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Highly Efficient Photochemical Generation of *o*-Quinone Methide from Mannich Bases of Phenol Derivatives

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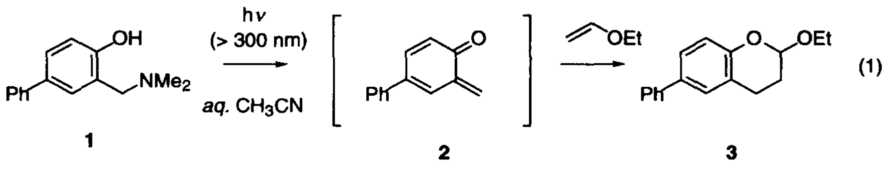
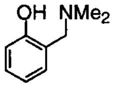
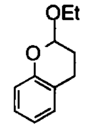
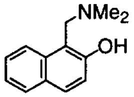
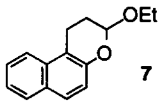
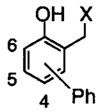
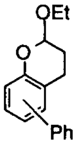
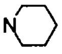
Abstract: *o*-Quinone methide was efficiently produced by photoirradiation of phenolic Mannich bases in aqueous acetonitrile with low energy UV light. The photoreaction proceeds most effectively at neutral pH in aqueous solvents. © 1997 Elsevier Science Ltd.

o-Quinone methide (*o*-QM) is an important synthetic precursor in organic synthesis, particularly as an oxabutadiene unit in inverse electron demand Diels-Alder reaction.[1] It is also known that the mode of action of potent anticancer drug mitomycin C involves an *o*-QM intermediate, which efficiently modifies DNA to result in a crosslinking of DNA.[2] Because of their synthetic utility and biological importance, various methods for generating *o*-QMs, *e.g.*, thermal and Lewis acid-catalyzed dehydration of *o*-hydroxybenzyl alcohol, and photoinduced cheletropic extrusion of carbon monoxide, carbon dioxide, and sulfur dioxide, have been reported.[1] Recently, Wan *et al.* have generated *o*-QM in aqueous solvents by photoirradiation of *o*-hydroxybenzyl alcohol at 254 nm.[3] We are particularly interested in DNA modification by highly electrophilic species generated by photoirradiation of chemically stable compounds,[4] and have focused our attention on the development of a new method for photochemical generation of *o*-QM at longer wavelength in aqueous solvents.[5] In order to devise such molecular systems that generate *o*-QM under mild photoirradiation conditions, we have examined the photoreaction of various types of phenol and naphthol derivatives having a leaving group at the benzylic position. We herein report that *o*-QM, *e.g.*, **2**, is efficiently generated by low energy UV irradiation (> 300 nm) of Mannich bases of phenol and naphthol derivatives in aqueous solvents (Eq. 1).



Photoreactions of substituted phenol and naphthol derivatives shown in Table 1 were carried out in aqueous acetonitrile by irradiation with high pressure mercury lamp through Pyrex filter in the presence of large excess of ethyl vinyl ether (EVE) as a trapping agent for *o*-QM (Eq. 1). All the phenol and naphthol derivatives having dimethylamino group as a leaving group could produce *o*-QM as evidenced by the formation of QM-EVE adducts **3**, **5**, **7**, **12**, and **13** (Table 1, entries 1-5). Among them, 4- and 6-phenyl substituted phenol derivatives **1** and **8** are the most efficient precursors (entries 5 and 3). Without photoirradiation, any detectable amount of QM-EVE adduct could not be observed. While other dialkylamino derivatives **10** and **11** also produced **3** under the photoirradiation conditions (entries 6 and 7), substitution of dimethylamino group by hydroxyl and methoxyl groups, *e.g.*, **12** and **13**, resulted in a drastic loss of the ability of generating *o*-QM (entries 8 and 9).

