Isolation of Bicyclo[3.2.1]oct-3-ene-2,8-dione Products (Formal 5 + 2 Cycloadducts) from Reactions of Styrenes with 2-Alkoxy-1,4-benzoquinones

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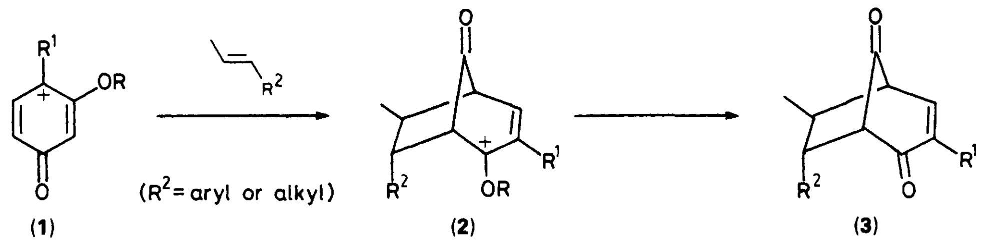
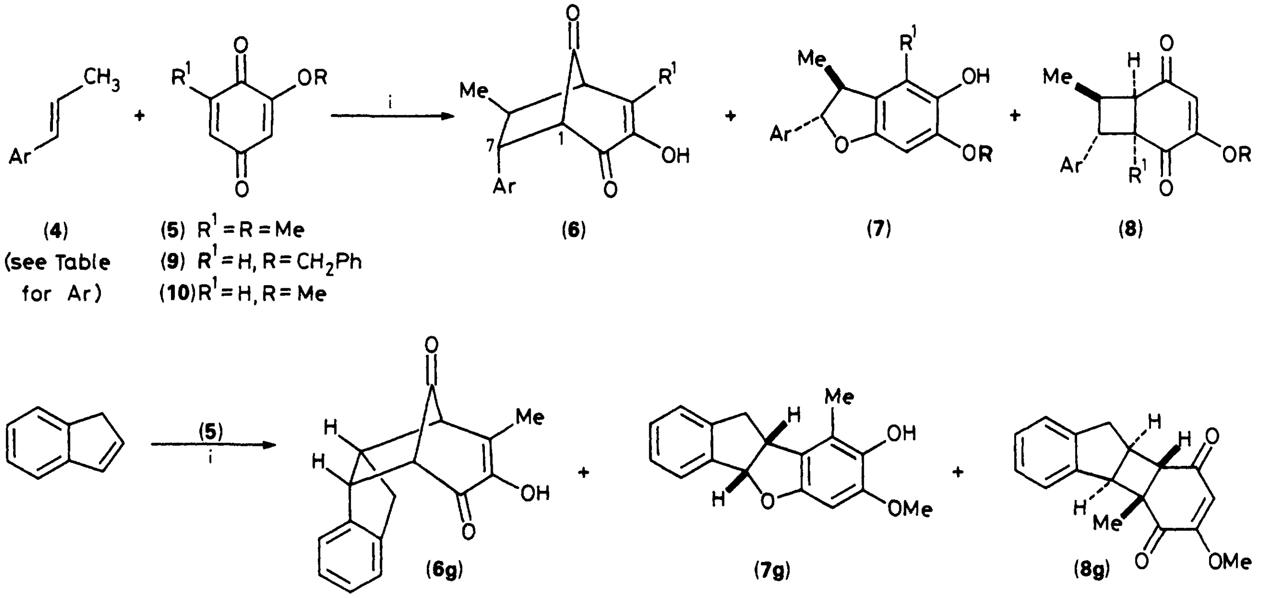
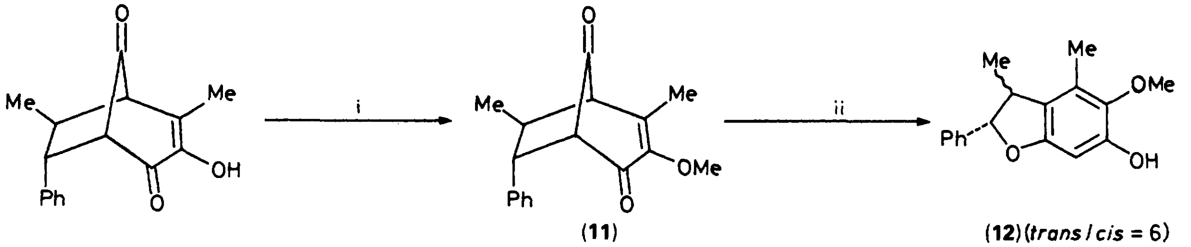
Titanium(IV) catalysed reactions of 2-alkoxy-1,4-benzoquinones and various *trans*-β-methylstyrenes stereoselectively produce 7-aryl-3-hydroxy-6-methylbicyclo[3.2.1]oct-3-ene-2,8-diones in moderate yield.

