## PREPARATION AND DIENOPHILICITY OF 3-METHYL-4, 5-BENZOFURANDIONE

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Summary: The o-quinone 3-methyl-4,5-benzofurandione, 1, was prepared in 94% overall yield from p-benzoquinone and 1-morpholino-propene. The cycloaddition chemistry of 1 with several dienes was examined and found to proceed in good to excellent yields.

The furano-o-benzoquinone and biogenically related functionalities are common features of the active principles of the Chinese traditional medicine, Dan-shen, Salvia miltiorrihza Bunge, used to treat heart disease,<sup>1</sup> viral hepatitis,<sup>2</sup> tuberculosis<sup>3</sup> and leprosy.<sup>4</sup> While the syntheses of several of these abietanoid pigments, such as tanshinone I and IIA, have been reported,<sup>5</sup> a more efficient route to these and other natural products could be provided via a Diels-Alder cycloaddition with the hitherto unknown furano-o-quinone 1 and appropriate dienes, Scheme 1. The cycloaddition chemistry of o-quinones, however, is very diverse. The carbocyclic double bonds<sup>6</sup> as well as the carbonyl double bond<sup>7</sup> have been reported to act as dienophiles in formal [4+2]-cycloadditions. Moreover, with dienophiles, either the cyclohexadiene<sup>8</sup> or the  $\alpha,\beta$ dicarbonyl<sup>9</sup> functionalities may react as dienes in [4+2]-cycloadditions. We now report the synthesis of 1 and our preliminary studies of its dienophilic reactivity.



o-Quinone 1 was prepared by two routes, Scheme 2. Method A, proceeding through the enamine condensation with p-benzoquinone in three steps, yielded 1 in 94% overall yield from simple starting materials. While both Fremy's salt<sup>10</sup> and benzeneseleninic anhydride<sup>11</sup> could be used to oxidize the phenol 3 to 1, the former reagent is more economical. In the second route, a mixture of the *E*- and *Z*-silylenol ethers formed from propanal underwent a photoinduced [2+2]cycloaddition with 2-methoxy-p-benzoquinone.<sup>12</sup> The cyclobutane adduct, 4, rearranged under acid catalysis, with subsequent dehydration to form the 3-methylbenzofuran, 5, in 66% overall yield. Periodate oxidation of 5 gave 1 in quantitative yield.<sup>13</sup> Method A was thus our preferred route to 1, proceeding in higher overall yield which could be readily scaled up, beginning with 5.0 g of p-benzoquinone and an equimolar amount of enamine, with no reduction in overall yield.



Scheme 2

(a) 0°C, benzene, 94%; (b) 5N HC1/THF, 99+%; (c) Fremy's salt, 99+%; (d) hν, benzene, 66%;
 (e) p-TsOH, benzene (reflux), 99+%; (f) NaIO<sub>4</sub>, 99+%.

o-Quinone 1 is a red solid, mp  $92-93^{\circ}$ C, stable at room temperature either in the solid state or in ether or benzene solution.<sup>14</sup> In halogenated hydrocarbons (CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>) or at elevated temperatures (100°C), decomposition slowly occurs overnight, though 1 was stable at 80°C (refluxing benzene) for 16 hrs. Protic acids also induced decomposition. Table 1 lists the results obtained in the cycloadditions with various dienes.

While reactive dienes (entries 1 - 3) gave good to excellent yields of cycloadducts, less reactive dienes gave only poor yields under various conditions, and the product mixtures were somewhat messy to work up.<sup>15</sup> In all reaction mixtures, tetra- and/or dihydro intermediates could be detected by NMR. Most of these intermediates slowly aromatized under ambient conditions or upon chromatography (SiO<sub>2</sub>) and were not isolated. Adduct  $\mathfrak{G}$ , however, could be isolated by recrystallization from ether/pet ether (bp 35 -  $60^{\circ}$ C), and subsequently tautomerized to the corresponding catechol diacetate in refluxing acetic anhydride.<sup>6</sup>e

Vinylcyclohexene dienes (items 5 and 6) are of special interest since their cycloadducts lead directly to abietanoid pigments. Using a polar solvent, methanol, (in comparison to benzene) led to a dramatic increase in yield.<sup>16</sup> A weak donor group on the diene, as in the silylvinylcyclohexene, also slightly promoted the cycloaddition in benzene, but not in methanol.<sup>17</sup> Given the instability of 1 in the presence of protic acids, and the known instability of *o*-quinones to most Lewis acids,<sup>15</sup> we hesitated to try Lewis acid catalysis in the cycloadditions. Using the relatively "soft" Lewis acid, Eu(fod)<sub>3</sub>,<sup>18</sup> the cycloaddition of vinylcyclohexene and 1 was promoted with improved regioselectivity (10:1). Decomposition of 1, however, was significant and cycloadducts were isolated in only 20 - 30% yield. Using less reactive dienes, entries 5 and 6, the best yields were obtained with high pressure (160,000 psi, 11.0 kBar). Under such conditions, the addition of the donor silyl group had no effect on the yield or regioselectivity (within experimental error).<sup>19</sup> The best yields of cycloadducts with 1 are therefore obtained using activated dienes or high pressure.

