Tetrahedron Letters, Vol. 34, No. 22, pp. 3505-3508, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Regioselective Photocycloadditions of Benzoquinones to Alkylidenecyclohexanes: A New Synthetic Resource

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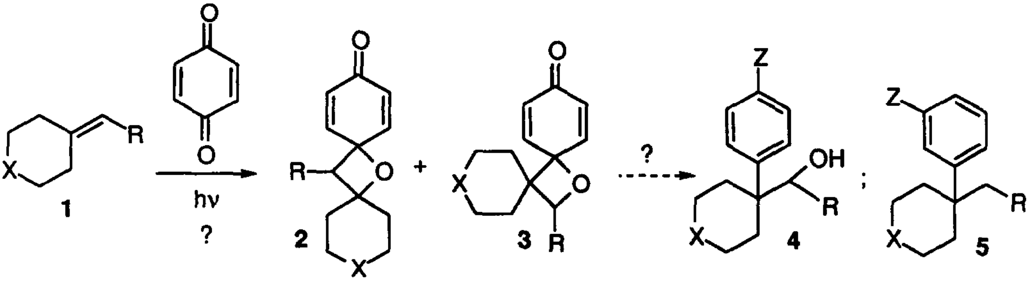
ABSTRACT: *Benzoquinones add regioselectively to alkylidenecyclohexanes. The photoadducts are converted into useful building blocks in good yield.*

This Letter describes new methodology for the expeditious assembly of subtargets **4** and **5**.[3] Structures of this type are found in compounds as diverse as amaryllidaceous alkaloids,[4] opioids,[5] prianos-latrunculia alkaloids,[6] etc. The construction of molecules such as **4** - **5** may be anticipated to pose unusual difficulties because of the quaternary nature of one of the carbon atoms.[7] With respect to **4**, we became particularly interested in achieving the regioselective 1,2-hydroxyarylation of olefins such as **1** (Scheme 1). Conceivably, this transformation might involve reductive cleavage of Paternò-Büchi oxetanes[8] obtained by photocycloadditions of benzoquinones to olefins,[9] e.g. **3**. The latter reactions often proceed in very good yield, especially if an argon ion laser is used as the light source,[10] but synthetic applications have been thwarted by the complete lack of regioselectivity observed with unsymmetrical olefins. Based on precedent, one would anticipate formation of products **2** and **3** in essentially a 1:1 ratio.[11] We confirmed the lack of regioselectivity in photocycloadditions with *acyclic* olefins, but we observed that *substantial margins of regioselectivity may be realized when the olefinic reactant is an alkylidenecyclohexane.*

Scheme 1



Irradiation of a cold benzene solution of freshly sublimed *p*-benzoquinones and 1.3 equivalents of an olefin with an argon ion laser running in the multimode configuration[12] invariably delivered the expected adducts in an 8-10 : 1 ratio in favor of product type **3**.[13] The mixture of cycloadducts was isolated in 60 -90 % yield by a simple filtration chromatography.[14] Key features of the new chemistry are evident from the summary of representative experiments that appears in Tables 1 - 2. A six-membered ring is necessary for regioselectivity, as shown by the modest 2:1 preference for structural type **3** in the reaction of benzoquinone with dimethallyl acetate (entry **a**). The olefinic component may incorporate acetal, ester, or amide groups.[15] An allylic acetate, present in several of the olefins for practical reasons, is not a *sine qua non* for selectivity (cf. entry **g**). The ring may be heterocyclic. Branching is tolerated both within the olefin (entries **e** and **f**)[16] and within the quinones. It is noteworthy that cycloadditions of monomethyl benzoquinone proceeded with 9:1 positional selectivity for the less sterically hindered carbonyl, while 2,6 benzoquinone reacted regiospecifically. Duroquinone failed to react. Regioselectivities were determined by integration of the resonance of the oxetane methine proton in ^{1}H NMR spectra of crude reaction mixtures. In **2**, this resonance is observed at ca. 3.00 ppm; in **3**, at about 4.70 ppm.

