Oxidation

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Photooxygenation of Masked *o*-Benzoquinones: An Efficient Entry into Highly Functionalized Cyclopentenones from 2-Methoxyphenols**

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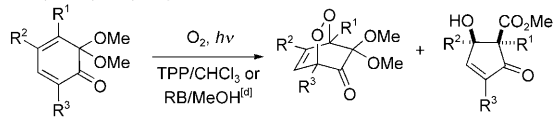
Singlet oxygen ($^1O_2$) is an essential excited molecule in both organic reactions[1,3] and biological pathways.[2] The reaction of $^1O_2$ with a 1,3-diene can take three potential pathways: [4+2] cycloaddition to form endoperoxides, the ene reaction, and [2+2] cycloaddition to obtain dioxetanes. The type of reaction is dependent on the solvent, steric, electronic factors and variations in the structure.[3] Among the few cases of photooxygenation with electron-deficient 2,4-cyclohexadienones, [4+2] cycloaddition was found to be the major pathway.[4] We have extensively investigated the [4+2] cycloaddition reactions of masked *o*-benzoquinones (MOBs) with a wide variety of dienophiles, including electron-rich dienophiles (benzyl vinyl ether, dihydrofuran, styrene, and phenyl vinyl sulphide), electron-deficient dienophiles (methyl acrylate, methyl vinyl ketone, and acrylonitrile), nitroso compounds, and *N*-phenyltriazolinedione. We have also demonstrated the great potential of MOBs in organic synthesis by developing various methodologies for the total synthesis of natural products.[5] We were interested in examining the substituent effect of the 6,6-dimethoxy groups of MOBs in photooxygenation, as a comparison with the corresponding reactions of other 2,4-cyclohexadienones. To our surprise, upon photoxygenation various MOBs produced not only endoperoxides, but also 4-hydroxy-2-cyclopentenones by ring contraction, depending on the solvents employed. We report herein the novel photooxygenation reactions of MOBs.

All the MOBs utilized in this study were prepared from oxidation of the corresponding 2-methoxyphenols with diacetoxyiodobenzene (DAIB) in methanol. Photooxygenations were performed on a solution of the appropriate MOB and a small amount of sensitizer bubbling with oxygen at −15 °C by irradiation with five 500 W halogen lamps. The photooxygenation of MOB **1a** (0.05 M) was carried out in chloroform with tetraphenylporphyrin (TPP) as the sensitizer. Endoperoxide **2a** (26%) and 4-hydroxy-2-cyclopentenone **3a** (50%) were isolated from the irradiated solution after treatment with thiourea (Table 1, entry 1). Interestingly, the reaction generated only **3a** in methanol, using Rose Bengal (RB) as the sensitizer. Initial product distributions clearly indicate the importance of solvent effects on reaction pathways.[6]

Table 1: Photooxygenation of MOBs **1a–f** to generate endoperoxides **2a–f** and 4-hydroxy-2-cyclopentenones **3a–c**.



1a-f **2a-f** **3a-c**

Entry	SM	R^1	R^2	R^3	Product in chloroform[a] (yield[c] [%])	Product in methanol[b] (yield[c] [%])
1	**1a**	H	*i*Pr	H	**2a** (26)[d] **3a** (50)[d]	**3a** (70)[d]
2	**1b**	H	*t*Bu	*t*Bu	**2b** (68)[d] **3b** (17)[d]	**3b** (78)[d]
3	**1c**	H	*i*Pr	Me	**2c** (87)	**3c** (75)[d]
4	**1d**	Me		H	**2d** (90)[e]	Recovery of SM[f]
5	**1e**	Me	H	H	**2e** (82)[e]	Recovery of SM[f]
6	**1f**	OMe	H	H	**2f** (90)[g]	**2f** (92)[f]

[a] Reaction conditions: Irradiation by 5×500 W lamps of a solution containing MOB (0.05 M) and a small amount of tetraphenylporphyrin (TPP) in chloroform with bubbling oxygen at −15 °C for entries 1–3 and at 0 °C for entries 4–6. [b] Under similar conditions with Rose Bengal (RB) as a sensitizer (in place of TPP). [c] Yield of isolated product. [d] After completion of reaction, the mixture was treated with thiourea. [e] Reaction time: 2 h. [f] Reaction time: 4 h. [g] Reaction time: 1 h.

