Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Mixed Quinone Monoketals via Iodobenzene Diacetate Oxidation

Amy E. Fleck [a] , Julie A. Hobart [a] & Gary W. Morrow [a]

[a] Department of Chemistry, The University of Dayton, 300 College Park, Dayton, Ohio, 45469-2357
Version of record first published: 23 Sep 2006.

To cite this article: Amy E. Fleck , Julie A. Hobart & Gary W. Morrow (1992): Mixed Quinone Monoketals via Iodobenzene Diacetate Oxidation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:1, 179-187

To link to this article: http://dx.doi.org/10.1080/00397919208021090

SYNTHETIC COMMUNICATIONS, 22(1), 179-187 (1992)

MIXED QUINONE MONOKETALS VIA IODOBENZENE DIACETATE OXIDATION

Amy E. Fleck, Julie A. Hobart, and Gary W. Morrow*
Department of Chemistry, The University of Dayton
300 College Park, Dayton, Ohio 45469-2357

Abstract: *Oxidation of p-methoxyphenol, 4-methoxynaphthol and 4-acetamidophenol with iodobenzenediacetate in various alcohols as solvent afforded the corresponding mixed quinone or naphthoquinone monoketals in good yield. Oxidation of p-methoxyphenol in the presence of sorbyl alcohol led to in situ intramolecular Diels-Alder reactions proceeding by way of the corresponding mixed quinone monoketal.*

As part of an investigation of steric effects in the conjugate reduction of quinone monoketals and related compounds,[1] we were interested in preparing mixed quinone monoketals **I** (-OR ≠ -OR') and the corresponding naphthoquinone derivatives **II** (**FIGURE 1**). There are few examples of the synthesis of these unusual quinone derivatives in the literature, although the simple symmetrical quinone monoketals, such as 4,4-dimethoxy-2,5-cyclohexadienone, are available by a variety of chemical or electrochemical methods.[2]

Tamura and co-workers[3] reported the oxidation of 3,4,5-trimethoxyphenol in a mixture of acetonitrile and methanol, ethanol or isopropanol to afford the corresponding mixed quinone monoketal derivatives in excellent yield, but the cost of the oxidizing agent, iodobenzene bis(trifluoroacetate), was unattractive. Pelter and Elgendy[4] demonstrated the utility of the less

*To Whom Correspondence Should Be Addressed.

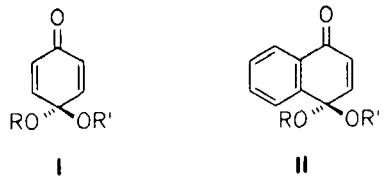
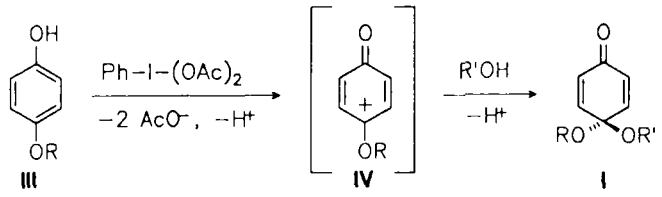


FIGURE 1. Mixed Quinone and Naphthoquinone Monoketals.



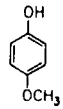
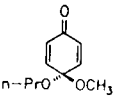
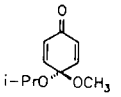
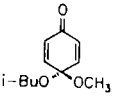
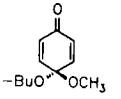
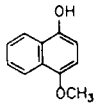
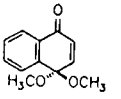
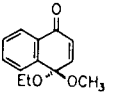
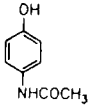
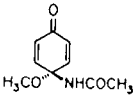
SCHEME 1. Phenoxonium Ion Intermediate in Phenol Oxidation.

expensive iodobenzenediacetate as a mild reagent for the preparation of quinone dimethylmonoketals from *p*-methoxyphenols in methanol as the solvent. We report herein our investigation into the synthesis of mixed quinone monoketals via this methodology as well as extension of these hypervalent iodine oxidations to naphthol and *p*-acetamidophenol derivatives.

The mechanism of the two-electron oxidation of para-substituted phenols **III** by iodobenzenediacetate has not been established, but may proceed via the phenoxonium ion **IV**[5] which would be trapped by nucleophilic solvent to afford the addition product **I** (**SCHEME 1**).

Steric demand at position 3 and 4 of the resulting dienone system could thus be conveniently modified through choice of the appropriate solvent/nucleophile system. Furthermore, it should be possible to incorporate groups with latent reactivity towards the dienone moiety via this methodology.

TABLE 1. IODOBENZENE DIACETATE OXIDATION OF PHENOLS.