Table 1: Reaction of Alkylidenecyclohexanes with Benzoquinone

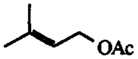
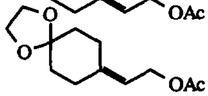
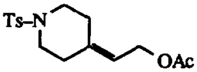
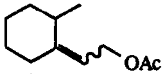
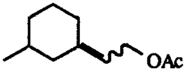
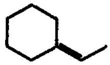
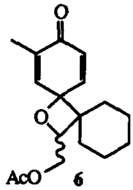
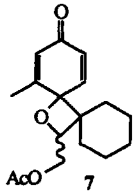
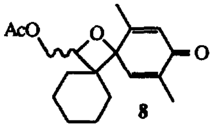
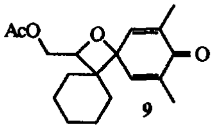
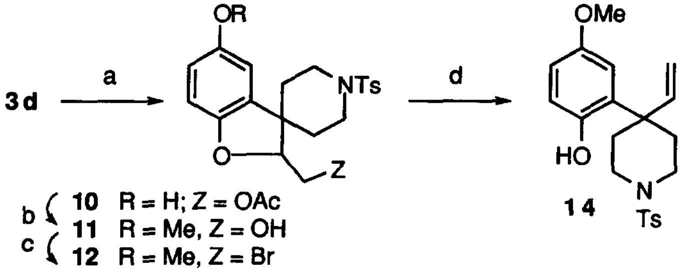
Entry	Olefin	Ratio 3:2^a
a		2 : 1 (79)
b		9 : 1 (90)
c		8 : 1 (60^b)
d		9: 1 (73^c)
e		7 : 1 (87)
f		10 : 1 (88)
g		7 : 1 (86)

Table 2: Reaction of Substituted Benzoquinones with Olefin **2b**

Quinone	Products	Ratio 3:2^a
2-Me	 **6**  **7** 9 : 1	9 : 1 (93)
2,5-Di-Me	 **8**	10 : 1 (76)
2,6-Di-Me	 **9**	9: 1 (77)

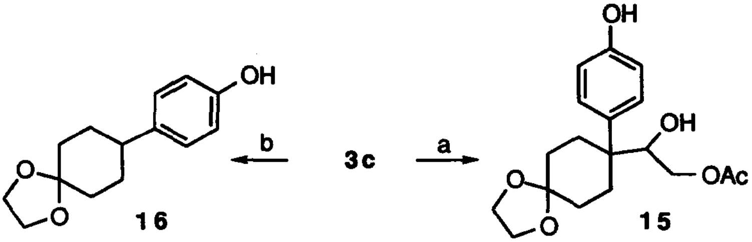
a. The number in parentheses is the yield of the mixture of regioisomers after filtration chromatography (see text); b. chromatographed yield after a single cycle: with this olefin the reaction darkens, so it is convenient to work up and resubmit recovered olefin to the photolysis. After two cycles, overall yields of 75 - 80 % are realized; c. chromatographed yield of adduct type 3: in this case the two regioisomers of the product were readily separable.

The conversion of adducts **3** to subgoals of the type **5** is easily realized as shown for **3d**. Exposure of this substance, m.p. 162-166 (dec.), to catalytic BF_3OEt_2 induced clean dienone-phenol rearrangement[8] to provide morphinoid benzofuran **10** (98 %, m.p. 74-76° C), which was advanced to opioid[5] building block **14** (cf. **5**), m.p. 162 - 164 °C, by reductive cleavage of the furan ring.



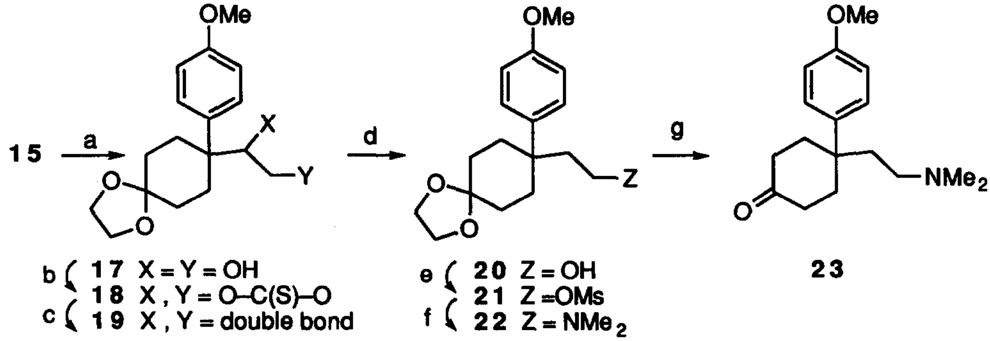
a.1% BF_3OEt_2 CH_2Cl_2, 0°C, 98 %; b. Me_2SO_4, K_2CO_3, Me_2CO, workup NH_3 (-Ac), 95 %; c. MsCl, Et_3N, LiBr, THF, 50°C, 97 %; d. Zn, NH_4Cl, EtOH, reflux, 85 %.

