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A NEW METHOD FOR THE GENERATION OF ISOBENZOFURANS:
A SIMPLE ENTRY TO SUBSTITUTED NAPHTHALENES.

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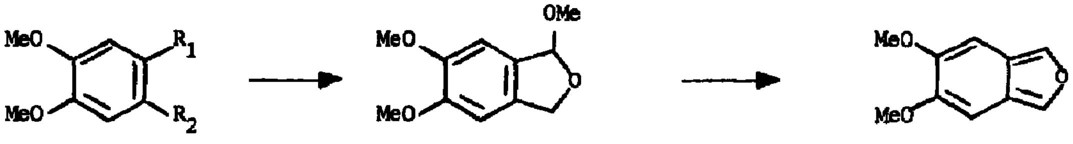
Abstract - 5,6-Dimethoxy isobenzofuran is generated in situ from the dimethylacetal of 6-hydroxymethyl veratraldehyde and intercepted by a variety of dienophiles to produce the expected oxygen-bridged adducts in good yield. Many of the latter are easily aromatised to naphthalenes.

The outstanding properties of isobenzofurans as dienes in the Diels-Alder reaction are well documented.[1] They have generally been obtained by the thermolysis of bridged polycyclic systems in reverse Diels-Alder processes and their widespread application to the construction of naturally occurring aromatic and hydroaromatic polycyclic systems has been limited only by the difficulty of preparing suitably substituted bicyclic precursors. One noteworthy exception is the isobenzofuran approach to anthracyclinone synthesis.[2] In recent years new preparations of isobenzofurans (not involving Diels-Alder reversions) have been developed.[3,4,5] Overall versatility is again limited i these procedures either by nature of the precursor[3,5] or by conditions of isobenzofuran generation[4] which preclude the isolation of non-aromatised products.

We now report a simple, efficient method for the generation of isobenzofurans which is both mild and versatile, permitting in principle the elaboration of most desired substitution patterns and the isolation of bridged adducts after reaction with various dienophiles. To avoid regiochemic problems at the present time we have chosen to illustrate our procedure with 5,6-dimethoxyisobenzofuran but our experience to date confirms the generality of the method with other non-symmetric var iants. Thus 6-bromoveratraldehyde 1 was quantitatively converted[6] to its dimethyl acetal 2, lithiated with n butyl lithium (halogen-metal exchange) and reacted with dry formaldehyde to provide 6-hydroxymethyl veratraldehyde dimethyl acetal 3 in virtually quantitative yield. The latter was a heavy oil which could not be distilled without decomposition and resisted crystallisation. Its structure was apparent however from the accrued spectroscopic data (M^+ = 242; δ($CDCl_3$) 3.01(t,1) (exchanges with D_2O), 3.35 (s,6), 3.85 (s,6), 4.59 (d,2) (collapses to singlet with D_2O), 5.41 (s,1

6.82 (s,1), 7.00 (s,1); IR γ^{neat}_{OH} = 3430 broad). Treatment of this compound with glacial acetic acid in a suitable refluxing solvent and in the presence of various dienophiles resulted in oxyge bridged adducts (of the type 6) in an average yield of 70%. The outcome of this reaction can onl be attributed to the formation and interception of the isobenzofuran 5 by the process shown in Scheme 1.

Scheme 1



1 R_1 = CHO, R_2 = Br
2 R_1 = $CH(OMe)_2$, R_2 = Br
3 R_1 = $CH(OMe)_2$, R_2 = CH_2OH

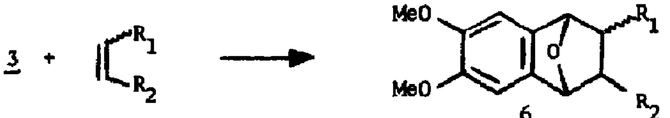
4

5

No direct evidence for the existence of 5 has been obtained, nor can such evidence be reali tically expected in view of the well-known instability of simple isobenzofurans,[1] but brief treat of 3 with acetic acid did produce the acetal 4 (δ ($CDCl_3$) 3.38 (s,3), 3.86 (s,3), 3.87 (s,3), 4.9 (d,1,J = 12.0 Hz), 5.16 (dd,1, J = 12.0, 2.2 Hz), 6.12 (d,1, J = 2.2 Hz), 6.75 (s,1), 6.88 (s,1)).