Entry	Phenol	Alcohol	Product	Yield(%)[a]
1	**1a** 	ethyl	**2a** 	78
2	**1a**	*n*-propyl	**2b** 	77
3	**1a**	*i*-propyl	**2c** 	59
4	**1a**	*i*-butyl	**2d** 	59
5	**1a**	*t*-butyl	**2e** 	0
6	**1b** 	methyl	**3a** 	74
7	**1b**	ethyl	**3b** 	63
8	**1c** 	methyl	**4** 	75

a) isolated yields, based on starting phenol.

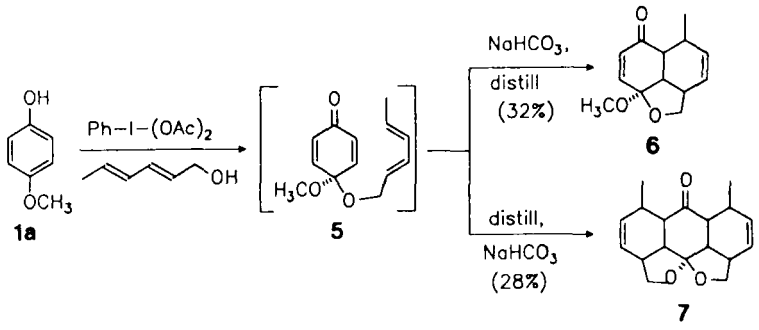
The initial results of the oxidation of various phenols with iodobenzene diacetate in alcohol solvents are summarized in TABLE 1.

The oxidations outlined in TABLE 1 were conducted at room temperature and were generally complete within 15 minutes. For oxidation of **1a**, the yield of the corresponding mixed monoketals was fair to good (entries 1 through 4). In the case where *t*-butyl alcohol was used as the solvent/nucleophile (entry 5), no evidence for a product corresponding to **2e** could be found, presumably due to a highly unfavorable steric effect.

The reaction was readily extended to the oxidation of 4-methoxy-1-naphthol in both methanol and ethanol (Entries 6 and 7), affording the corresponding naphthoquinone monoketals **3a** and **3b** in reasonable yield. Interestingly, oxidation of *p*-acetamidophenol **1c** in methanol afforded the corresponding N-acyl-N,O-ketal **4** in good yield, although the reaction failed altogether in ethanol, affording only polymeric material. Work is underway to exploit this oxidation process for the preparation of *p*-benzoquinone imide, a proposed toxic metabolite of acetaminophen.[7]

It was also found that reaction of *p*-methoxy phenol with iodobenzene diacetate in a mixture of sorbyl alcohol (*E,E*-2,4-hexadien-1-ol) and THF afforded product **6**, arising from an *in situ* intramolecular Diels-Alder reaction, presumably via the intermediate mixed quinone monoketal **5,** containing the appended diene moiety. Furthermore, the product obtained in this sequence was found to be a function of the isolation procedure employed. Thus, if base ($NaHCO_3$) was added prior to removal of excess sorbyl alcohol by distillation, **6** was obtained, but if distillation was carried out *prior* to base addition, further workup afforded only spiroketal **7**, which presumably arises from an alcohol exchange reaction during the distillation, catalyzed by acetic acid, followed by a second Diels-Alder reaction (SCHEME 2).

While the yields are modest and un-optimized, these transformations represent the rapid, one-pot assembly of highly functionalized ring systems in a single step. Further investigations into the preparation and utility of mixed quinone monoketal derivatives will be reported in due course.



SCHEME 2. Intramolecular Diels-Alder via Mixed Monoketals.

EXPERIMENTAL SECTION

Infrared spectra (IR, bands reported in cm^{-1}) were recorded on a Perkin-Elmer Model 283B spectrometer. Routine ^1H nuclear magnetic resonance spectra (NMR, signals reported in ppm) were determined at 60 MHz on a Varian EM360 spectrometer using either CCl_4 with tetramethylsilane (1%) as the standard or deuterochloroform as solvent with residual chloroform as the standard. High-field ^1H (270 MHz) and ^{13}C (68 MHz) NMR spectra were obtained on a JEOL FX-270 spectrometer. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Silica gel (230-400 mesh) was obtained from Merck. Solvents were used as received without further purification. Throughout the experimental the following abbreviations or formulas are used: diethyl ether (Et_2O), ethyl acetate (EtOAc), and thin-layer chromatography (TLC).

