general procedure for the conversion of phthalides **1** to alkyl isobenzofurans **4** is described and illustrated with nine examples. Thus, the alkylidene phthalans **3** produced from the phthalides **1** in one step are in acid catalyzed equilibrium with the alkyl isobenzofurans **4** which are trapped *in situ* by dienophiles as the inter- and intramolecular Diels-Alder adducts **5**-**9**.

The development of new synthetic routes to isobenzofurans and their use in the elaboration of natural products is a subject that has received much attention[1] in the last decade. Phthalans and phthalides have been popular precursors in the synthesis of isobenzofurans but the expeditious conversion of a phthalide to a 1-alkyl isobenzofuran is a useful transformation that has not been reported as yet. Phthalides are readily available, but in general they do not react cleanly with Girgnard reagents to provide simple mono-addition products[2] (hydroxy phthalans) that might be dehydrated to isobenzofurans. A recent discovery[3] that an undefined organotitanium species generated from 1,1-dibromohexane, titanium tetrachloride and zinc dust, reacted with phthalide to afford 1-hexylidene phthalan in reasonable yield seemed to offer a solution to the problem. It has been known[4] for some time that benzylidene phthalan (**3B**) exists in acid catalysed equilibrium with benzyl isobenzofuran (**4B**), but this route to isobenzofurans has hitherto been restricted to the arylidene phthalans due to the lack of convenient methods for the synthesis of the alkylidene derivatives. Thus, although several polycyclic aromatic hydrocarbons have been efficiently synthesised by this route very recently,[5] its scope, generality and applicability to intramolecular Diels-Alder chemistry in particular, remained uncertain.



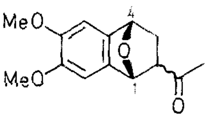
2	R^2	2	R^2
a	H	**d**	$CH_2CH{=}CH_2$
b	Ph	**e**	$(CH_2)_2CH{=}CH_2$
c	CH_2Ph	**f**	$(CH_2)_3CH{=}CH_2$

3-5	R^1	R^2	3-5	R^1	R^2
A	H	H	**E**	OMe	Ph
B	H	Ph	**F**	OMe	$CH_2CH{=}CH_2$
C	H	CH_2Ph	**G**	OMe	$(CH_2)_2CH{=}CH_2$
D	H	$CH_2CH{=}CH_2$	**H**	H	$(CH_2)_3CH{=}CH_2$

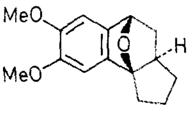
The results of our investigations on this subject, summarized in Tables 1 to 3 were obtained with two phthalides (**1**, R^1 = H, OMe) and six dibromides **2a**-**f**. The alkyl isobenzofurans **4** were not isolable but were intercepted *in situ* with dienophiles to provide nine examples of inter (**5A**-**F**, **6**) and intramolecular (**8** and **9**) Diels-Alder adducts in two steps from the starting phthalide. Overall yields for the two steps (Table 3) are only moderate, mainly because the intermediates are sensitive materials, very prone to darkening and decomposition. The phthalides however, are readily available in large quantity and the process has the advantage of being convergent.

Four dibromides **2c**-**f** were prepared in yields ranging from 61-82% by the alkylation[6] of lithiated dibromomethane with the requisite bromide or iodide. Two of these compounds **2a**, **2b** are commercial materials and two **2c** and **2d** have been previously described.[6] All of them are sensitive liquids, which darken on storage, and should be used soon after distillation. The alkylidenation reaction is very dependent on the purity of the zinc powder. In our experiments the zinc was washed successively with 10% aqueous hydrochloric acid, methanol and diethyl ether and then dried before use. The eight alkylidene phthalans **3A–H** could be isolated in moderate yield (40–55%) but in general these compounds too were unstable and it was better to carry them through the next step without rigorous purification. The properties of four new alkylidene phthalans that could be isolated and characterized are detailed in Table 2. The ^{1}H-NMR spectra of these compounds indicate the existence of a single geometric isomer (probably the *Z*). The phthalans **3A**, **G** and **H** were used without purification and **3B** is a known compound.[2]