Various 3,4-dialkoxy- or 3-alkoxy-4-alkyl-cyclohexa-2,5-dien-1-one-4-yl cations (**1**), generated from acid catalysed solvolysis of *p*-quinone monoketals[1] or *p*-quinol ethers[2] or by electrochemical oxidation of 3,4-dialkoxyphenols,[3] react with alkenes to yield bicyclo[3.2.1]octenyl cations (**2**) perhaps *via* a concerted, thermally allowed 5 + 2 (4π + 2π) cycloaddition (equation 1).[4] Dealkylation of (**2**) then produces the isolable bicyclo[3.2.1]oct-3-ene-2,8-dione adducts (**3**). These reactions are intermolecular variants of the remarkable perezone to pipitzol rearrangement[5] and have been used in elegant,





Scheme 1. *Reagents and conditions*: i, $TiCl_4/Ti(OPr^i)_4$, CH_2Cl_2, −78 °C.



Scheme 2. *Reagents and conditions*: i, K_2CO_3 (2 equiv.), MeI (20 equiv.), acetone, room temp., 12 h, 81%; ii, H_2SO_4 (1 equiv.)/HOAc (10 equiv.), CH_2Cl_2, 24 h, 48% at 60% conversion.

efficient syntheses of neolignans,[1—3] sesquiterpenes,[1,3] and tropolones.[6] To our knowledge, the formation of formal 5 + 2 cycloadducts has not been routinely observed in reactions of 1,4-benzoquinones directly with alkenes under thermal or Lewis acid catalysed conditions, in spite of their prominent use in synthesis.[4,7] We now report the isolation of bicyclo[3.2.1]octenedione products from titanium(IV) catalysed reactions of styrenes with 2-alkoxy-1,4-benzoquinones,[8] which extends the generality of formal 5 + 2 cycloaddition processes of pentadienyl cations[4c] to include reactions of Ti^{IV}-1,4-benzoquinone complexes with styrenes.

Thus, addition of *trans*-β-methylstyrenes (**4a—d**) to a mixture of $TiCl_4/Ti(OPr^i)_4$ and 2-methoxy-6-methyl-1,4-benzoquinone (**5**), in dichloromethane at −78 °C produces, after aqueous bicarbonate quench, extraction and silica gel chromatography, the bicyclo[3.2.1]octenediones (**6**), dihydrobenzofurans (**7**), and bicyclo[4.2.0]octenediones (**8**) (Scheme 1 and Table 1).† In a similar manner, 2-benzyloxy-1,4-benzoquinone (**9**) and styrene (**4a**) afford (**6e**) and (**7e**), and 2-methoxy-1,4-benzoquinone (**10**) reacts with (**4b**) to give (**6f**), (**7f**), and (**8f**). Indene reacts with quinone (**5**) to give (**6g**), (**7g**), and (**8g**). Adduct (**6a**) does not give dihydrobenzofuran or bicyclo[4.2.0]octenedione products related to (**7**) or (**8**) upon exposure to protic [H_2SO_4, *p*-TsOH (Ts = $OSO_2C_6H_4Me$), CF_3CO_2H, room temp. to 80 °C] or Lewis