The table summarises our results with various dienophiles. It is noteworthy that even acid sensitive materials like butenolide and methyl vinyl ketone can be successfully used.

Table



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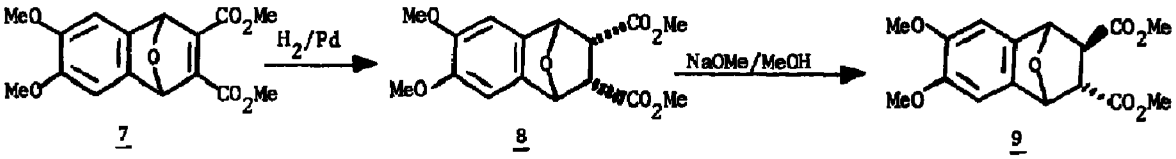
	Dienophile	Isolated Yield (%)	Solvent (Time)	Endo/Exo by (p.m.r.)
1.	dimethylacetylenedicarboxylate	99	none (20 min)	--
2.	benzoquinone	60	CH_2Cl_2 (15 h)	7:3
3	naphthaquinone	86	$CHCl_3$ (1 h)	3:1
4.	methylvinyl ketone	80	CCl_4 (6 h)	3:2
5.	2-butenolide	72	$CHCl_3$ (48 h)	1:2[†]
6.	acrylonitrile	64	$CHCl_3$ (4 h)	9:1
7.	α-chloroacrylonitrile	70	CH_2Cl_2 (15 h)	3.7[*]
8.	maleic anhydride	60	CH_2Cl_2 (24 h)	7:3
9.	methyl acrylate	50	$CHCl_3$ (10 h)	3:2

[†] based on individually isolated isomers.

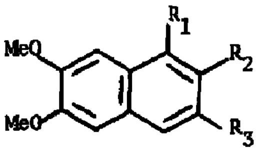
[*] with respect to cyano group.

Endo/exo mixtures can usually be readily detected and estimated by inspection of the p.m.r. spectra. Bridgehead protons appear as singlets in the exo-adducts but are doublets (J = 4.5-5.1 Hz) in the endo-adducts. Separations have been achieved in certain instances by a combination of column chromatography and fractional crystallisation (entries 4 and 5). In other cases the endo isomers have been isolated from the mixtures as crystalline solids (entries 3,6,9). The reaction with dimethyl fumarate produced the trans diester in a disappointing yield of ca. 5%. However, the same compound 9 was obtained in two steps from the acetylene dicarboxylate adduct 7 in an overall yield of 82%. (Scheme 2)

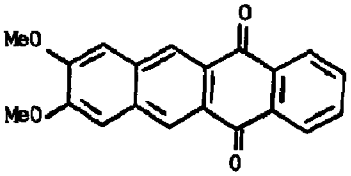
Scheme 2



Naphthalenes 10, 11, 12 and 13 were obtained from the corresponding oxygen-bridged compounds by brief acid treatment;[12] the synthesis of substituted naphthalenes has recently attracted some attention.[7] Quinone 14 was prepared by similar aromatisation (adduct of entry 3).[8]



10 R_1 = OH, $R_2 = R_3 = CO_2Me$
11 R_1 = H, $R_2 = R_3 = CO_2Me$
12 $R_1 = R_2$ = H, R_3 = CN
13 $R_1 = R_2$ = H, R_3 = COMe



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These results combined with our recent directed lithiation procedure[9] for aromatic acetals provides a method of great potential for the synthesis of many natural products. It has already been exploited[10] in a short synthesis of some aryl naphthalide lignans. A further interesting aspect now being actively investigated is the generation of furopyridines[11] and other heterocyclic analogues.

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8. Compounds 3 and 4 were unstable oils which could not be purified without decomposition. All other new compounds prepared in this study had analytical and spectroscopic properties consistent with their structures. Mixtures of exo-endo isomers if not separable were analysed as such.
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12. Refluxing in toluene for 3 h. with a catalytic quantity of para-toluene sulfonic acid, followed by chromatography (silica).

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