

Photochemical Cyclization with Release of Carboxylic Acids and Phenol from Pyrrolidino-Substituted 1,4-Benzoquinones Using Visible Light

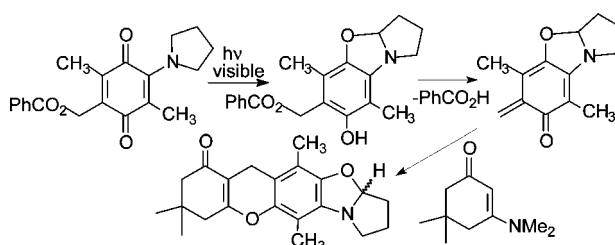
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Received June 10, 2005

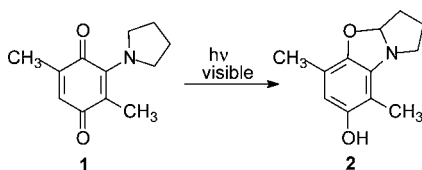
ABSTRACT



Visible light irradiation of 5-acyloxymethyl- and 5-phenoxy-methyl-2-pyrrolidino-1,4-benzoquinones effects photoisomerization to labile oxazolidines, which undergo elimination of carboxylate or phenolate leaving groups in high yields to generate trappable α -quinone methide intermediates.

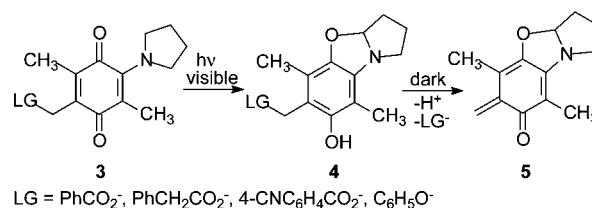
Early studies have shown that the photochemical cyclization of 2-amino-1,4-benzoquinones to oxazolidines can be effected with sunlight.¹ This photocyclization is exemplified by 2-pyrrolidino-1,4-benzoquinone **1**, which gives oxazolidine **2** as a photoproduct (Scheme 1).² In the case of the

Scheme 1



structurally related 2-pyrrolidino-1,4-benzoquinone **3** (Scheme 2), the photocyclization product **4** should be unstable with

Scheme 2



respect to “dark” elimination of a leaving group (LG), such as a carboxylate group or a phenolate group. Thus, visible light would serve to activate a photoremovable protecting group for release or unmasking of functionality in a

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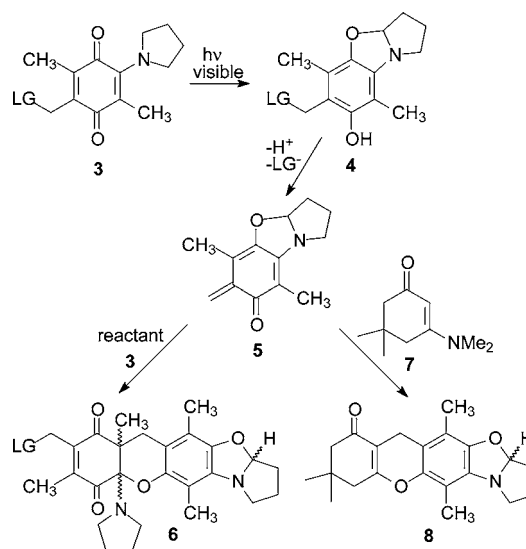
(2) (a) Oxazolidine **2** could be isolated in excellent yield after silica gel column chromatography, eluting with EtOAc in hexane. The high-field spectral data were as follows: ¹H NMR (CDCl₃) δ 1.87 (m, 2 H), 2.07 (s, 3 H), 2.14 (s, 3 H), 2.21 (m, 2 H), 2.97 (m, 1 H), 3.35 (m, 1 H), 5.15 (br s, 1 H), 5.81 (t, J = 3.3 Hz, 1 H), 6.61 (s, 1 H); ¹³C NMR (CDCl₃) δ 10.8, 15.3, 24.2, 32.8, 55.8, 102.8, 110.8, 111.1, 115.2, 140.5, 145.0, 148.3. (b) Falci, K. J.; Franck, R. W.; Smith, G. P. *J. Org. Chem.* **1977**, 42, 3317–3319.

subsequent step. The use of visible light for unmasking of functionality is of fundamental importance for the development of selective methods for photodeprotection of polyfunctional molecules,³ where selectivity in the deprotection would depend on the color of the incident light. Progress in this area has been hindered by the dearth of photocleavable protecting groups that can be removed with visible light. With few exceptions,^{4,5} the usable wavelength region for photoremoval of protecting groups typically lies below about 400 nm.

