

Novel generation of an *o*-quinone methide from 2-(2'-cyclohexenyl)phenol by excited state intramolecular proton transfer and subsequent C–C fragmentation

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Formation of an *o*-quinone methide via C–C fragmentation of a zwitterion formed by intramolecular excited state proton transfer from an *o*-allylphenol derivative is reported for the first time.

o-Quinone methides (6-alkylidencyclohexa-2,4-dienones) are very useful synthetic intermediates with both electrophilic and nucleophilic properties.¹ Their biological activity is also very interesting, as they appear to be the ultimate cytotoxins responsible for the effect of some antitumor drugs, antibiotics and DNA alkylators.²

Intermediates of this type have been generated in the past by several routes, including light-induced water elimination from *o*-hydroxybenzyl alcohols or excited state intramolecular proton transfer (ESIPT) in *o*-hydroxystyrenes (Fig. 1).^{3–5}

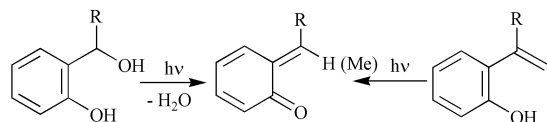


Fig. 1 Generation of *o*-quinone methides by dehydration of *o*-hydroxybenzyl alcohols or ESIPT in *o*-hydroxystyrenes.

In aqueous solution, *o*-quinone methides undergo hydronium-ion catalyzed hydration by a reaction mechanism that involves rapid equilibrium protonation of the substrate on its carbonyl oxygen followed by rate-determining nucleophilic capture of the ensuing carbocation by water. The only photoproducts are the corresponding benzyl alcohols. Trapping can also be achieved with other nucleophiles (MeOH, SCN⁻, Br⁻, etc.) and with electron rich alkenes, to give [4 + 2] cycloaddition products (Fig. 2).^{4,5}

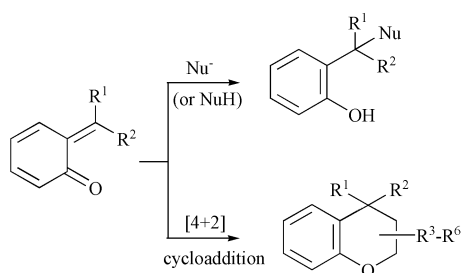


Fig. 2 Trapping of *o*-quinone methides by nucleophiles and dienophiles.

These species are relatively stable intermediates; they have been detected by means of laser flash photolysis of both *o*-hydroxybenzyl alcohols and *o*-hydroxystyrene precursors and display characteristic transient absorption at 400 nm.^{3–5} *o*-Allylphenols such as **1a** are closely related to *o*-hydroxystyrenes and are also known to undergo ESIPT upon photolysis; the resulting zwitterions photocyclise to 5- (or 6-) membered ring products.^{6–9} The β -cyclodextrin inclusion complexes undergo photohydration of the olefin as the major process.¹⁰ Thus, insertion of a methylene group between the phenol and the olefin moieties appears to prevent formation of *o*-quinone methides, which have never been generated in the photolysis of *o*-allylphenols.

We wish now to report on the use of an *o*-allylphenol analogue as the source of an *o*-quinone methide. Thus, 2-(2'-cyclohexenyl)phenol **1b**⁶ was irradiated for 6 h in several organic solvents using the quartz-filtered light of a medium pressure mercury lamp. The photomixtures were analysed by GC, GC-MS and ¹H-NMR, using adequate standards for quantitation. The major products were isolated and spectroscopically characterised. Their structures are shown in Chart 1, and their yields are summarised in Table 1.