The Diels–Alder reactions with dimethyl acetylene dicarboxylate (DMAD) using the dienophile as solvent were complete in 10 minutes with a catalytic quantity of glacial acetic acid at steam bath temperatures. One example with methyl vinyl ketone (MVK) as the dienophile produced the *ortho*-adduct as expected.[1] The *endo*-configuration at C-2 was assigned to the product isolated from this reaction. This is based on the chemical shifts of the acetyl methyl group and proton at, C-2 which are diagnostic of the configuration at this carbon. Thus **6** [δ = 3.06 (H-2), 1.69 ($COCH_3$)] and *endo*-**7** [δ = 3.40 (H-2), 1.99 ($COCH_3$)] have similar values reflecting the shielding of the *endo* methyl group in each compound but in *exo*-**7** (δ = 2.59 (H-2), 2.28 ($COCH_3$) H-2 is shielded instead.[7] Intramolecular Diels–Alder reactions were successful with **3G** and **3H** yielding adducts **8** and **9** respectively even in the presence of DMAD. Cyclobutane rings could not be formed however from **3D** and **3F**: both these alkylidene phthalans reacted in the intermolecular Diels–Alder fashion with DMAD and MVK. Both adducts **8** and **9** are assigned the *exo*-configurations by analogy with an earlier report[8] concerning the configuration of the closely related adduct **10**. The preferential formation of the *exo*-adducts in these intramolecular cycloadditions has been rationalized[1] by comparison of the steric interactions for the *exo*- and *endo*-transition states. Models show that the latter is much more crowded in the intramolecular cycloaddition of isobenzofurans. Our attempts to prepare alkylidene phthalans containing carbon–carbon triple bonds in the alkyl group were foiled, presumably by the formation of titanocyclobutenes[9] by reaction of the triple bond with the putative organotitanium reagent. Thus no identifiable alkylidene phthalan could be obtained from the reaction of phthalide with 6,6-dibromo-1-hexyne (**11**).



7 (*endo* + *exo*)



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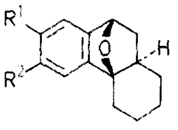

9 R^1, R^2 = H
10 R^1, R^2 = OMe

All solvents were dried and distilled. CH_2Br_2 benzal bromide, benzylbromide, 3-bromopropene, 4-bromobutene, and 5-bromopentene were purchased from Aldrich and used after distillation. Zinc powder purchased from Fischer was purified as described earlier.[10] DMAD and MVK were freshly distilled.

Melting points were determined on a Mel Temp apparatus and are uncorrected. Low resolution Mass spectra were obtained on a VG 7070 instrument and high resolution data were collected on a VG ZAB-E spectrometer at the South-Western Ontario Regional Mass Spectrometry Centre at McMaster University, Hamilton, Ontario. NMR spectra were recorded on Bruker AM 250 or AC 200 spectrometers. IR spectra were obtained on a Perkin Elmer 983 spectrophotometer. Microanalyses were performed by MHW Laboratories of Phoenix, Arizona.

Table 1. New Geminal Dibromides Prepared

Compound	Yield (%)	bp (°C)/ mbar	Molecular Formula	HRMS, m/z (M^+)		IR (neat) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
				calculated	found		
2e	69	68/20	$C_5H_8Br_2$ (227.9)	227.8972	227.8956	1639 (C=C)	2.25–2.75 (m, 4H, CH_2); 5.04–5.14 (m, 2H, $CH{=}C\underline{H}_2$); 5.68–5.85 (m, 2H, $C\underline{H}Br_2$; $C\underline{H}{=}CH_2$)
2f	66	72/20	$C_6H_{10}Br_2$ (242.0)	241.9141	241.9128	1638 (C=C)	1.61, 2.16, 2.37 (m, 6H, CH_2); 5.13 (m, 2H, $CH{=}C\underline{H}_2$); 5.70 (t, 1H, J = 6, $CHBr_2$); 5.78 (m, 1H, $C\underline{H}{=}CH_2$)
11	61	90/20	$C_6H_8Br_2$ (239.9)	239.8956	239.8961	2118 (C≡C)	1.95–2.70 (m, 7H, CH_2 + C≡CH); 5.72 (t, 1H, J = 6, $CHBr_2$)