2-Amino-1,4-benzoquinones generally absorb light in the 450–650 nm wavelength region.⁶ Although the available energy in this wavelength region (44–63 kcal mol⁻¹) is insufficient to directly cleave relatively strong bonds, it is capable of effecting the photocyclization of **1**. In the case of **3**, the release of the leaving group is expected to occur after such a photocyclization, in a dark elimination step that would be expected to be pH dependent. Nevertheless, one concern is that no quantum yield has been reported for the photocyclization of a 2-amino-1,4-benzoquinone. We thus conducted a preliminary investigation with **1** and found that upon irradiation at 458 nm the photocyclization occurs in 100% chemical yield with a quantum efficiency of 0.091 in CH₂Cl₂ as the solvent.⁷

The photocyclizations with release of carboxylic acids from **3** were initially investigated with a benzoate leaving group (LG = PhCO₂⁻). Irradiation of 0.02 M solutions in 30% D₂O in CD₃CN with a 120 W sunlamp produced benzoic acid in 58% yield at 100% conversion. An additional product was isolated as a ca. 1:1 mixture of diastereomers in 36% yield by column chromatography. Its structure, which was assigned as **6** (LG = PhCO₂⁻),⁸ suggested that it was produced via cycloaddition of an *o*-quinone methide intermediate **5** with unreacted starting material (Scheme 3), which would account for the low yields of photoreleased benzoic acid. Similar results were obtained upon photolysis of **3** (LG = PhCO₂⁻) at 542 nm with light passed through a monochromator.

Scheme 3



The intermediacy of *o*-quinone methide **5** was probed by photolyzing the benzoate derivative of **3** (LG = PhCO₂⁻) with 0.1 M 3-(dimethylamino)cyclohexen-1-one **7** as a trapping reagent (Scheme 3). In addition to 92% yield of benzoic acid, a cycloadduct was obtained in 87% yield, which was identified as **8** after chromatographic isolation.⁹ With other carboxylate leaving groups (LG = PhCH₂CO₂⁻ or LG = 4-CNC₆H₄CO₂⁻), the cycloadduct **8** was obtained in 79% and 82% yields, along with 92% and 89% yields of the corresponding carboxylic acids. Evidently, the presence of the electron-releasing pyrrolidino and the dimethyl groups in **5** reduces its reactivity compared to other *o*-quinone methides,¹⁰ since attempts to trap **5** with various electron-rich alkenes (ethyl vinyl ether, vinylene carbonate, methyl trimethylsilyldimethylketene acetal) failed to produce the corresponding cycloadducts.

The intermediacy of *o*-quinone methide **5** could account for new absorption bands that were observed at 339 and 455 nm after 30 min of photolysis of 5×10^{-4} M aminoquinone **3** (LG = PhCO₂⁻) at 2 °C in 30% aq CH₃CN with a sunlamp (Figure 1) or at 542 nm. Upon warming to 20 °C, the new absorptions disappeared, and the rate of disappearance was strongly accelerated by adding 8×10^{-3} M dimethylamino-cyclohexenone **7**.^{11a} In 30% phosphate buffer in CH₃CN at

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(6) Herre, W.; Wunderer, H. *Tetrahedron* **1972**, 28, 5433–5443.

(7) (a) Quantum yield determinations were performed at 458 nm. The ferrioxalate actinometer concentration was increased to ensure that all of the long-wavelength light was absorbed, as prescribed in ref 7b. (b) Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*, 2nd ed.; Marcel Dekker: New York, 1993; pp 301, 303.

(8) The spectral data for the ca. 1:1 diastereomeric mixture of **6** (LG = PhCO₂⁻) were as follows (minor diastereomer carbons are in parentheses): ¹H NMR (CDCl₃) δ 1.40 (s, 3 H), 1.44 (s, 3 H), 1.68 (m, 8 H), 1.86 (s, 6 H), 1.85 (m, 4 H), 2.13 (s, 3 H), 2.15 (s, 3 H), 2.17 (m, 4 H), 2.19 (s, 3 H), 2.20 (s, 3 H), 2.45 (m, 2 H), 2.73 (m, 6 H), 2.88 (m, 4 H), 2.99 (m, 2 H), 3.34 (m, 2 H), 5.23 (d, J = 12 Hz, 2 H), 5.32 (d, J = 12 Hz, 2 H), 5.76 (m, 2 H), 7.41 (t, J = 7.8 Hz, 4 H), 7.54 (t, J = 7.8 Hz, 2 H), 7.95 (d, J = 7.8 Hz, 4 H); ¹³C NMR (CDCl₃) δ 10.7 (10.6), 11.6, 13.2 (13.1), 17.9 (17.8), 24.1, 25.0 (24.9), 32.61 (32.58), 36.6, 48.0 (47.9), 52.3 (52.0), 55.9 (55.8), 58.6, 94.94 (94.92), 102.6, 110.9 (110.8), 112.0 (111.8), 112.5, 128.7, 129.8, 133.5, 138.98 (138.96), 139.3, 145.0 (144.8), 145.6 (145.5), 146.9 (146.7), 166.2, 193.8 (193.4), 199.1. Anal. Calcd for C₃₃H₃₆N₂O₆: C, 71.15; H, 6.52; N, 5.03. Found: C, 70.76; H, 6.58; N, 4.99.