The preparation of **4** from **3** by hydrogenolysis[8] suffered from competing reduction of the dienone, but reductive cleavage with metallic zinc in refluxing pyridine[8] is quite effective. A regioselective 1,2-hydroxyarylation of an olefin was thus achieved upon conversion of **3c** to **15**. It is noteworthy that vigorous reductive conditions, such as sodium in liquid ammonia, induced a novel fragmentation that led to a 4-substituted phenol, as shown for the conversion of **3c** to **16**, m.p. 148-150 °C. This unusual reaction might be useful as an alternative to Friedel-Crafts methods for the introduction of acid-sensitive substituents (cf. the acetal in **16**) into aromatic rings.



a. Zn, pyridine, reflux, 70 %; b. Na, liq. NH$_3$, 98 %.

As an application of this chemistry, we describe a synthesis of O-methyldihydrojoubertiamine, **23**,[17] a simple *Sceletium* alkaloid that has been a popular target to test new methodologies. As seen below, a Corey-Winter olefination[18] of **17** was carried out as a prelude to the introduction of the dimethylamino functionality.



a. Me$_2$SO$_4$, K$_2$CO$_3$, Me$_2$CO, workup NH$_3$ (-Ac), 76 %; b. CSCl$_2$, Et$_3$N, CH$_2$Cl$_2$, 77 %; c. (MeO)$_3$P, reflux, 60 %; d. BH$_3$·SMe$_2$, then H$_2$O$_2$, 93 %; e. MsCl, Et$_3$N, CH$_2$Cl$_2$, 98 %; f. Aq. Me$_2$NH, 95 %; g. Aq. HCl, 85 %.

In summary, the new photochemical protocol offers a particularly attractive route to systems such as **4**-**5**, because of its conciseness, its ease of execution, and because of the elements of novelty associated with it. While batches of 15 - 20 grams of photoadduct may be generated without difficulty by the use of the laser (10-12 hrs. irradiation time), light from common fluorescent tubes, which emit significantly in the blue region of the spectrum, appears to be equally effective and particularly advantageous for large-scale work. Reaction times tend to be longer, but no adverse effect is observed on yields and selectivity. This should render the new chemistry widely accessible. We also note that not all alkylidene cycloalkanes behave like **1**. Alkylidene cyclopentanes, cyclobutanes, and cyclopropanes react with quinones with regioselectivity opposite that observed for the cyclohexanes. Regioselectivity is significantly eroded with alkylidene cycloheptanes, and vanishes altogether with cyclooctane substrates, which therefore resemble acyclic olefins. These observations provide important clues to the mechanism of the reaction, which is still controversial despite extensive investigations. A detailed discussion of these phenomena and of their mechanistic implications will be presented in a forthcoming paper.[19]

Acknowledgement: Financial support from the NSF (CHE 91-16820), the NIH (CA-55268), and the R. A.

Welch Foundation (C-1007) is gratefully acknowledged. Warmest thanks go to Professor Philip R. Brooks and Dr. Michael D. Barnes, of this Department, for making available their laser facilities and for technical assistance.