Table 2. New Alkylidenephthalans Prepared

Compound	Yield (%)	Molecular Formula	HRMS (EI), m/z (M^+)		IR (neat) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
			calculated	found		
3C	42	$C_{16}H_{14}O$ (222.3)	222.1045	222.1048	1683 (C=C)	3.66 (d, 2H, J = 7.5, $C\underline{H}_2Ph$); 5.13 (t, 1H, J = 5.75, =CH); 5.37 (s, 2H, CH_2O); 7.32 (m, 9H_{arom})
3D	42	$C_{12}H_{12}O$ (172.2)	172.0888	172.0890	1674 (exocyclic C=C), 1636 (C=C)	3.04 (dd, 2H, J = 6.8, 3.8, $C\underline{H}_2CH{=}CH_2$); 5.04 (m, 3H, $CH{=}CH_2$); 5.17 (s, 2H, CH_2O); 5.91 (m, 1H, =CH); 7.34 (m, 4H_{arom})
3E	53	$C_{17}H_{16}O_3$ (268.3)	268.1042	268.1043	1657 (C=C)	3.92, 3.96 (2s, 3H each, OMe); 5.45 (s, 2H, CH_2O); 5.77 (s, 1H, =CH); 6.81, 7.01 (2s, 1H each, H_{arom}); 7.05–7.45 (m, 3H_{arom}); 7.70 (d, 2H_{arom}, J = 7.3)
3F	51	$C_{14}H_{16}O_3$ (232.3)	232.0881	232.0890	1644 (exocyclic C=C), 1636 (terminal C=C)	3.03 (dd, 2H, J = 6.8, 3.8, $C\underline{H}_2CH{=}CH_2$); 3.89, 3.90 (2s, 3H each, OMe); 4.75 (t, 1H, J = 7.5, $C\underline{H}{=}CH_2$); 5.04 (m, 2H, $CH{=}C\underline{H}_2$); 5.26 (s, 2H, CH_2O); 5.95 (m, 1H, =CH); 6.75, 6.88 (2s, 1H each, H_{arom})

Table 3. Diels-Alder Adducts **5**, **6**, **8**, **9** Prepared

Adduct	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula	HRMS, m/z (M^+)		IR (neat or nujol)	^{1}H-NMR (CDCl$_3$/TMS) δ, J(Hz)
				calculated	found		
5A	12	–	$C_{15}H_{14}O_5$ (274.3)	274.0841	274.0848	1733, 1704 (ester C=O); 1625 (C=C)	1.76 (s, 3H, CH$_3$); 3.73, 3.85 (2s, 3H each, OCH$_3$); 5.42 (s, 1H, H-4); 7.51 (m, 4H$_{arom}$)
5C	63	–	$C_{22}H_{20}O_5$ (364.4)	364.1310	364.1318	1714 (br, ester C=O); 1635 (C=C)	2.52–2.95 (m, 4H, CH$_2$); 3.76, 3.78 (2s, 3H each, OMe); 5.96 (s, 1H, H-4); 7.01–7.46 (m, 9H$_{arom}$)
5D	67	–	$C_{18}H_{18}O_5$ (314.3)	314.1138	314.1146	1718 (br, ester C=O); 1639 (C=C)	2.40 (m, 4H, CH$_2$); 3.76, 3.80 (2s, 3H each, OMe); 5.05 (m, 2H, CH=C$\underline{H}_2$); 5.87 (m, 1H, CH=CH$_2$); 5.92 (s, 1H, H-4); 7.21 (m, 4H$_{arom}$)
5E	57	120–121 (Et$_2$O)	$C_{23}H_{22}O_7$ (410.4)	410.1365	410.1377	1713 (br, ester C=O)	3.59, 3.81 (d, 2H, J = 10, CH$_2$); 3.68, 3.71 (2s, 3H each, CO$_2$Me); 3.86, 3.90 (2s, 3H each, OCH$_3$); 5.92 (s, 1H, H-4); 7.03, 7.06 (s, 1H each, H$_{arom}$); 7.24–7.35 (m, 5H$_{arom}$)
5F	53	–	$C_{20}H_{22}O_7$ (374.4)	374.9358	374.9358	1716 (br, ester C=O); 1635 (C=C)	2.21–2.81 (m, 4H, CH$_2$); 3.76, 3.81 (2s, 3H each, CO$_2$Me); 3.86, 3.87 (2s, 3H each, OMe); 5.03–5.12 (m, 2H, CH=C$\underline{H}_2$); 5.85–5.96 (m, 1H, C$\underline{H}$=CH$_2$); 5.88 (s, 1H, H-4); 6.94, 7.04 (s, 1H$_{arom}$)
6	18	–	$C_{18}H_{22}O_4$ (302.4)	302.1519	302.1510	1696 (C=O); 1635 (C=C)	1.69 (s, 3H, COCH$_3$); 2.27–2.62 (m, 6H, CH$_2$); 3.06 (dd, 1H, J = 9.96, 4.15, C$\underline{H}$COCH$_3$); 3.85, 3.87 (2s, 3H each, OMe); 4.97–5.29 (m, 2H, CH=C$\underline{H}_2$); 5.32 (d, 1H, J = 4.87, OCH); 6.02 (m, 1H, C$\underline{H}$=CH$_2$); 6.67, 6.87 (2s, 1H each, H$_{arom}$)
8	44	139–141 (Et$_2$O/ hexane)	$C_{15}H_{18}O_3$ (246.3)	246.1256	246.1245	1600	1.42–2.43 (m, 9H, ring CH$_2$ + CH); 3.86–3.88 (2s, 3H each, OMe); 5.31 (d, 1H, J = 4.5, CHO); 6.79, 6.86 (2s, 1H each, H$_{arom}$)
9	55	–	$C_{14}H_{16}O$ (200.3)	200.1199	200.1201	1600	1.72 (m, 11H, ring CH$_2$ + CH); 5.34 (d, 1H, J = 4.6, OCH); 7.16 (m, 4H$_{arom}$)