(9) Compound **8**, mp 194–196 °C. The spectral data were as follows: ¹H NMR (CDCl₃) δ 1.08 (s, 3 H) 1.09 (s, 3 H) 1.86 (m, 2 H) 2.05 (s, 3 H) 2.16 (s, 3 H) 2.21 (m, 2 H) 2.29 (s, 2 H) 2.39 (s, 2 H) 2.93 (m, 1 H) 3.24 (m, 2 H) 3.34 (m, 1 H) 5.79 (m, 1 H); ¹³C NMR (CDCl₃) δ 10.8, 11.7, 20.1, 24.1, 28.6, 32.4, 32.7, 41.6, 50.9, 56.0, 102.9, 107.7, 111.5, 113.9, 114.4, 138.8. Anal. Calcd for C₂₁H₂₅NO₃: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.28; H, 7.56; N, 4.20.

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(11) (a) The 550 nm band in Figure 1 is due to unreacted starting material. At low concentrations ($< 5 \times 10^{-4}$ M) of reactant **3** (LG = PhCO₂⁻) present, trapping of the *o*-quinone methide is not significant. (b) The pseudo-first-order decay kinetics observed under buffered conditions is consistent with hydration of the *o*-quinone methide. Hydration of *o*-quinone methide can be uncatalyzed and can be catalyzed by hydrogen ion and hydroxide ion.^{11c} (c) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, 123, 8089–8094.

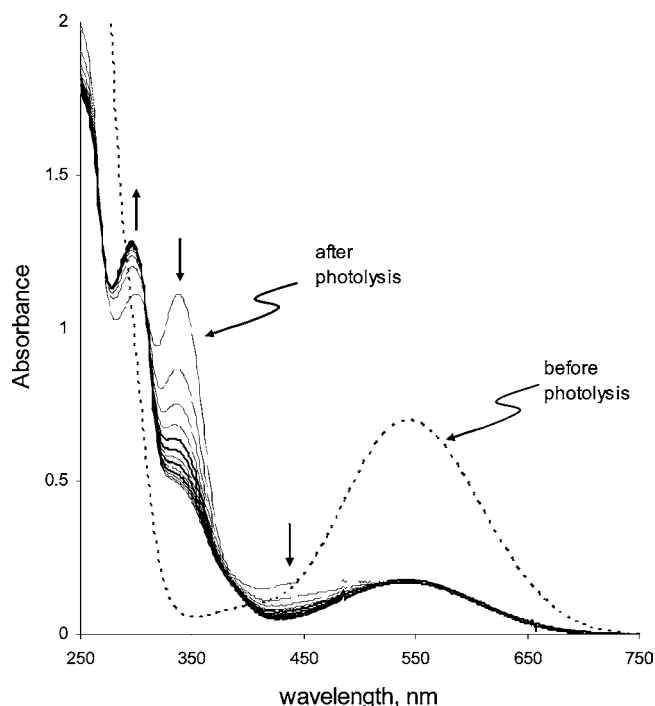


Figure 1. Absorption spectrum of **3** (LG = $\text{C}_6\text{H}_5\text{CO}_2^-$) before photolysis in 30% aq CH_3CN (---) at 2 °C and after photolysis (—) at 20 °C with a sunlamp. Bands at 339 and 455 nm are attributed to **5**. Scans after photolysis also show decay of the intermediate at 10 min time intervals and increases in product at 295 nm.

pH 6.95 the decay of **5** followed pseudo-first-order kinetics and had a half-life of 3.5 h at 20 °C.^{11b} The new absorption bands are similar to those of other long-lived *o*-quinone methide intermediates that have been reported previously.¹²

