13254 *J. Am. Chem. Soc.* **1998,** *120,* 13254−13255

Furans Act as Dienophiles in Facile Diels−Alder Reactions with Masked *o*-Benzoquinones

Chien-Hsing Chen, Polisetti Dharma Rao, and
Chun-Chen Liao*

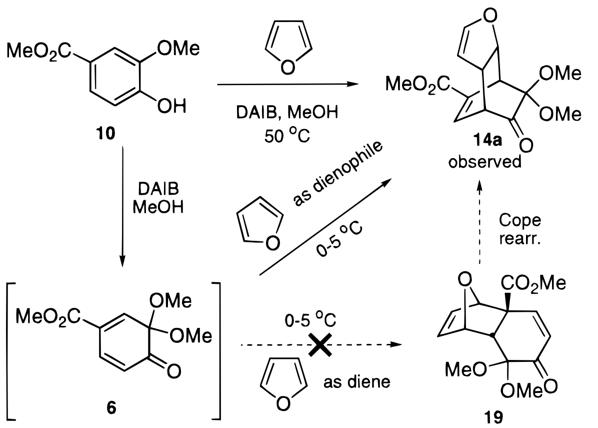
*Department of Chemistry
National Tsing Hua University
Hsinchu, Taiwan 300*

Received August 19, 1998

Despite its aromaticity, furan functions as a diene in [4+2] and [4+3] cycloaddition reactions,[1−4] as an olefin in [2+2] photocycloadditions,[5] and as a dipolarophile in 1,3-dipolar cycloadditions.[6] Indeed, furans have been widely used as dienes in Diels−Alder reactions despite the fact that harsh reaction conditions (high pressures and temperatures) are often required and the adducts are susceptible to retro-Diels−Alder reactions.[3] In contrast, furans in general do not efficiently participate as dienophiles in Diels−Alder reactions.[7−10] For example, furan itself was found to be an inefficient dienophile from the yields of the adducts in its only two reported reactions with tetrachloro-*o*-benzoquinone (2%) and tropone (11%).[7,8] This fundamental problem has been addressed sporadically,[7−10] and the requirements for furans to efficiently play the role of dienophiles remain to be identified.[9,10] We now wish to report that furan (**1**) and its derivatives **2**−**5** efficiently function as dienophiles in facile Diels−Alder reactions with masked *o*-benzoquinones **6**−**9**, generated in situ from 2-methoxyphenols **10**−**13**, to furnish the adducts **14**−**18**.

Masked *o*-benzoquinones are one of the most easily accessible 2,4-cyclohexadienones and are commonly used as dienes in Diels−Alder reactions.[11] However, it has been recently shown that they can also behave as dienophiles in competetive Diels−Alder reactions with electron-rich dienes to provide highly substituted *cis*-decalins and naphthalenes.[12,13] To ascertain the degree of dienophilic nature of masked *o*-benzoquinones, the reaction of masked *o*-benzoquinone (**6**) with furan (**1**) was carried out. The adduct **14a**, which is highly unexpected, considering the strongly enophilic nature of furan, was obtained in 80% yield as a single stereoisomer (Scheme 1).

Scheme 1



In fact, there are two possible pathways to the observed adduct **14a**: (i) a direct cycloaddition in which masked *o*-benzoquinone acts as the diene and (ii) a tandem process involving first a Diels−Alder reaction in which furan plays the role of the diene to produce adduct **19** followed by a Cope rearrangement under the reaction conditions (Scheme 1). To find out if the latter pathway is in operation, the reaction was carried out in deuterated methanol at 0−5 °C in an NMR tube and monitored by ^{1}H NMR spectroscopy. During the entire course of the reaction, only a single product **14a** was observed. Understandably, the cycloaddition was very slow, and no reaction occurred at temperatures lower than 0 °C. In the absence of any evidence for the formation of adduct **19**, the tandem process seems improbable; however, it cannot be completely excluded.