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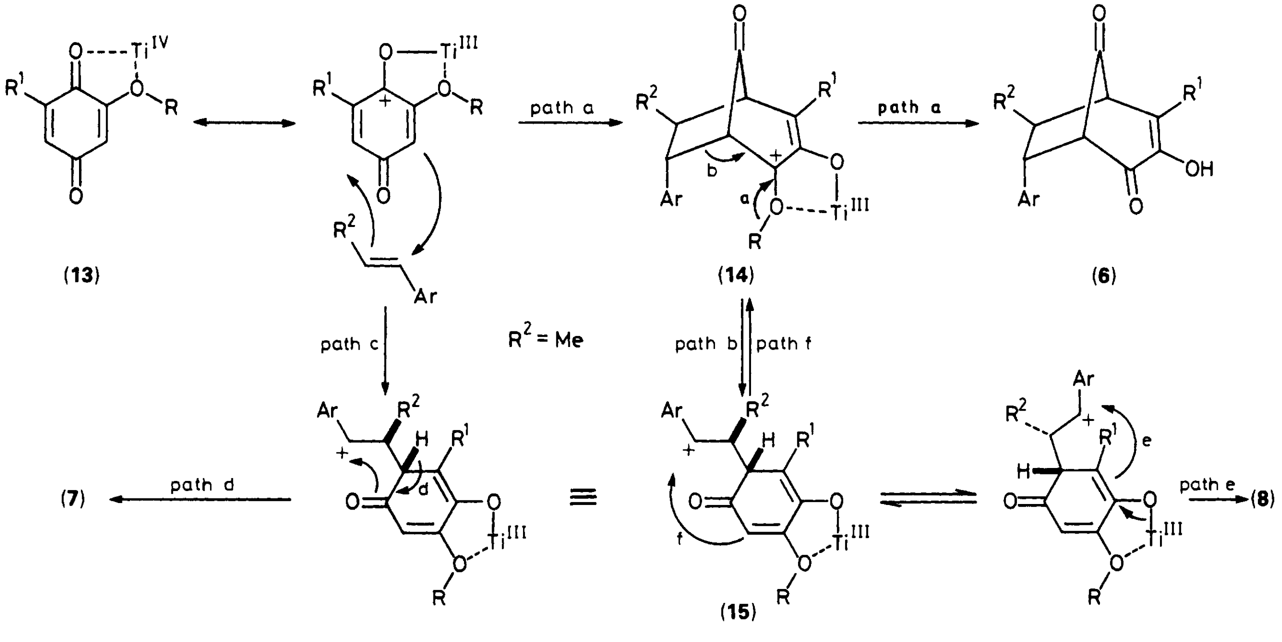
† All new compounds exhibited satisfactory spectra (^1H and ^{13}C n.m.r., i.r., mass and u.v.), elemental analysis, and/or exact mass.

Table 1. Titanium(IV) catalysed reactions of 2-alkoxy-1,4-benzoquinones with styrenes.

Styrene	Quinone	$TiCl_4 : Ti(OPr^i)_4$	Products (% yield)		
a; Ar = Ph b; Ar = 2-MePh c; Ar = 4-MePh d; Ar = 4-ClPh		[equiv. Ti^{+4}/equiv. quinone = 1.0]	(**6a**) R^1 = Me, Ar = Ph (**6b**) R^1 = Me, Ar = 2-MePh (**6c**) R^1 = Me, Ar = 4-MePh (**6d**) R^1 = Me, Ar = 4-ClPh (**6e**) R^1 = H, Ar = Ph (**6f**) R^1 = H, Ar = 2-MePh	(**7a**) or (**8a**) R^1 = R = Me, Ar = Ph (**7b**) or (**8b**) R^1 = R = Me, Ar = 2-MePh (**7c**) or (**8c**) R^1 = R = Me, Ar = 4-MePh (**7d**) or (**8d**) R^1 = R = Me, Ar = 4-ClPh (**7e**) or (**8e**) R^1 = H, R = CH_2Ph, Ar = Ph (**7f**) or (**8f**) R^1 = H, R = Me, Ar = 2-MePh	
(**4a**)	(**5**)	3:1	(**6a**) (41)	(**7a**) (10)	(**8a**) (17)
(**4b**)	(**5**)	2:1	(**6b**) (44)	(**7b**) (2)	(**8b**) (32)
(**4c**)	(**5**)	2:1	(**6c**) (21)	(**7c**) (10)	(**8c**) (37)
(**4d**)	(**5**)	3:1	(**6d**) (27)[a]	(**7d**) (2)[a]	(**8d**) (8)[a]
(**4a**)	(**9**)	3:1	(**6e**) (15)	(**7e**) (11)	—
(**4b**)	(**10**)	3:1	(**6f**) (13—22)	(**7f**) (4—10)	(**8f**) (44—60)
Indene	(**5**)	3:1	(**6g**) (32)	(**7g**) (3)	(**8g**) (22)

[a] In this experiment, 33% of quinone (**5**) was recovered; the yields reported are not based on recovered starting material.



Scheme 3

acids [$TiCl_4$, $Me_3SiOSO_2CF_3$, $Bu^t_2Si(OSO_2CF_3)_2$, $BF_3{\cdot}Et_2O$, −78 to 80 °C]. Interestingly, however, methylation of (**6a**) to (**11**) followed by treatment with H_2SO_4 does produce dihydrobenzofuran (**12**) (Scheme 2)[9] and the acid catalysed rearrangements of (**8**) to (**7**) have been previously reported.[8]

Compounds (**7c**) and (**8c**) have been previously characterized[8] and the structure of (**6a**) was established from spectral data.[2,6,9] An *endo* orientation of the aryl substituents in (**6a**—**g**) is consistent with an observed 7—8 Hz coupling constant between H-1 and H-7. The stereochemistry of the cyclobutane adducts (**8**) is assigned from ^1H–^1H nuclear Overhauser enhancement (n.O.e.) experiments[8] at 300 or 500 MHz where all of the ^1H resonances are distinct and readily assigned by decoupling experiments. Structures of the other products were established by spectral comparison to (**6a**), (**7c**), or (**8c**).