When **1b** was photolysed in methanol (Table 1, entry 1), the major product exhibited a MS with molecular ion M⁺ at *m/z* 206,

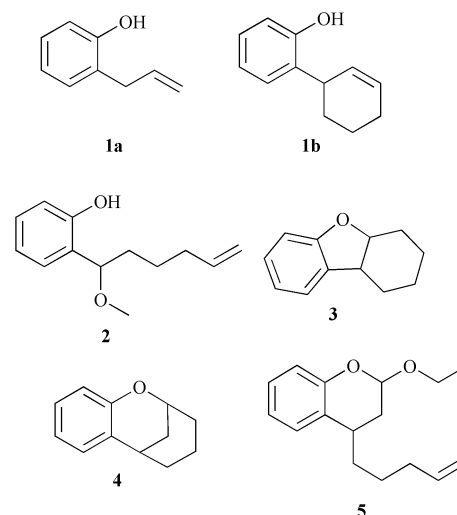


Chart 1

Table 1 Photochemistry of **1b**^a

Entry	Solvent ^a	Conversion (%)	Mass balance (%)	Product yield (%)		
				2 (or 5)	3 + 4	Others
1	A	91	68	93	2	5 ^b
2	B	54	40	67	27	6 ^b
3	C	75	45	—	91	9 ^c
4	D	38	78	—	97	3 ^b

^a A: methanol; B: ethyl vinyl ether; C: benzene; D: cyclohexane. ^b Unidentified products. ^c Includes a benzene addition product and a **1b** dimer.¹⁴

clearly indicating incorporation of the solvent. In principle, we would have expected simple addition of methanol to the double bond, as previously described in the literature for *o*-allylphenol derivatives.¹¹ However, the ¹H-NMR spectrum of the isolated photoproduct indicated that its structure was that of the open chain terminal olefin **2**.¹² Although the reaction was clean, the quantum yield (as determined by potassium ferrioxalate actinometry) was *ca.* 0.02. Traces of the cyclic ethers **3** and **4** (previously reported as the main photoproducts of **1b** in benzene)⁶ were also found. In a control experiment, a mixture of **3** and **4** was irradiated under the same conditions; the lack of formation of **2** allowed us to rule out a possible secondary photoreaction as the origin of this product.

The proposed mechanism to explain formation of **2** is shown in Fig. 3. Initial ESIPT from the phenolic subunit to the double bond would lead to the zwitterionic intermediate **I**. Subsequent C–C bond fragmentation with concomitant ring opening explains generation of the *o*-quinone methide **II**. In the presence of methanol, **II** would be trapped by the solvent giving rise to **2**.

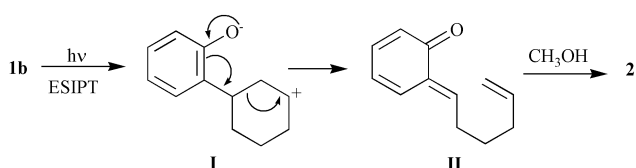


Fig. 3 Mechanism explaining formation of **2** upon photolysis of **1b** in methanol.

If the *o*-quinone methide were actually formed, it should be possible to achieve its trapping using ethyl vinyl ether as dienophile.⁵ As a matter of fact (Table 1, entry 2), the major photoproduct in neat ethyl vinyl ether as solvent was dihydrobenzopyran **5**, whose structure was established based on the spectral data of the isolated compound.¹³ The two possible isomers of **5** (*cis* and *trans*) were obtained in comparable amounts. Again, the usual photocyclisation products **3** and **4** were formed, with yields somewhat higher than in the methanol irradiation.

Direct evidence for the involvement of an *o*-quinone methide was provided by laser flash photolysis. Using 266 nm as the excitation wavelength and acetonitrile as solvent, a well defined signal with two maxima around 300 and 400 nm was recorded. The spectrum (shown in Fig. 4) is in agreement with those previously reported for similar intermediates.^{3–5}

For comparison, irradiation of **1b** was also carried out in benzene and cyclohexane. In benzene (Table 1, entry 3), a mixture of **3** and **4** was obtained, confirming previous observations by Fräter and Schmid.⁶ Besides, trace amounts of non-reported byproducts were detected by GC-MS:¹⁴ the *m/z* values of their molecular ions indicate that these byproducts