Reactions of benzofuran, which can only behave as a dienophile, were also studied. It is pertinent to mention that in contrast with isobenzofuran, benzofuran has not been used much in Diels−Alder reactions because of its inertness owing to high aromaticity. Moreover, in the few cases recorded, a strong driving force was required.[14] In the present study benzofuran provided results similar to those of furan (Scheme 2). In light of these facts, the conclusion that furan acts as a dienophile in these reactions was reached. To examine the generality with regard to both of the components, the reactions of various furans **1**−**5** with selected masked *o*-benzoquinones **6**−**9**, generated in situ by oxidation of 2-methoxyphenols **10**−**13** with (diacetoxy)iodobenzene (DAIB) in methanol were carried out at suitable temperatures (Scheme 2, Table 1).[15,16]

In each of the successful cases, a single Diels−Alder adduct was produced. However, in the reactions of masked *o*-benzoquinones **8** and **9** with furan derivative **2**, and **6**, **7**, and **8** with **3**, the ^{1}H NMR spectra of the crude reaction mixtures showed

---

* Correspondence author. Fax: 886-3-5711082. E-mail: ccliao@faculty.nthu.edu.tw.

(1) Sargent, M. V.; Dean, F. M. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol 4, pp 619−642.

(2) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.

(3) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *42*, 14179.

(4) Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis, Combining C-C π-bonds*; Trost, B. M., Flemming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol 5, pp 593−615.

(5) Porco, J. A., Jr.; Schreiber, S. L. In *Comprehensive Organic Synthesis, Combining C-C π-bonds*; Trost, B. M., Flemming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol 5, pp 151−192.

(6) (a) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134. (b) Muller, I.; Jager, V. *Tetrahedron Lett.* **1982**, *23*, 4777. (c) Jager, V.; Muller, I.; Paulus, E. F. *Tetrahedron Lett.* **1985**, *26*, 2997.

(7) Horspool, W. M.; Tedder, J. M.; Din, Z. U. *J. Chem. Soc. (C)* **1969**, 1694.

(8) (a) Sugiyama, S.; Tsuda, T.; Mori, A. *Chem. Lett.* **1986**, 1315. (b) Sugiyama, S.; Tsuda, T.; Mori, A.; Takeshita, H.; Kodama, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3633.

(9) (a) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188. (b) Jung, M. E.; Street, L. J.; Usui, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6810. (c) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 867.

(10) (a) Ghisalberti, E. L.; Jefferies, P. R.; Payne, T. G. *Tetrahedron* **1974** *30*, 3099. (b) Heller, H. G.; Hughes, D. S.; Hursthouse, M. B.; Levell, J. R.; Ottaway, M. J. *J. Chem. Soc., Chem. Commun.* **1995**, 837.

(11) (a) Chu, C.-S.; Lee, T.-H.; Liao, C.-C. *Synlett* **1994**, 635. (b) Hsiu, P.-Y.; Lee, Y.-C.; Liao, C.-C. *Tetrahedron Lett.* **1998**, *39*, 659.

(12) (a) Hsiu, P.-Y.; Liao, C.-C. *J. Chem. Soc., Chem. Commun.* **1997**, 1085. (b) Carlini, R.; Higgs, K.; Older, C.; Randhawa, S. *J. Org. Chem.* **1997**, *62*, 2330. (c) Rao, P. D.; Chen, C.-H.; Liao, C.-C. *J. Chem. Soc., Chem. Commun.* **1998**, 155. (d) Carlini, R.; Higgs, K.; Rodrigo, R.; Taylor, N. *J. Chem. Soc., Chem. Commun.* **1998**, 65.

(13) Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1995**, *117*, 10889.

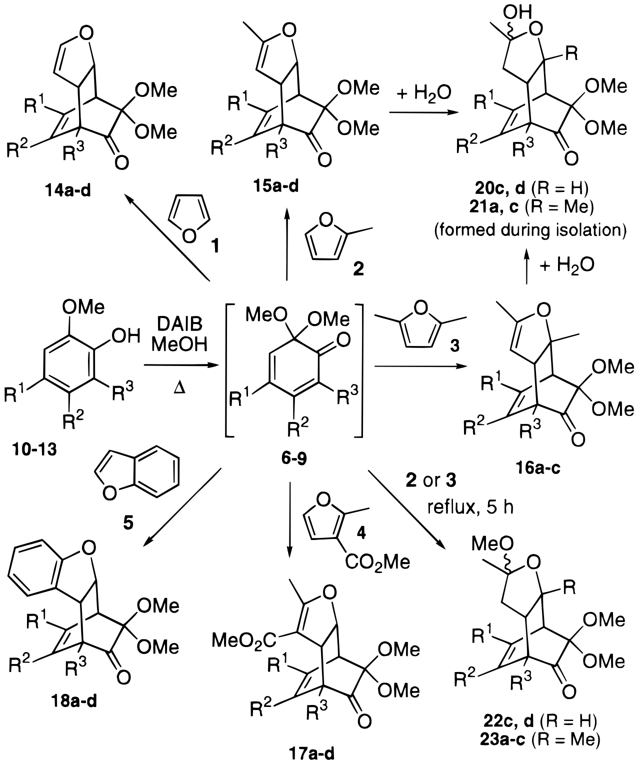
(14) (a) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261. (b) Markgraf, J. H.; Patterson, D. E. *J. Heterocycl. Chem.* **1996**, *33*, 109 and references therein.