Phenol Oxidations: General Procedure. To a stirred solution of the phenol substrate (1.0 g of para-methoxyphenol, 4-methoxynaphthol or 4-acetamidophenol) in the desired alcohol (25 mL) was added iodobenzenediacetate (1.2 equiv) all at once at room temperature. The reaction was monitored by TLC (2:1 hexane/EtOAc) and deemed complete after 15 min. The mixture was then poured into an equal volume of sat. $NaHCO_3$ solution to neutralize the residual acetic acid. The bulk of the alcohol solvent was removed via rotary evaporator or short path distillation in vacuo. The organic residue was dissolved in Et_2O (50 mL), the layers

were separated, the organic layer was extracted with brine (2 x 25 mL), dried over a $CaSO_4$ cone and concentrated in vacuo. The pure products were isolated by flash chromatography on silica gel using 9:1 hexane/EtOAc mixture as eluant.

4-ethoxy-4-methoxy-2,5-cyclohexadienone 2a. 1.06 g, (78%), as a clear oil: spectroscopic data were in good agreement with literature[3a] values.

4-methoxy-4-propoxy-2,5-cyclohexadienone 2b. 1.13 g, (77%), as a clear oil: IR (NaCl plates, cm^{-1}) 1690 (s), 1640 (s), 1385 (m), 1328 (m), 1178 (m), 1103 (s), 1080 (s), 1061 (s), 1030 (s), 852 (m); ^1H NMR, 7.1 (d, J = 11 Hz, 2H), 6.5 (d, J = 11 Hz, 2H), 3.6 (t, J = 6 Hz, 2H), 3.4 (s, 3H), 1.6 (m, J = 7 Hz, 2H), 0.9 (t, J = 7 Hz, 3H); Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.75. Found: C, 65.32; H, 7.44.

4-isopropoxy-4-methoxy-2,5-cyclohexadienone 2c. 0.794 g, (59%) as a clear oil: IR (NaCl plates, cm^{-1}) 1690 (s), 1640 (s), 1385 (m), 1180 (m), 1100 (s), 1035 (s), 932 (m), 860 (m); ^1H NMR ($CDCl_3$) 7.4 (d, J = 12 Hz, 2H), 6.7 (d, J = 11 Hz, 2H), 4.4 (m, J = 7 Hz, 1H), 3.6 (s, 3H), 1.3 (d, J = 7 Hz, 6H); Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.92; H, 7.70. Found: C, 65.62; H, 7.55.

4-isobutoxy-4-methoxy-2,5-cyclohexadienone 2d. 0.861 g, (59%) as a clear oil: IR (NaCl plates, cm^{-1}) 1695 (s), 1642 (s), 1387 (m), 1180 (m), 1105 (s), 1060 (s), 1032 (s), 975 (m), 852(m); ^1H NMR ($CDCl_3$) 6.5 (d, J = 11 Hz, 2H), 5.9 (d, J = 11 Hz, 2H), 3.3 (s, 3H), 3.2 (d, J = 5 Hz, 2H), 1.8 (m, J = 7 Hz, 1H), 0.9 (d, J = 7 Hz, 6H); Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.20. Found: C, 66.82; H, 7.91.

4,4-dimethoxy-1-naphthalenone 3a. 0.872 g, (74%) as a light blue oil: Spectroscopic data were in good agreement with literature[6] values.

4-ethoxy-4-methoxy-1-naphthalenone 3b. 0.784 g, (63%) as a light blue oil: IR (NaCl plates, cm^{-1}) 1676 (s), 1600 (m), 1300 (s), 1060 (s), 762 (m); ^1H NMR ($CDCl_3$) 8.2 (m, 4H), 7.3 (d, J = 11 Hz, 2H), 7.0 (d, J = 11 Hz, 1H), 3.6 (q, further coupled, J = 9 Hz, 2H), 3.38 (s, 3H), 1.2 (t, J = 7 Hz, 3H); Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.50. Found: C, 71.54; H, 6.66.

4-acetamido-4-methoxy-2,5-cyclohexadienone 4. 0.904 g, (75%) as white crystals from CH_2Cl_2: mp 143-144°C (dec); IR (KBr pellet, cm^{-1}) 3200 (br, m), 1678 (m), 1650 (s), 1630 (m), 1070 (m); ^1H NMR ($CDCl_3$) 7.2 (d, J = 11 Hz, 2H), 6.7 (d, J = 11 Hz, 2H), 3.4 (s, 3H), 2.1 (s, 3H); Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12. Found: C, 59.95; H, 6.17.

