Regiospecific Cycloaddition of 1-Substituted Isobenzofurans to Quinone Acetals

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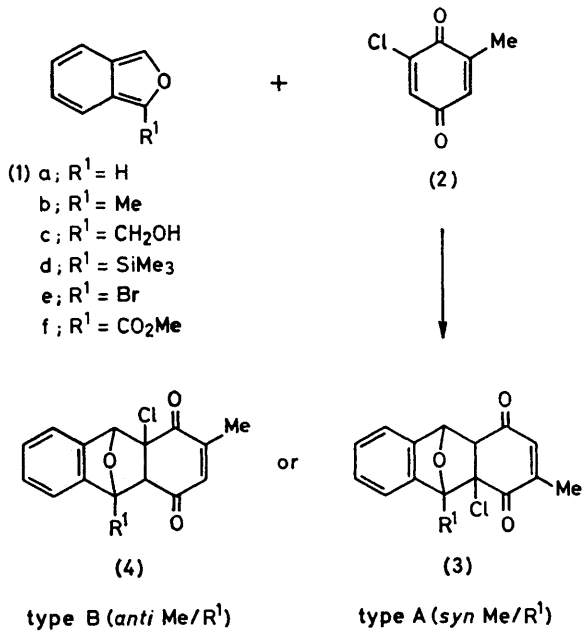
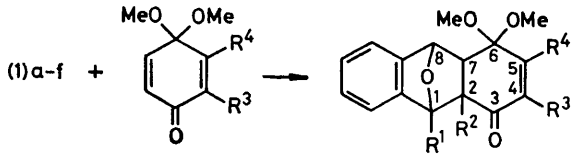
Summary The cycloaddition reaction of 1-substituted isobenzofurans to quinone acetals is highly stereo-, site-, and regio-specific; the degree of regiocontrol is maintained over a wide range of substituents.

QUINONES enter into cycloaddition reactions with dienes, but the regiospecificity may vary upon changing the substituent on either partner.[1,2] Thus reaction of the chloromethylbenzoquinone (**2**) with 1-bromoisobenzofuran (**1c**) yields *syn*-regioisomers of type A (**3**);[3] on the other hand 1-trimethylsilylisobenzofuran yields the *anti*-regioisomers of type B (**4**).[3] Clearly each reaction is regiospecific, but the reaction lacks the necessary control where type A or type B adducts can be generated on demand (regiocontrol).

Quinone acetals have recently emerged as versatile reagents in organic synthesis[4,5] and good methods for their preparation are available.[6] While interest has concentrated on anionic and carbanionic addition to these reagents, we show here that they are valuable dienophiles,[7,8] which react with 1-substituted isobenzofurans in a *regiocontrolled* fashion.[9] In this way type A or type B substitution can be obtained by judicious location of the R^3/R^4 substituent on the dienone *e.g.* (**5a**—**d**). Transfer of this site location to the adduct is assured since a single product is formed in the cycloaddition reaction,[10] irrespective of the nature of the 1-substituent on the isobenzofuran. In all cases the regioisomer with general structure (**6**), *i.e.* with the R^1-substituent of the isobenzofuran having a *syn*-relationship with the carbonyl group of the dienone, is obtained.



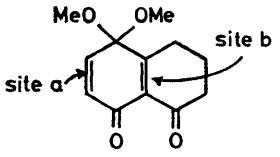


(5) a-d (6) a-l

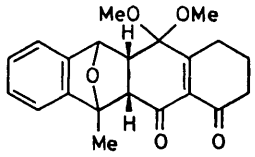
a; $R^1 = R^2 = R^3 = R^4 = H$
b; $R^1 = R^2 = R^3 = H$, $R^4 = Me$
c; $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
d; $R^1 = R^2 = R^4 = H$, $R^3 = Me$
e; $R^1 = Me$, $R^2 = R^3 = R^4 = H$
f; $R^1 = Me$, $R^2 = D$, $R^3 = R^4 = H$
g; $R^1 = R^4 = Me$, $R^2 = R^3 = H$
h; $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = OMe$
i; $R^1 = R^3 = Me$, $R^2 = R^4 = H$
j; $R^1 = SiMe_3$, $R^2 = R^3 = R^4 = H$
k; $R^1 = CH_2OH$, $R^2 = R^3 = R^4 = H$
l; $R^1 = CO_2Me$, $R^2 = R^3 = R^4 = H$