In the above photolyses with **3** (LG = PhCO_2^- , $\text{PhCH}_2\text{CO}_2^-$, $4\text{-CNC}_6\text{H}_4\text{CO}_2^-$), the corresponding photocyclization products **4** were never observed. However, with a less labile phenolate leaving group, product **4** (LG = $\text{C}_6\text{H}_5\text{O}^-$) was readily obtained in quantitative yields upon irradiation of 0.014 M aminoquinone **3** (LG = $\text{C}_6\text{H}_5\text{O}^-$) in CD_2Cl_2 , neat CD_3CN , or 30% phosphate buffer in CD_3CN at pD 5.6 at 25 °C. Compound **4** (LG = $\text{C}_6\text{H}_5\text{O}^-$) eliminated phenol at neutral or basic pH, and the elimination could also be effected under nonaqueous conditions by adding Et_3N to solutions of **4** (LG = $\text{C}_6\text{H}_5\text{O}^-$) in CD_2Cl_2 or CD_3CN . In 30% phosphate buffer in CD_3CN (pD 7) at 17 °C, the elimination displayed first-order kinetics with a half-life of 9.1 h. Under identical buffered conditions photolysis of **3** (LG = $\text{C}_6\text{H}_5\text{O}^-$) produced **4** (LG = $\text{C}_6\text{H}_5\text{O}^-$) in 73% yield along with 2.7% of **6** (LG = $\text{C}_6\text{H}_5\text{O}^-$) and 8% phenol at 86% conversion (Figure 2), and the phenol produced by this photolysis could be accounted for by “dark” elimination from **4** (LG = $\text{C}_6\text{H}_5\text{O}^-$). While monitoring the elimination of phenol from **4** by ^1H NMR spectroscopy, broad peaks were observed to

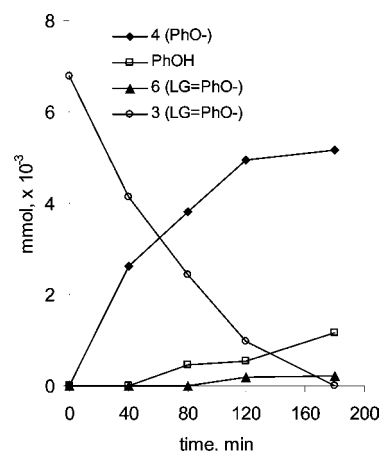


Figure 2. Change in mmole versus photolysis time of **3** (LG = $\text{C}_6\text{H}_5\text{O}^-$).

appear in the spectrum, suggestive of formation of a high molecular weight material which could not be readily identified.

Quantum yields for disappearance of 10^{-3} M **3** (LG = $\text{C}_6\text{H}_5\text{O}^-$) at 458 nm were 0.10 in CH_2Cl_2 but were lower in the more polar solvent, CH_3CN ($\Phi = 0.04$). Under aqueous conditions (30% H_2O in CH_3CN), quantum yields for disappearance of aminoquinones **3** (LG = PhCO_2^- , $\text{PhCH}_2\text{CO}_2^-$, and $4\text{-CNC}_6\text{H}_4\text{CO}_2^-$) were only ca. 0.005–0.006. These latter values were determined in the presence of 0.1 M dimethylaminocyclohexenone trapping agent **7** to prevent trapping of **5** by unreacted **3**. For the phenolate derivative, the quantum yields correspond to photocyclization to **4** (LG = $\text{C}_6\text{H}_5\text{O}^-$). For the carboxylate derivatives of **3**, the quantum yields likely correspond to the efficiencies for the photocyclization step in the photochemical mechanism, which is thought to occur prior to the expulsion of the carboxylate leaving groups.

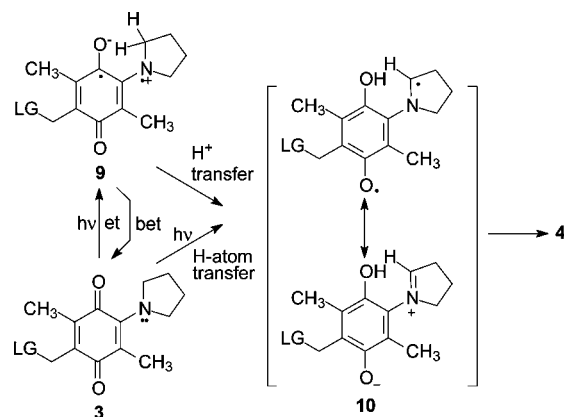
Although the initial photochemical step in the photocyclization of **3** could involve an excited-state hydrogen atom transfer from the pyrrolidino group to the 1,4-benzoquinone (Scheme 4), the decreased efficiencies for photocyclization and leaving group release in going to polar solvents suggests the existence of a photoinduced electron-transfer step (labeled as et in Scheme 4) that would be subject to back-electron transfer (bet) to regenerate the ground state of the reactant. Electron transfer¹³ from the pyrrolidino group to the 1,4-benzoquinone moiety in the lowest triplet excited state¹⁴ would generate an intramolecular charge-transfer excited state, e.g., **9**, which could undergo proton transfer followed by cyclization of intermediate **10** to give **4**. The bet would be competing with proton transfer in **9** and is expected to be promoted by stabilization of this intramolecular charge-transfer excited state in polar solvent.