REFERENCES AND FOOTNOTES

1. Fellow of the A. & H. Fujimoto Foundation (Tokyo), 1990-1992.
2. Robert A. Welch Predoctoral Fellow, 1987-1988
3. These materials are available by various multistep sequences, e.g.: (a) Solé, D.; Bonjoch, J. *Tetrahedron Lett.* **1991**, *32*, 5183; (b) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. See also refs. 4 and 17.
4. Reviews: Martin, S. F., in: *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1987; Vol. 30, Ch. 3, p. 252; Jeffs, P. W., in: *The Alkaloids*; Manske, R. H. F.; Rodrigo, R. G. A., Eds.; Academic Press: New York, NY, 1981; Vol. 19, Ch. 1, p. 1.
5. Lenz, G. R.; Evans, S. M.; Walters, D. E.; Hopfinger, A. J. *Opiates*; Academic Press: Orlando, FL, 1986.
6. E.g.: (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4126; (b) Cheng, J. F.; Ohizumi, Y.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. I. *J. Org. Chem.* **1988**, *53*, 4621.
7. Martin, S. F. *Tetrahedron* **1980**, *36*, 419.
8. Bryce-Smith, D.; Gilbert, A.; Johnson, M. G. *J. Chem. Soc. (C)* **1967**, 383.
9. For an excellent review see: Jones, G., II, in: *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, NY, 1981; Vol. 5, Ch. 1, p. 1, and references cited therein.
10. Wilson, R. M.; Wunderly, S. W.; Walsh, T. F.; Musser, A. K.; Outcalt, R.; Geiser, F.; Gee, S. K.; Brabender, W.; Yerino, L., Jr.; Conrad, T. T.; Tharp, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 4429.
11. Bunce, N. J.; Hadley, M. *Can. J. Chem.* **1975**, *53*, 3240, and references cited therin. We found that even electronically biased susbtrates such as 2-acetoxypropene gave a 1:1 ratio of adducts.
12. Emission at 514.5, 501.7, 496.5, 488.0, 476.5, and 457.9 nm. Equally good results are obtained in the tunable mode: λ = 457.9 nm (ca. 1 W) or λ = 476.5 nm (ca. 2 W).
13. Laser photolyses are best conducted in an Erlenmeyer flask. The neck of the flask is sealed with a septum that has been cored and fitted with a diverging lens (glass, –2.5 cm focal length), through which the beam enters the apparatus. Flaring of the beam produces a larger irradiation volume within the solution. The system is purged with argon before the reaction, and the setup is kept in an ice bath during irradiation. The power of the laser is attenuated to 6W to prevent overheating and consequent erosion of yield. The cyclic olefins were prepared from corresponding ketones by a. (MeO)$_2$P(O)CH$_2$COOEt, NaH, DME; b. LAH, ether; c. Ac$_2$O, pyridine (60-80% overall yield). Ethylidenecyclohexane was purchased from Aldrich.
14. The photoproducts are considerably more polar than the starting materials. The crude reaction mixture is applied to a silica gel column, starting materials are washed off with 20:80 EtOAc/hexanes, and the adduct is flushed out with 60:40 EtOAc / hexanes.
15. Free alcohols or ketones are not well tolerated. Olefins containing such groups appeared to suffer from H atom transfer to the excited quinone (ppt. of hydroquinone), and formed complex mixtures of products.
16. Substituted alkylidenecyclohexanes react with facial selectivity. This observation has implications in the mechanism of the reaction and will be discussed in detail in a forthcoming full paper.
17. a. Arndt, R. R.; Kruger, P. E. J.*Tetrahedron Letters*, **1970**, 3237; b. Nieuwenhuis, J. J.; Stelow, F.; Strauss, H. F.; Wiechers, A. *J. Chem. Soc., Perkin Trans.1*,**1981**, 284.; c. Stevens, R. V.; Lai, J. T. *J. Org. Chem.*, **1972**, *37*, 2138. See also refs. 4 and 7.
18. Cf. Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979.
19. Spectral data of selected compounds: **3c**: ^{1}H: 7.34 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.9 Hz), 7.18 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.9 Hz), 6.22 (dd, 1H, J_1 = 10.2 Hz, J_2 = 1.9 Hz), 6.20 (dd, 1H, J_1 = 10.2 Hz, J_2 = 1.9 Hz), 4.70 (t, 1H, J = 6.0 Hz), 4.36 (d, 2H, J = 6.0 Hz), 3.88 (s, 4H), 2.11 (s, 3H), 1.98 (m, 4H), 1.57 (m, 4H). ^{13}C: 183.6, 169.8, 147.1, 146.7, 128.8, 128.3, 106.5, 82.6, 80.2, 63.6, 63.4, 50.1, 31.0, 30.6, 25.2, 20.1. IR: 1742. MS: 334 (M$^+$), 274, 246, 233, 232, 225, 203, 188, 166 (100%), 99, 86. HRMS: calc. 334.1416 obs. 334.1419. **15**: ^{1}H: 7.22 (d, 2H, J = 8.7 Hz), 6.79 (d, J = 8.7 Hz), 5.65 (br.s, 1H, OH), 4.10 (m, 1H), 4.00-3.88 (m, 4H), 3.72-3.62 (m, 2H), 2.50-1.50 (cm, 8H), 2.01 (s, 3H). ^{13}C: 171.5, 154.4, 130.7, 129.1, 115.4, 108.9, 77.2, 66.3, 64.2 (2 overl. signals), 44.0, 30.9, 30.8, 29.5, 29.1, 20.9. IR: 3402, 1736, 1605. MS: 336 (M$^+$), 334, 233, 199, 171, 99, 43 (100%). HRMS: calc. 336.1573 obs. 336.1569. **23** ^{1}H: 7.28 (d, 2H, J = 8.9 Hz), 6.90 (d, 2H, J = 8.9 Hz), 3.80 (br.s, 3H), 2.12 (br.s, 6H), 2.5-1.7 (cm, 12H). ^{13}C: 211.5, 157.8, 134.6, 127.5, 114.0, 55.2, 54.8, 45.3, 41.3, 39.5, 38.0, 35.9. IR: 2765, 1716. MS: 275 (M$^+$), 260, 203, 187, 135, 121, 58 (100%). HRMS: calc. 275.1885, obs. 275.1881.

(Received in USA 9 March 1993; accepted 26 March 1993)