Reaction of 1-methylisobenzofuran† (**1b**) with the parent benzoquinone acetal (**5a**) at room temperature yields a single adduct, m.p. 125 °C, in essentially quantitative yield as judged by ^1H n.m.r. spectroscopic monitoring of the crude reaction mixture. The *endo*-stereochemistry assignment follows from the coupling ($^3J_{7,8}$ 5·5 Hz) observed between 7-H and 8-H. The regiospecificity was determined by selective deuteriation (Na in MeOD) of 2-H, which did not affect the $^3J_{7,8}$ coupling or the $^4J_{5,7}$ coupling,‡ a result consistent with regioisomer (**6e**), but not the alternative. Representative compounds (**6a**—**k**) were prepared by this method employing a variety of isobenzofurans (**1a**—**d**) and dienones (**5a**—**d**).§ In all cases the regioisomer was shown to be that represented by general formula (**6**).

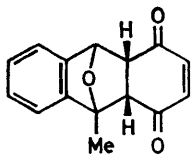
The regiocontrolled synthesis of 4-ring systems is valuable in anthracycline syntheses,[4] and the potential application of the present method is illustrated by the reaction of 1-methylisobenzofuran (**1b**) with the dienone (**7**). Total site selectivity at the external π-bond (site a) is confirmed by the lack of olefinic resonances in the ^1H n.m.r. spectrum of the sole product (**8**). The regioselectivity follows from a comparison of chemical shift data of (**8**) with those of (**6g**) and the 1-methylisobenzofuran/*p*-benzoquinone adduct (**9**).



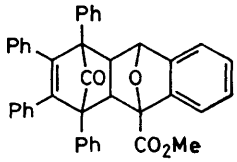
(7)



(8)



(9)



(10)

Electron-withdrawing substituents reduce the reactivity of the isobenzofuran and no reaction was observed between 1-bromo- (**1e**) or 1-methoxycarbonyl-isobenzofuran (**1f**) and the parent quinone acetal (**5a**) at room temperature. Adducts are obtained at higher temperatures using the Fieser technique to generate the isobenzofuran.[11] Thus thermal decomposition of (**10**) in diglyme at 140 °C in the presence of dienone (**5a**) yields the oily adduct (**6l**). This reaction is less clean and proceeds in lower yield (47%) than those utilising the *s*-tetrazine route to the isobenzofuran, but does proceed with the same regiospecificity.¶

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† Prepared by treatment of 1-methyl-1,4-dihydro-1,4-endo-oxynaphthalene with 3,6-di(2-pyridyl)-*s*-tetrazine in chloroform solution in the presence of the appropriate dienone, according to our published method (R. N. Warrener, *J. Am. Chem. Soc.*, 1971, **93**, 2346).

‡ The dienones show $^4J_{2,6}$ coupling but no $^4J_{3,5}$ coupling. In contrast, the adducts exhibit coupling derived from 3-H and 5-H, but not from 2-H and 6-H.

§ All new crystalline compounds gave satisfactory n.m.r., mass spectral, and microanalytical data: m.p.'s are: (**6a**), 136—138, (**6b**), 114—116, (**6c**), 180—181, (**6d**), 154—155, (**6e**), 123—125, (**6g**), 117—119, (**6h**), 147—149 and (**6i**), 78—79 °C; (**6j**), oil, (**6k**), oil, and (**6l**), oil.

¶ We thank David A. C. Evans for performing this experiment.

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[10] In some cases there is a small leakage in stereoselectivity, *i.e.* 5% of the *exo*-isomer was observed in the reaction between (**1b**) and (**5a**).
[11] L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, 1965, **43**, 1599.