Table 1. Photoirradiation of Phenol and Naphthol Derivatives Having a Leaving Group at the Benzylic Position in the Presence of Ethyl Vinyl Ether.[a]

entry	substrate	product	yield[b]
1	 **4**	 **5**	38%
2	 **6**	 **7**	17%
3	 **8** : 6-Ph, X = NMe$_2$	 **12** : 6-Ph	76%
4	**9** : 5-Ph, X = NMe$_2$	**13** : 5-Ph	36%
5	**1** : 4-Ph, X = NMe$_2$	**3** : 4-Ph	71% (87%)[c]
6	**10** : 4-Ph, X = NEt$_2$	**3** : 4-Ph	64%
7	**11** : 4-Ph, X = 	**3** : 4-Ph	57%
8	**12** : 4-Ph, X = OH	**3** : 4-Ph	< 2%[c,d]
9	**13** : 4-Ph, X = OMe	**3** : 4-Ph	< 2%[c,d]

[a] A solution of substrate (1 mM) in 50% aqueous acetonitrile in the presence of ethyl vinyl ether (100 mM) was irradiated with a high pressure mercury lamp (400 W) through Pyrex filter at 0 °C for 3 h. [b] Isolated yield after silica gel chromatography unless otherwise noted. [c] Yield determined by HPLC analysis of the crude products. [d] Starting material was recovered unchanged.

The efficiency for the photochemical generation of *o*-QM from **1** is highly affected by the solvent used in the photoreaction (Table 2). The fact that *o*-QM formation is highly accelerated in aqueous solvents than in aprotic solvents suggests that the reaction may proceed via an ionic species. Increased absorbance of **1** at the region over 300 nm due to the spectra broadening and hypochromic shift in aqueous acetonitrile compared to that in pure acetonitrile may also suggest the enhanced QM formation (Figure 1).[6]

Table 2. Relative Efficiency of *o*-QM Formation in Different Solvents[a]

entry	solvent	relative efficiency[b]
1	50% *aq.* CH_3CN	1.00
2	50% *aq.* CH_3OH	0.57
3	CH_3CN	0.09
4	DMSO	0.06

[a] Photoreaction of **1** was carried out in the presence of ethyl vinyl ether by irradiation with a high pressure mercury lamp (400 W) through Pyrex filter for 10 min. [b] Relative efficiency of *o*-QM formation was determined by HPLC analysis at low conversion.

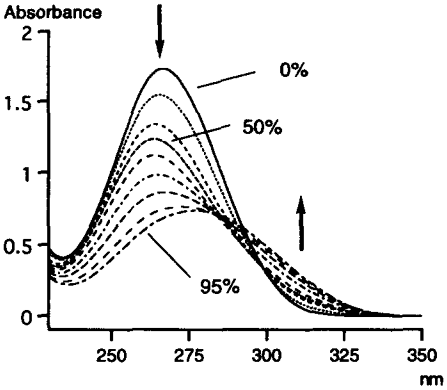
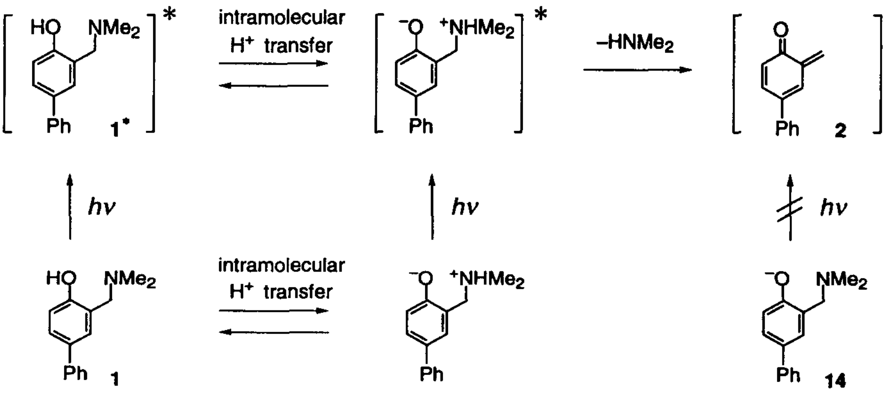


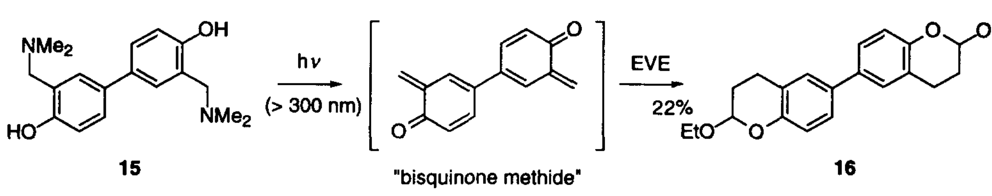
Figure 1. UV spectra of **1** (100 μM) recorded in acetonitrile containing various amount of water (0, 20, 40, 50, 60, 70, 80, 90 and 95%).