Mono Diels-Alder Adduct 6. To a solution of para-methoxyphenol (1.0 g) in THF (5 mL) was added sorbyl alcohol (9.4 mL), followed by iodobenzenediacetate (3.9 g, 1.5 equiv) whereupon the mixture turned dark green. After stirring for 2 h, 4 g of solid $NaHCO_3$ was added, the THF was removed via rotary evaporator, then the excess sorbyl alcohol was removed via vacuum distillation at 40 °C/1.0 mm Hg. Next, water (100ml) was added, followed by ether (150ml). The layers were separated and the organic phase was extracted with brine (50 mL) and dried over $CaSO_4$. The ether was removed via rotary evaporator and the residue was chromatographed on silica gel (6" x 1" column, 5% hexane/EtOAc as eluant) to afford the title compound (0.560 g, 32%) as a white solid: mp 54-56°C; IR (KBr pellet): 2940 (m), 1680 (s), 1090 (m), 1068 (m), 1010 (m); ^1H NMR (270 MHz, $CDCl_3$) 6.45 (AB_q, J_{AB} = 10 Hz, 2H), 5.92 (q, J = 5 Hz, further coupled, 1H), 5.65 (m, 1H), 4.2 (t, J = 8 Hz, 1H), 3.47-3.45 (m, partially obscured, 1H), 3.39 (s, 3H), 3.1-3.0 (str m, 2H), 2.78 (d of d, J = 5 Hz, 1H), 2.4 (m, 1H), 1.15 (d, J = 8 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) 18.080 (1C), 32.142 (1C), 36.650 (1C), 44.315 (1C), 45.967 (1C), 48.937 (1C), 72.090 (1C), 103.603 (1C), 125.698 (1C), 131.513 (1C), 134.034 (1C), 140.240 (1C), 200.560 (1C); Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.61; H, 7.34.

Bis Diels-Alder Adduct 7. Sorbyl alcohol (9.4 mL, 10 equivalents) was added to para-methoxyphenol (1.0 g) dissolved in THF (5 mL). Next, iodobenzenediacetate (3.9 g, 1.5 equiv) was added and the resulting mixture was stirred overnight. After concentration via rotary evaporator, the mixture was vacuum distilled at 40°C/1.0 mm Hg to remove the excess sorbyl alcohol. The residue was dissolved in Et_2O (100 ml) and the solution was poured into sat $NaHCO_3$ (100ml) to neutralize residual acetic acid. The organic layer was then extracted with brine (2 x 50 ml) and dried through a $CaSO_4$ cone. After concentration in vacuo, the residue was dissolved in methanol (25 mL) and cooled in a -12°C freezer overnight.

The resulting crystals were collected by suction filtration, washed with cold methanol and air dried to afford 0.635 g (28%) of the title compound: mp 124-126°C; IR (KBr pellet) 2880 (m), 1692 (m), 1210 (s), 982 (s), 960 (m), 779 (m); ^{1}H NMR (270 MHz, $CDCl_3$) 5.95 (q, J = 5 Hz, 2H), 5.75 (q, J = 5 Hz, 2H) 4.05 (t, 2H), 3.55 (d of d, 2H), 3.05 (br m, 2H), 2.95 (t, J = 9 Hz, 2H), 2.7-2.4 (str m, 4H), 1.0 (d, J = 7 Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) 17.541 (2C), 31.417 (2C), 35.912 (2C), 41.106 (2C), 46.704 (2C), 71.912 (2C), 114.445 (1C), 127.771 (2C), 132.170 (2C), 217.107 (1C); Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.70. Found: C, 75.65; H, 7.93.

Acknowledgement: This research was supported by a grant from Research Corporation.

REFERENCES

1. Doty, B.J.; Morrow, G.W. *Tetrahedron Lett.* **1990**, 31, 6125.

2. (a) for a recent review of the preparation and chemistry of quinone monoketals, see: Swenton, J. S., *The Chemistry of Quinonoid Compounds*; Rappoport, Z., Patai, S., Eds.; John Wiley: New York, 1988, Vol. 2, Part 2, p 899; (b) for the synthesis of mixed silyl-methyl quinone monoketals, see: Stern, A.; Swenton, J.S. *J. Org. Chem.*, **1987**, *52*, 2763.

3. (a) Tamura, Y.; Yakura, T.; Haruta, J.; and Kita, Y. *J. Org. Chem.*, **1987**, *52*, 3927; (b) Kita, Y.; Tohma, T.; Kikuchi, K.; Inagake, M.; and Yakura, T. *J. Org. Chem.*, **1991**, *56*, 435.

4. Pelter, A.; Elgendy, S. *Tetrahedron Lett.*, **1988**, *29*, 677.

5. For a discussion of phenol oxidations and nucleophilic trapping of electrochemically-derived phenoxonium ions, see: Rieker, A.; Beisswenger, R.; Regier, K. *Tetrahedron*, **1991**, *47*, 645.

6. Henton, D.R.; Anderson, K.; Manning, M.J.; and Swenton, J.S. *J. Org. Chem.*, **1980**, *45*, 3422.

7. Novak, M.; Bonham, G.A.; Mulero, J.J.; Pelecanou, M.; Zemis, J.; Buccigross, J.M.; Wilson, T.C. *J. Am. Chem. Soc.*, **1989**, *111*, 4447, and references cited therein.

(Received in US 26 July, 1991)