<u>Acknowledgement</u>: We thank the Donors of The Petroleum Research Fund, administered by the American Chemical Society, Research Corporation, and The Camille and Henry Dreyfus Foundation, Inc. for support.

Entry	Diene	Conditions	Product(s) <sup>b</sup>	Yield (%) <sup>C</sup>
1	$\bigcirc$	0º C, benzene, 1.5 hr		91%
2	OAc	reflux, benzene 16 hr		62%
3	ОТМЯ	1. reflux, benzene, 16 hr 2. 11 kBar, toluene, 2 hr, rt		1. 60% 2. 61%
4		neat, -78ºC to rt		<10%
5	SiMe <sub>3</sub>	1. reflux, benzene, 12 hr 2. reflux, MeOH, 4 hr 3. 11 kBar, MeOH, 2 hr, rt	$ \begin{array}{c} \circ & \downarrow \\ \downarrow & \downarrow \\ SiMe_3 \end{array} $	1. 18% (3.5:1) 2. 28% (3:2) 3. 61% (3.5:1)
6		<ol> <li>1. 110° C, benzene, 12 hr, sealed tube</li> <li>reflux, MeOH, 16 hr</li> <li>11 kBar, MeOH, 2 hr, rt</li> <li>Eu(fod)<sub>3</sub> 0.08 eq, benzene, rt 1 hr, reflux 1 hr</li> <li>Eu(fod)<sub>3</sub> 0.08 eq, MeOH</li> </ol>		1. <10% 2. 40% (2.5:1) 3. 67% (6:1) 4. 31% (10:1) 5. 20% (10:1)

## Table 1. Cycloadditions of 1 with Various Dienes<sup>a</sup>

- a) All reactions were run with 100 mg (0.62 mmol) of 1 and a 3-fold excess of diene.
- b) The structures of all cycloadducts were established by spectroscopic analysis: <sup>1</sup>H- and <sup>13</sup>C-NMR, HRMS, FTIR, and UV spectra. Reductive acetylation (Zn, NaOAc, Ac<sub>2</sub>O) to the diacetates which were likewise analyzed supported the assigned structures. Assignment of **6** as the endo adduct derives from the observed NOE's between the methylene bridge and the methines at the fusion centers derived from the o-quinone. Regioisomers (items 5 and 6) were distinguished by selective INEPT experiments, (3-bond <sup>13</sup>C,<sup>1</sup>H polarization transfer from the aromatic protons to carbons in the o-quinone ring), and by NOE analyses of the reduced diacetates (enhancements observed upon saturation of the 5-acetyl methyl resonance).
- c) All yields are isolated yields of cycloadducts after aromatization (except 6) and are the average of duplicate experiments.