Photoreactions of **1** at various pHs showed that the formation of QM-EVE adduct **3** was most efficient at neutral pH and the efficiency decreased with increasing pH at an alkaline region. The result clearly indicates that excitation of phenolate **14** does not lead to the QM formation, and is quite different from the observation by Wan *et al.*, *i.e.*, the efficiency of QM formation from *o*-hydroxybenzyl alcohol at 254 nm increased with increasing pH.[3b] Based on these experimental observations, the most likely mechanism for the photochemical generation of *o*-QM from **1** is shown in Scheme 1.

Scheme 1



We have then examined the formation and trapping of "bisquinone methide" as a potent DNA crosslinker. Photoirradiation of Mannich base **15** in aqueous acetonitrile in the presence of EVE produced bis(QM-EVE) adduct **16**[7] in 22% yield (Eq. 2).



(2)

In summary, we have developed a new photochemical method for quinone methide generation from readily available Mannich bases of phenol derivatives. The photoreaction effectively proceeds in aqueous solvents at neutral pH by irradiation at > 300 nm. The results described here suggest that Mannich base of phenol derivatives may be used as a potentially useful DNA alkylation or crosslinking agent.[8]

References and Notes

(1) For a review, see: Boger, D. L.; Weinreb, S. N. in *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, NY, **1987**, pp. 167–213.

(2) For a review, see: Tomasz, M. in *Advances in DNA Sequence Specific Agents*; Hurley, L. H. Ed.; JAI Press; Greenwich, CT, **1992**, Vol 1, pp. 247–261.

(3) (a) Diao, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369–5370. (b) Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y. *Can. J. Chem.* **1996**, *74*, 465–475.

(4) (a) Saito, I.; Takayama, M.; Sakurai, T. *J. Am. Chem. Soc.* **1994**, *116*, 2653–2654. (b) Nakatani, K.; Shirai, J.; Tamaki, R.; Saito, I. *Tetrahedron Lett.* **1995**, *36*, 5363–5366.

(5) DNA crosslinking by photochemically and non-photochemically generated quinone methides has been reported. (a) Chatterjee, M.; Rokita, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 6397–6397. (b) Chatterjee, M.; Rokita, S. E. *J. Am. Chem. Soc.* **1994**, *116*, 1690–1697. (c) Zeng, Q.; Rokita, S. E. *J. Org. Chem.* **1996**, *61*, 9080–9081.

(6) In the case of 4-phenylphenol, neither spectra broadening nor hypochromic shift was observed by increasing water content in acetonitrile.

(7) **16**: ^{1}H NMR($CDCl_3$, 200 MHz) δ 7.3–7.2 (4H), 6.84 (d, 1H × 2, J = 8.0 Hz), 5.25 (t, 1H × 2, J = 2.8 Hz), 3.89 (dq, 1H × 2, J = 9.7, 7.1 Hz), 3.64 (dq, 1H × 2, J = 9.7, 7.1 Hz), 3.1–2.9 (2H), 2.75–2.6 (2H), 2.1–1.9 (4H), 1.19 (t, 3H × 2, J = 7.0 Hz); MS (EI) (%) *m/z* 354 (M^+) (100), 309 [$(M-OEt)^+$] (38), 282 (65); HRMS (EI) calcd for $C_{22}H_{26}O_4$ (M^+) 354.1832, found 354.1847.

(8) Cleavage of supercoiled pBR322 DNA by **1** under photoillumination at 312 nm in sodium cacodylate buffer (pH 7.0) at 0 °C was enhanced by heating (37 °C, 1 h) the photolysate, suggesting that DNA alkylation by QM may be actually involved in the photocleavage.

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