Compounds (**6a**—**g**) may result from an allowed 5 + 2 (4π + 2π) cycloaddition of the pentadienyl cation moiety of the quinone–Ti^{IV} complex (**13**) with the styrenes to give cation (**14**) (Scheme 3, path a)[9] which is then dealkylated by chloride ion in the reaction mixture or upon aqueous quench. Bicyclic cation (**14**) may also be an intermediate in the formation of the dihydrobenzofurans or the bicyclo[4.2.0]octenediones (**7**) or (**8**), respectively, *via* fragmentation to (**15**) (Scheme 3, path b).[8‡] Alternatively, (**14**) may be formed in competition with cation (**15**) (path c) which leads to (**7**) and (**8**) *via* paths d and e, respectively, or (**14**) may be formed from (**15**) *via* path f. In any event, the isolation of bicyclo[3.2.1]octenediones (**6**), reported herein, does indicate that products of formal 5 + 2 cycloaddition between *p*-benzoquinones and styrenes can occur under Ti^{IV} catalysed conditions. We are continuing to explore the mechanism, generality and synthetic utility of these reactions.

[‡] The failure of (**6a**) to give products related to (**7**) or (**8**) does not rule out (**14**) as an intermediate in the formation of (**7**) or (**8**) since the complex formed from (**6a**) and an acid is not the same as (**14**) or as the complex formed on protonolysis of (**11**).

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References

1 G. Büchi and P.-S. Chu, *Tetrahedron*, 1981, **37**, 4509.

2 S. V. Mortlock, J. K. Seckington, and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2305.

3 Y. Shizuri, Y. Okuno, H. Shigemori, and S. Yamamura, *Tetrahedron Lett.*, 1987, 6661.

4 (a) R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Academic Press, New York, 1970, p. 87; (b) H. H. McGregor, Jr., Ph.D. Thesis, Harvard University, 1971; (c) see also, W. Heilmann, R. Koschinsky, and H. Mayr, *J. Org. Chem.*, 1987, **52**, 1989; (d) P. Mamont, *Bull. Soc. Chim. Fr.*, 1970, 1557, 1564 and 1568.

5 P. Joseph-Nathan, M. E. Garibay, and R. L. Santillan, *J. Org. Chem.*, 1987, **52**, 759.

6 C.-P. Mak and G. Büchi, *J. Org. Chem.*, 1981, **46**, 1.

7 For a compilation of many examples, see G. Desimoni, G. Tacconi, A. Barco, and G. Piero Pollini, 'Natural Product Synthesis Through Pericyclic Reactions,' ACS Monograph 180, American Chemical Society, Washington, DC, 1983; G. R. Allen, in 'Organic Reactions,' ed. W. G. Dauben, Wiley, New York, 1973, vol. 20, p. 358; M. A. Brimble, J. J. Gibson, R. Baker, M. T. Brimble, A. A. Kee, and M. J. O'Mahony, *Tetrahedron Lett.*, 1987, **28**, 4891; P. Kuser, E. F. Frauenfelder, and C. H. Eugster, *Helv. Chim. Acta*, 1971, **54**, 969; C. H. Eugster and S. E. Fumagalli, *ibid.*, 1971, **54**, 959; K. Maruyama, Y. Naruta, and H. Uno, *Tetrahedron Lett.*, 1981, 5221; J. Banville, J. L. Grandmaison, G. Lang, and P. Brassard, *Can. J. Chem.*, 1974, **52**, 80; K. C. Brannock and R. D. Burpitt, U.S. Patent 3 285 937 (*Chem. Abstr.*, 1967, **66**, 37762p); E. Bernatek, *Acta Chem. Scand.*, 1953, **7**, 677; C. A. Giza and R. L. Hinman, *J. Org. Chem.*, 1964, **29**, 1453; Y. Inouye and H. Kakisawa, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 563; M. Ishibashi, T. Tsuyuki, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2357 and ref. 4.

8 T. A. Engler, K. D. Combrink, and J. E. Ray, *J. Am. Chem. Soc.*, 1988, **110**, 7931.

9 G. Büchi and P.-S. Chu, *J. Org. Chem.*, 1978, **43**, 3717.