- 1) a) In: "Zhong Cao Yao Xue", Part 3, p. 947; Nanjing Yao Xue Yuan, 'Zhong Cao Yao Xue' Bian Xie Zu, Jiangsu Ren Min Chu Ban She, Nanjing, 1976. b) M.K. Chien, P.T. Young, W.H. Ku, Z.X. Chen, H.T. Chen, H.C. Yeh, Acta Chim. Sin., 36, 199 (1978). Chem. Abst. 90, 138047k (1979).
- 2) Q. Zhou, in: "Advances in Chinese Materials Research", H.M. Chang, H.W. Yeung, W.W. Tso, and A. Koo, Eds., p. 215, World Scientific Publishing Co., Singapore, 1985. H. Luo, B. Wu, M. Wu, Z. Yong, Y. Jin, <u>Acta Pharm. Sin., 20</u>, 542 (1985). <u>Chem. Abst.</u> 103,
- 3) 175425q (1985).
- 4) a) J. Tong, J. Clin. Dermatology, 4, 210 (1986). b) H. Luo, Nanjing College of Pharmacy, personnal communication.
- a) H. Kakisawa, Y. Inouye, J. Chem. Soc. Chem. Commun., 1327 (1968). b) A.C. Baille, R.H. Thomson, J. Chem. Soc. (C), 48 (1968). c) H. Kakisawa, M. Tateishi, T. Kusumi, <u>Tetrahedron Lett.</u>, 3783 (1968). d) Y. Inouye, H. Kakisawa, <u>Bull. Chem. Soc. Jpn.</u>, 42, 3318 (1969). e) M. Tateishi, T. Kusumi, H. Kakisawa, <u>Tetrahedron</u>, <u>27</u>, 237 (1971). f) S. Imai, J. Sci. <u>Hiroshima Univ., Ser. A</u>, <u>35</u>, 171 (1971). g) R. Huot, P. Brassard, <u>Can. J. Chem.</u>, <u>52</u>, 88 5) (1974).
- (1974). An early controversy in the cycloaddition between o-quinones and cyclopentadiene as to which is the diene and which the dienophile was clarified by the demonstration that the initially formed adduct, with the o-quinone as the dienophile, undergoes a Cope rearrangement upon distillation: a) M.F. Ansell, A.F. Gosden, V.J. Leslie, R.A. Murray, J. Chem. Soc (C), 1401 (1971) and references therein. For other examples of o-quinone carbocyclic double bonds as dienophiles, see: b) L.F. Fieser, A.M. Seligman, J. Am. Chem. Soc., 56, 2690 (1934). c) M. Gates, W.F. Newhall, J. Am. Chem. Soc., 70, 2261 (1948). d) M.F. Ansell, A.J. Bignold, A.F. Gosden, V.J. Leslie, R.A. Murray, J. Chem. Soc. (C), 1414 (1971). e) Y. Omote, T. Komatsu, <u>Bull. Chem. Soc. Jpn.</u>, 47, 3128 (1974). f) S. Mazza, S. Danishefsky, P. McCurry, J. Org. Chem., 39, 3610 (1974). g) S. Danishefsky, P.F. Schuda, S. Mazza, K.Kato, J. Org. Chem., 41, 3468 (1976). h) R. Al-Hamdany, B. Ali, J. Chem. Soc. Chem. Commun., 397 (1978). i) D.D. Weller, E.P. Stirchak, J. Org. Chem., 48, 4873 (1983). a) M.F. Ansell, V.J. Leslie, J. Chem. Soc. (C), 1423 (1971). b) M.F. Ansell, R.A. Murray, J. Chem. Soc. (C), 1429 (1971). c) W. Friedricksen, C. Kruger, E. Kujath, G. Liebezeit, S. Mohr, Tetrahedron Lett., 237 (1979). a) M.G. Veliev, M.M. Guseinov, E.S. Mamedov, R.F. Gakhramanov, <u>Synthesis</u>, 337 (1984). b) T. 6)
- 7)
- a) M.G. Veliev, M.M. Guseinov, E.S. Mamedov, R.F. Gakhramanov, Synthesis, 337 (1984). b) T. 8) Molz, P. Konig, R. Goes, G. Gauglitz, H. Meier, Ber., 117, 833 (1984).
- a) W. Friedrichsen, I. Schwarz, <u>Tetrahedron Lett.</u>, 3581 (1977). b) A. Dondoni, M. Fogagnolo, A. Mastellari, P. Pedrini, F. Ugozzoli, <u>Tetrahedron Lett.</u>, <u>27</u>, 3915 (1986). 9)
- 10) H. Zimmer, D.C. Lankin, S.W. Horgan, Chem. Rev., 71, 229 (1971).
  11) D.H.R. Barton, A.G. Brewster, S.V. Ley, C.M. Read, M.N. Rosenfeld, J. Chem. Soc., Perk. Trans. I, 1473 (1981) and references therein.
- H.J. Liu, W.H. Chan, Can. J. Chem., 58, 2196 (1980).
   E. Adler, R. Magnusson, Acta Chem. Scand., 16, 529 (1962).
- CH<sub>3</sub>).  ${}^{13}$ C-NMR (CDCl<sub>3</sub>)  $\delta$  181.9 (s), 174.1 (s), 159.6 (s), 143.2 (d), 131.5 (d), 125.7 (d), 123.0 (s), 122.7 (s), 8.78 (q).
- 15) Similar difficulties were reported in the cycloaddition of o-quinones in the synthesis of rosmariquinone: S. Knapp, S. Sharma, J. Org. Chem., <u>50</u>, 4996 (1985).
- 16) Dramatic solvent effects were also reported in the Diels-Alder reactions of other o quinones: S. Danishefsky, P.F. Schuda, W. Caruthers, J. Org. Chem., 42, 2179 (1977).
- 17) While the cycloaddition chemistry of silylated dienes has not been widely investigated, internally (2- or 3-position) silylated dienes undergo cycloadditions in excellent yields: a) A.R. Chamberlin, J.E. Stemke, F.T. Bond, J. <u>Org. Chem.</u>, 43, 147 (1978). b) D.G. Batt, B. Ganem, <u>Tetrahedron Lett.</u>, 3323 (1978). In contrast, terminally (1- or 4-position) silylated dienes are less reactive: c) I. Fleming, A. Percival, <u>J. Chem. Soc. Chem. Commun.</u>, 681 (1976). d) I. Fleming, A. Percival, J. Chem. Soc. Chem. Commun., 178 (1978). 18) S. Danishefsky, C.J. Murray, J. Am. Chem. Soc., 107, 1269 (1985).
- 19) Relatively poor regioselectivity in the cycloadditions of o-quinones with vinylcyclohexene has been recently reported: D. Pitea, M. Gastaldi, F. Orsini, F. Pelizzoni, A. Mugnoli, E. Abbondanti, J. Org. Chem., 50, 1853 (1985).

(Received in USA 21 April 1987)