Similar results were found in the photooxygenation of MOBs **1b** and **1c**, (R^1 = H, Table 1, entries 2 and 3). The reactions generated the corresponding 4-hydroxy-2-cyclopentenones **3b** and **3c** exclusively in methanol, whereas reactions in chloroform yielded mixtures of endoperoxides (**2b** and **2c**, respectively) and 4-hydroxy-2-cyclopentenones (**3b** and **3c**, respectively). As a comparison with **1a**, alkyl group substituents at R^3 favored the formation of endoperoxides in the reactions of **1b** and **1c** in chloroform. This result is in accord with those from the reported examples of [4+2] cycloaddition of singlet oxygen with 1,4-disubstituted naphthalenes and 4-substituted phenol derivates, where endoperoxide products substituted with electronic-donating groups (alkyl and hydroxy) at the bridgehead position of the dienes were favored.[7]

The reactions of MOBs **1d–f** (R^1 = CH_3 or OCH_3, Table 1, entries 4–6) in chloroform yielded endoperoxides **2d–f** exclusively. Interestingly, the reaction of **1f** in methanol was considerably slower than that in chloroform (4 h vs 1 h), and gave exclusive formation of the [4+2] adduct **2f**, whereas, in the cases of **1d** and **1e**, starting materials were recovered after 4 h, with traces of uncharacterized product. These results implied that non-hydrogen substituents at R^1 prohibit the rearrangement pathway for photooxygenation. MOBs **1d** and

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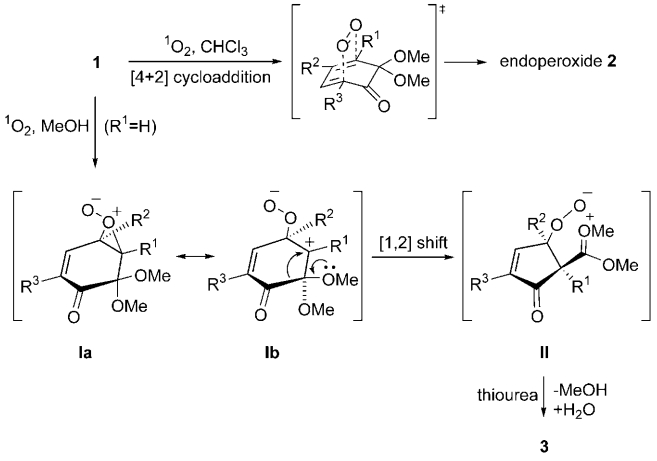
1e, which are less electron-rich than **1f**, are inert towards photooxygenation in methanol, in which the lifetime of singlet oxygen is considerably shorter than in chloroform.[8]

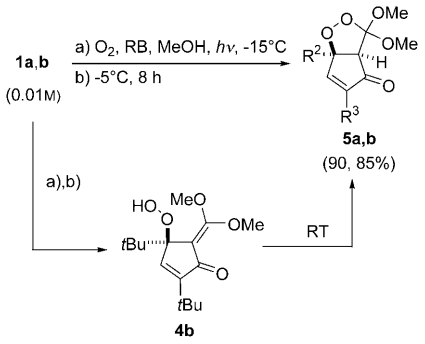
A proposed mechanism of competing reaction pathways, depicted in Scheme 1, explains the above substituent and solvent effects in the photooxygenation of MOBs. For MOBs containing an electron-donating group at R^1, [4+2] cycloaddition, to form the corresponding endoperoxide **2**, is preferred. This tendency could be explained by the nature of MOB in the [4+2] cycloaddition, where the bond next to the dimethoxy group is formed prior to that adjacent to the carbonyl group in a concerted reaction.[5a] Thus an alkyl group at R^1, would promote the formation of endoperoxide **2**. Conversely, electron-deficient MOBs with $R^1 = H$ tend to yield 4-hydroxy-2-cyclopentenones **3** as the major products of photooxygenation. This ring-contraction reaction to form a 5-membered ring is likely to be the result of a rare [1,2] acyl shift,[9] in which the initial attachment of $^1O_2$ provoked the rearrangement process from intermediate **I** (Scheme 1, with resonance structures **Ia** and **Ib**); the stabilization of the carbocation **II** by the dimethoxy group would drive a [1,2] shift. The *cis*-relationship of R^1 and R^2 in cyclopentenone **3** hinted at a back-side-attack during the migration, and the prohibition of the rearrangement by installation of R^1 substituents could be rationalized by the potential steric hindrance in forming two fully substituted carbon centers adjacent to each other in **II**. Past research has supported the tendency of $^1O_2$ to undergo [4+2] cycloaddition in nonpolar solvents. According to previous research in our group,[5a] [4+2] reactions of MOBs are considered to be concerted and, therefore, less affected by solvent polarity.[10] The high solvent preference for the formation of rearrangement product **3** in methanol (rather than $CHCl_3$) could be rationalized by the greater solvation of the proposed intermediates in polar solvents.[3e,l,11]



Scheme 1. Proposed reaction pathways for formation of endoperoxide **2** and cyclopentenone **3**.

