Synthesis of Stable Bromo-substituted Masked *o*-Benzoquinones and their Application to the Synthesis of Bicyclo[2.2.2]octenones

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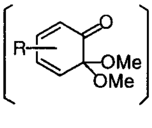
Abstract: Preparation of stable equivalents of some unstable masked *o*-benzoquinones and their use in the preparation of bicyclo[2.2.2]octenones is described.

Masked *o*-benzoquinones **1**, *i.e.*, 6,6-dialkoxy-2,4-cyclohexadienones compared to their counterparts derived from *p*-benzoquinones are relatively under utilized class of compounds.[1] Prior to our studies, there are a few sporadic reports relating to their chemistry.[2] We have been interested in both synthetic applications[3] and photochemistry[4] of masked *o*-benzoquinones. During our studies we found that some of the masked *o*-benzoquinones are unstable to react with dienophiles even when generated *in situ*, and produce Diels-Alder dimers. Andersson *et al.* made a similar observation.[2] We now report a method for generation of stable equivalents of unstable masked *o*-benzoquinones and their reactions with dienophiles to produce versatile bicyclo[2.2.2]octenones **2**.



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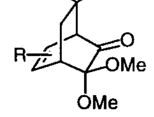
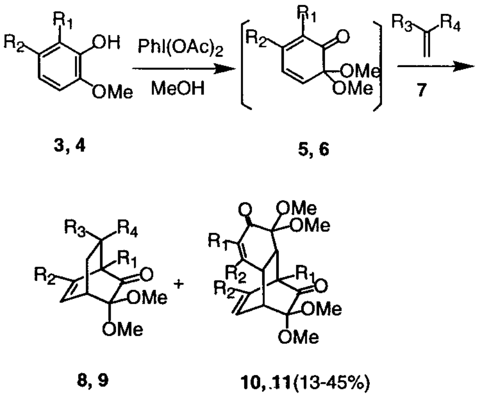


2

Bicyclo[2.2.2]octenones **2** are very useful and interesting class of compounds. They have got a special place in both synthesis and photochemistry.[5-8] They have been widely used in the synthesis of polysubstituted cyclohexane,[5] decalin[6] and di- or triquinane[7] based natural products. They are generally prepared by the Diels-Alder reaction of 2,4-cyclohexadienones and dienophiles.[9] We have previously reported a methodology based on inter- and intramolecular Diels-Alder reactions of masked *o*-benzoquinones.[3b] During subsequent studies, we found that the masked *o*-benzoquinones **5** and **6** generated from phenols **3** and **4** dimerize easily and produce the desired bicyclo[2.2.2]octenones in poor yields in most cases (method A, scheme I). Dimerization has been a serious deterrent in the chemistry of masked *o*-benzoquinones. It is our observation that if there is a substituent present in the 4-position of masked *o*-benzoquinones, the dimerization has been greatly retarded. It is obvious that one can not always have unwanted substituents in 4-position. In order to circumvent this problem, we planned to introduce an additional removable substituent. We believed that bromine which can be introduced and removed easily would serve the purpose.

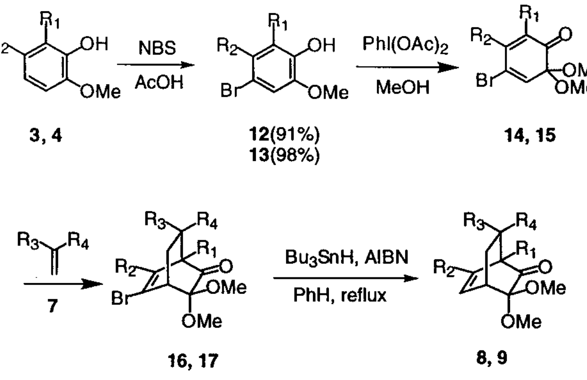
Accordingly we brominated phenol **3** with NBS in acetic acid using modified literature procedure to obtain phenol **12**.[10] Phenol **12** upon oxidation with iodobenzene diacetate (IBD) in presence of an excess of methyl methacrylate in methanol produced the bicyclo[2.2.2]octenone derivative **16a** in very good yield.[11] The compound **16a** was subjected to debromination by tributyltin hydride in refluxing benzene to yield compound **8a** (method B, scheme II).[12] The overall yield of **8a** is much higher than that obtained in one step by method A. Encouraged by these results, we immediately extended this approach to other dienophiles and phenol **4**. The results are listed in table I.