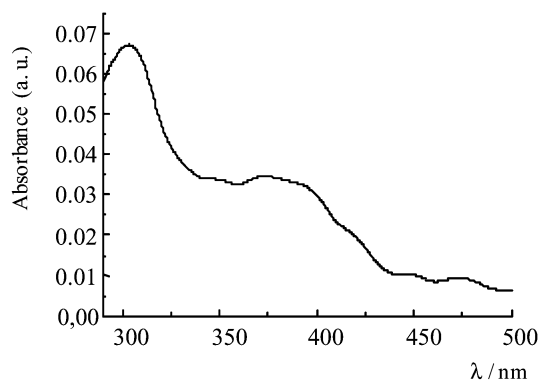


Fig. 4 Transient absorption spectrum obtained upon laser flash photolysis (266 nm) of **1b** in acetonitrile.

arise from **1b** via benzene addition and dimerization. This is compatible with the reactivity expected for the cationic character of the proposed zwitterionic intermediate **I**.

In cyclohexane (Table 1, entry 4) the only photoproducts were the cyclic ethers **3** and **4**.

In summary, a new route to 6-alkylidenecyclohexa-2,4-dienones (*o*-quinone methides) via intramolecular excited state proton transfer of *o*-allylphenols derivatives and subsequent C–C fragmentation has been observed for the first time. These intermediates have been trapped by methanol and ethyl vinyl ether and detected by laser flash photolysis. At the moment, the reason why **1b** exhibits this behaviour is not clear. It could be due to the combined effect of three factors: (a) enhanced protonation at the α -carbon, to give the secondary carbocation **I** (instead of a primary carbocation, as would have occurred with the parent allyl phenol **1a** and related compounds), (b) higher stability of **II**, due to substitution of the double bonds and (c) conformational effects associated with the cyclohexene ring. Our ongoing studies in this field are directed to gain further mechanistic insight and to elucidate the scope and limitations of this new photogeneration of *o*-quinone methides.

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- Compound **2**: ¹H-NMR (CDCl₃, TMS as internal standard) δ (ppm): 1.30–2.10 (m, 6H, CH₂CH₂CH₂), 3.37 (s, 3H, OCH₃), 4.25 (m, 1H, CHOCH₃), 4.95 (m, 2H, CH=CH₂), 5.75 (m, 1H, CH=CH₂), 6.76–6.96–7.21 (m, 4H, ArH); MS (*m/z*, %): 206 (M⁺, 10), 174 (29), 159 (14), 145 (20), 137 (100), 133 (58), 131 (25), 120 (22), 107 (21), 105 (20).
- Compound **5**: ¹H-NMR (CDCl₃, TMS as internal standard) δ (ppm): 1.22–1.27 (t, 3H, *J* = 7.1 Hz, CH₃), 1.38–2.20 (m, 6H, CH₂CH₂CH₂), 2.89 (m, 1H, CHCH₂CH₂CH₂), 3.60 + 4.00 (m + m, 2H, *trans* + *cis* OCH₂CH₃), 4.90–5.20 (m, 3H, CH=CH₂ + OCHO), 5.82 (m, 1H, CH=CH₂), 6.80–7.20 (m, 4H, ArH); MS (*m/z*, %): 246 (M⁺, 10), 201 (6), 200 (8), 177 (100), 174 (15), 149 (16), 133 (22), 131 (35), 121 (30), 120 (17), 91 (15).
- Benzene addition product: MS (*m/z*, %): 252 (M⁺, 100), 211 (40), 198 (18), 183 (32), 165 (19), 145 (21), 144 (19), 115 (19), 91 (16); 77 (20); **1b** dimer: MS (*m/z*, %): 348 (M⁺, 21), 279 (100), 173 (19), 145 (13), 133 (12), 131 (18), 115 (8), 107 (45), 91 (10).