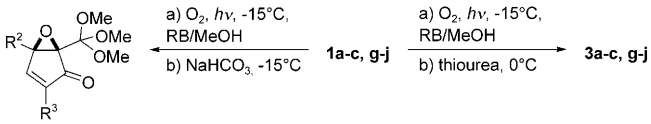
After the photooxygenated solutions of MOBs **1a** and **1b** were kept at −5 °C overnight and then warmed to room temperature, cyclic peroxyorthoesters **5a** and **b** were obtained respectively in excellent yields (90, 85 %), offering further evidence for the proposed mechanism of the rearrangement process. Hydroperoxide **4b** could also be isolated at −5 °C, and was subsequently transformed to **5b** upon warming up, presumably by 1,4-addition (Scheme 2). The structural information for cyclopentenones **4** and **5** gives indirect evidence of the existence of intermediate **II** (Scheme 1).

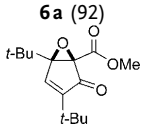
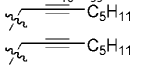
To further expand the scope of the new photooxygenation-rearrangement reaction, two work-up treatments were applied to the photooxygenated solution to furnish cyclopentenones with structural variations (Table 2). Method A, as previously described, with the addition of thiourea to the photooxygenated product in methanol, afforded 4-hydroxy-2-cyclopentenones **3a–c**, **g–j**, isolated in good yield (50–79 %). Method B, treating the photooxygenated solutions with excess sodium bicarbonate at −15 °C, led to the formation of the epoxycyclopentenones bearing orthoester groups, **6a–c**,



Scheme 2. Generation of hydroperoxide **4b** and cyclic peroxyorthoester **5a,b** from photooxygenation of **1a,b**.

Table 2: Examples of post-treatments of photooxygenation to form **3**, **6**, and **7b**.



Entry	SM[a]	R^2	R^3	Product A[b] (yield[d] [%])	Product B[c] (yield[d] [%])
1	**1a**	*i*Pr	H	**3a** (73)	**6a** (92)
2	**1b**	*t*Bu	*t*Bu	**3b** (72)	 **7b** (90)
3	**1c**	*i*Pr	Me	**3c** (70)	**6c** (95)
4	**1g**		H	**3g** (75)	**6g** (92)
5	**1h**	*n*-$C_{16}H_{33}$	H	**3h** (65)[e]	**6h** (85)
6	**1i**		H	**3i** (79)	**6i** (90)
7	**1j**		Cl	**3j** (50)	**6j** (70)

[a] Irradiation by 5×500 W lamps of a solution of MOB (0.01 M) and Rose Bengal in methanol at −15 °C with bubbling oxygen. [b] After completion of reaction, the mixture was treated with thiourea at 0 °C; [c] After completion of reaction, the mixture was treated with excess sodium bicarbonate at −15 °C. [d] Yield of isolated product. [e] **3h** is untenone A.

g–j, and **7b** (with a methyl ester group) in excellent yields (70–95%).

Untenone A (**3h**) is a natural product with inhibitory activity against inhibits the cell proliferation of L1210 leukemia and mammalian DNA polymerases.[12] Using this new photooxygenation reaction to construct 4-hydroxy-2-cyclopentenone, we have completed a short and fluent synthesis of (±)-untenone A (**3h**) from 4-hexadecyl-2-methoxyphenol. It is interesting to note that there are a number of biologically active natural products containing 4-hydroxy-2-cyclopentenone moieties, such as clavulone, chlorovulone, bromovulone, iodovulone, carijenone, fusicoauritone, and ligulolide A (Figure 1).[13]

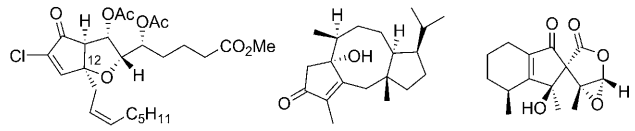


Figure 1. Selected examples of natural products containing 4-hydroxy-2-cyclopentenone moiety.

In summary, this investigation on the photooxygenation of substituted MOBs has shown intriguing results of novel reactions. The reaction allows access to a variety of functionalized cyclopentenones resulting from controlling solvent and substituent effects.

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