(13) An analogous electron transfer occurs from triethylamine to the benzophenone triplet excited state: Peters, K. S.; Shaefer, C. G. *J. Am. Chem. Soc.* **1980**, *102*, 7566–7567.

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Scheme 4

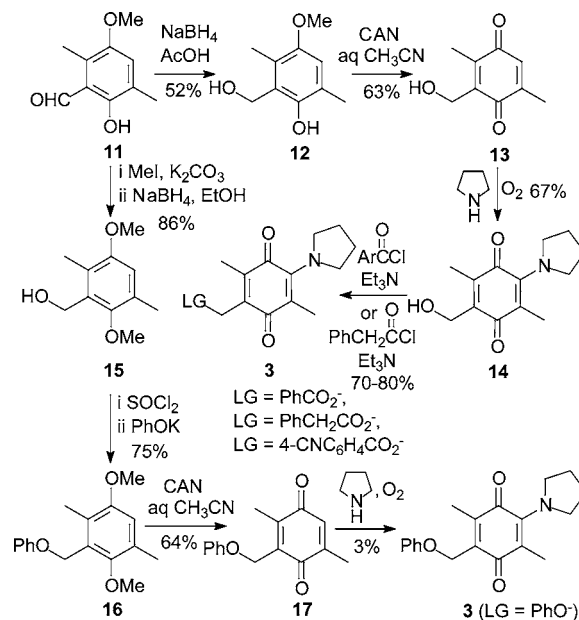


The photochemical mechanism (Scheme 4) offers the possibility that the leaving group could be dispelled from zwitterionic intermediate **10** prior to the formation of **4**. This alternate, zwitterionic elimination mechanism is similar to that proposed by our studies of α -keto amides.¹⁵ Although we are unable to rule it out in the case of carboxylate leaving groups, it is clearly not a significant pathway when the leaving group is phenolate (LG = $\text{C}_6\text{H}_5\text{O}^-$).

2-Pyrrolidino-1,4-benzoquinone **3** (LG = PhCO_2^- , $\text{PhCH}_2\text{CO}_2^-$, $4\text{-CNC}_6\text{H}_4\text{CO}_2^-$) was obtained from acylation of quinone **14** with the corresponding acid chlorides (Scheme 5). The addition of pyrrolidine to **13** likely involves air oxidation of a hydroquinone intermediate to furnish **14**. For **3** (LG = PhO^-), low yields were encountered in the analogous reaction of **17**, probably due to competing elimination of phenolate.

In summary, 2-amino-1,4-benzoquinones **3** undergo photocyclization with visible light, which activates the system toward elimination of a suitably placed carboxylate or phenolate leaving group. With phenolate as the leaving group, the cyclized photoproduct is isolable but undergoes pH-dependent elimination of phenol in the dark, whereas

Scheme 5



more labile carboxylate leaving groups undergo elimination such that the unstable photoproduct is not observed. The leaving group eliminations afford an *o*-quinone methide intermediate, which is observable by absorption spectroscopy. The intermediate is readily trapped by β -aminoalkenones or unreacted starting material to give cycloadducts. Photocyclization is efficient in intermediate polarity solvents but becomes less efficient with increasing polarity of the solvent.

Acknowledgment. We thank Mr. Adam Nothnagel for technical assistance in the synthesis of **3** (LG = PhO^-). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supporting Information Available: Procedures for the synthesis of **3** (LG = PhCO_2^- , $\text{PhCH}_2\text{CO}_2^-$, $4\text{-CNC}_6\text{H}_4\text{CO}_2^-$, PhO^-). ^1H and ^{13}C NMR spectra of **2**, **3** (LG = PhO^-), **4** (LG = PhO^-), **6** (LG = PhCO_2^-), and **8**. ^1H NMR spectra of intermediates in the synthesis of **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL051362K

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