For **3**, **5**, **8** and **10**
R_1 = Me, R_2 = H
For **4**, **6**, **9** and **11**
R_1 = H, R_2 = Me

For **7**, **8** and **9**
a. R_3 = CO_2Me, R_4 = Me
b. R_3 = CO_2Me, R_4 = H
c. R_3 = C(O)Me, R_4 = H

Scheme I. Method A



For **3**, **8**, **12**, **14** and **16**
R_1 = Me, R_2 = H
For **4**, **9**, **13**, **15** and **17**
R_1 = H, R_2 = Me

For **7**, **8**, **9**,**16** and **17**
a. R_3 = CO_2Me, R_4 = Me
b. R_3 = CO_2Me, R_4 = H
c. R_3 = C(O)Me, R_4 = H

Scheme II. Method B

All the new compounds were thoroughly characterized by IR, ^{1}H & ^{13}C NMR and mass spectral analysis. The structure of compound **16a** was further confirmed by single crystal X-ray diffraction method. The stereochemical assignments of other compounds were based on analogy and H-H coupling constants. We could isolate only one product in all these intermolecular Diels-Alder reactions showing that they are highly regio- and stereoselective. They always produced *ortho* and *syn*-products that resulted from *endo* addition. These results are in good accordance with frontier molecular orbital (FMO) theory.

The bromo group performed impeccably in the reaction. It helped increase thermal stability of the masked *o*-benzoquinones **14** and **15**. It greatly retarded the dimerization, allowing us to isolate the masked *o*-benzoquinones **14** and **15** in pure form and in good yields. A feat that is not achieved before in case of masked *o*-benzoquinones with

Table I:

Diels-Alder Reaction				Debromination	Overall Yields of **8** or **9**	
Phenol	Dienophile	Time	Product (Yield/%)	Product (Yield/%)	Method A	Method B
12	**7a**	22 hr	**16a** (72)	**8a** (93)	**8a** (43)	**8a** (61)
	7b	17 hr	**16b** (75)	**8b** (96)	**8b** (86)	**8b** (66)
	7c	17 hr	**16c** (83)	**8c** (81)	**8c** (22)	**8c** (61)
13	**7a**	60 hr	**17a** (62)	**9a** (87)	**9a** (19)	**9a** (53)
	7b	36 hr	**17b** (72)	**9b** (85)	**9b** (35)	**9b** (60)
	7c	10 hr	**17c** (90)	**9c** (77)	**9c** (25)	**9c** (68)

substituents relatively small in size. All the previously isolated masked *o*- benzoquinones, have got substituents such as *n*-propyl, isopropyl and *tert*-butyl groups.[2,13]

Our findings provide a new dimension to the chemistry of masked *o*-benzoquinones. The increased thermal stability and reduced propensity of these bromo-substituted masked *o*-benzoquinones to dimerize made it possible to use stoichiometric amounts or slight excess of dienophiles in a general way. This is an important advantage of our approach, especially with regard to expensive chiral dienophiles. Admittedly, this approach requires two additional synthetic steps albeit quite simple. But it provides valuable products which are otherwise difficult to prepare in good yields. Apart from all this, our hypothesis proved to be correct and practical. In fact we have already made use of this approach in the synthesis of a *cis*-clerodane diterpenic acid. The starting material for the above total synthesis could not be prepared by our original method.[14] We are also actively pursuing the development of an asymmetric version to this reaction.

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11. *General procedure for Diels-Alder Reaction:* To a suspension of IBD (5.5 mmol) and KHCO$_3$ (7.5 mmol) in methanol (25 ml) was added a solution of phenol (5mmol) in methanol (25 ml) in one portion at 0 °C under nitrogen atmosphere. After 5 min, dienophile (7.5 mmol) was added and the reaction mixture was allowed to warm up to room temperature and stirring was continued for a period of time (Table I). Then methanol was removed on a rotavapor. The residue was dissolved in dichloromethane (50 ml) and washed with water followed by brine. Dried the organic layer over anhydrous MgSO$_4$. Removal of solvent followed by column chromatography using a mixture of appropriate ratio of ethyl acetate and hexane as eluent yielded pure products.
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