[a] Overall yield starting from **1** and **2**.

[b] Viscous oils that could not be distilled without decomposition except for **5E** and **8**.

Geminal Dibromides 2; General Procedure:

To a solution of diisopropyl amine (1.1 mmol) in dry THF (2.2 mL) and Et$_2$O (1.5 mL) under N$_2$ and cooled to −20 °C is slowly added a 1.6N solution of BuLi in hexane (0.68 mL, 1.1 mmol) over 15 min. The mixture is allowed to warm to 0 °C, stirred for 10 min and recooled to −100 °C. A solution of CH$_2$Br$_2$ (174 mg, 1 mmol) in THF (1 mL) is added slowly maintaining the temperature below −95 °C, stirred for 15 min and cooled back to −100 °C. A solution of hexamethylphosphoramide (179 mg, 1 mmol) in THF (1 mL) is added, stirred for 10 min and followed by the addition of the corresponding bromo or iodoalkane (1 mmol) in THF (1 mL). After stirring for 15 min the mixture is allowed to warm to −55 °C, maintained at this temperature for 4 h and 2N HCl (1 mL) is added slowly. The mixture is diluted with water (50 mL), and the product extracted with Et$_2$O (3 × 50 mL). The combined Et$_2$O extracts are dried (MgSO$_4$), concentrated and distilled under reduced pressure in a semi-micro distillation unit. The liquids are stored in the dark in the freezer, over Calcium chloride. The properties of the three new dibromides **2e**, **2f** and **11** prepared by this method are found in Table 1.

Alkylidenephthalans 3; General Procedure:

Liquid TiCl$_4$ (0.43 mL, 4 mmol) is added slowly at 0 °C to THF (10 mL) under an Ar atmosphere. To the yellow solution at 25 °C is added freshly distilled TMEDA (1.2 mL, 8.0 mmol) and the mixture is stirred at 25 °C for 10 min. Activated Zn dust (0.59 g, 9.0 mmol) is then added, and the mixture is stirred for 30 min at 25 °C. Dibromide **2** (2.2 mmol) and the phthalide **1** (1 mmol) in THF (2 mL) are added and the mixture is stirred until it becomes brown (ca. 4 h). It is then cooled to 0 °C, stirred for another 30 min, diluted with Et$_2$O (20 mL) and filtered rapidly through a short column of basic alumina (activity III) using Et$_2$O/Et$_3$N (200:1) as the eluent. The resulting yellow solution is concentrated and chromatographed on basic alumina (activity III), using an appropriate mixture of EtOAc/hexane as the solvent, to remove the remaining starting materials. The resulting alkylidene phthalide is vacuum dried for 2 h to remove residual Et$_3$N and directly used for the next step. (Table 2)

Diels-Alder Adducts 5–9; General Procedure:

The alkylidene phthalide (100 mg) is dissolved in excess DMAD or MVK (3 mL) and a catalytic amount (ca. 0.1 mL) of glacial HOAc is added and heated on the steam bath for 10 min. Excess DMAD is removed by vacuum distillation and the product is purified by preparative TLC on silica gel. Intramolecular Diels-Alder reactions are carried out by refluxing the alkylidenephthalan (100 mg) in benzene (10 mL) with glacial HOAc (0.1 mL) for 12 h (Table 3).

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