(15) General procedure for Diels−Alder reactions: A flask containing phenol (1 mM) and a furan derivative (10 mM) in MeOH (3 mL) was immersed in an oil bath kept at the appropriate temperature (Table 1) and [diacetoxy]iodobenzene (DAIB) (1.5 mM) in MeOH (4 mL) was added during a period of time (Table 1) using a syringe pump. Ten minutes after the DAIB addition (see Table 1 for specific cases), methanol and excess furan derivative were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using 25% ethyl acetate in hexanes as eluent to obtain the desired adducts.

(16) All of the new compounds were thoroughly characterized by IR, ^{1}H and ^{13}C NMR, and low- and high-resolution mass spectral analyses; most of the compounds provided satisfactory elemental analyses. Furthermore, the structure of compound **17d** was confirmed by single-crystal X-ray diffraction analysis.

10.1021/ja982974l CCC: $15.00

Scheme 2



For **14-18** and **20-23**:

6 & 10: R^1 = CO_2Me, R^2 = R^3 = H
7 & 11: R^1 = CO_2Me, R^2 = H, R^3 = OMe
8 & 12: R^1 = COMe, R^2 = R^3 = H
9 & 13: R^1 = R^3 = H, R^2 = CO_2Me

a: R^1 = CO_2Me, R^2 = R^3 = H
b: R^1 = CO_2Me, R^2 = H, R^3 = OMe
c: R^1 = COMe, R^2 = R^3 = H
d: R^1 = R^3 = H, R^2 = CO_2Me

exclusive formation of the expected products **15c**, **15d**, **16a**, **16b**, and **16c**, respectively. However, the isolation of these primary adducts was found to be difficult because of hydrolytic cleavage of the enol ether moiety, producing mixtures of primary adducts **15c**, **15d**, **16a**−**c** (**16b** was produced in traces),[17] and the corresponding hemiacetals **20c**, **20d**, **21a**, and **21c**. Consequently, the reaction time was extended by 5 h in these cases with the expectation that the enol ether moiety would undergo acid-catalyzed addition of methanol. These reactions produced exclusively compounds **22c**, **22d**, and **23a**−**c** (**23b** was produced in traces),[17] respectively, in good yields (Scheme 2, Table 1). Although, compounds **22c**, **22d**, **23a**, and **23c** are stereochemically pure, the orientation of the methoxy group in these compounds could not be determined by NMR spectroscopy including NOE experiments.

Table 1. Diels−Alder Reactions of Furans with Masked *o*-Benzoquinones (MOBs)

entry	furan	phenol	MOB	*T* (°C)[a]	*t* (min)[b]	prod./Y(%)[c]
1	**1**	**10**	**6**	50	40	**14a**/80
2		**11**	**7**	50	60	**14b**/68
3		**12**	**8**	50	30	**14c**/60
4		**13**	**9**	50	180	**14d**/36
5	**2**	**10**	**6**	rt	30	**15a**/85
6		**11**	**7**	rt	60	**15b**/77
7		**12**	**8**	reflux	30[d]	**22c**/84
8		**13**	**9**	reflux	120[d]	**22d**/84
9	**3**	**10**	**6**	reflux	50[d]	**23a**/81
10		**11**	**7**	reflux	120[d]	**23b**/trace[e]
11		**12**	**8**	reflux	60[d]	**23c**/73
12		**13**	**9**	reflux	120	*f*
13	**4**	**10**	**6**	reflux	40	**17a**/90
14		**11**	**7**	reflux	40	**17b**/76
15		**12**	**8**	reflux	30	**17c**/89
16		**13**	**9**	reflux	300	**17d**/66
17	**5**	**10**	**6**	reflux	25	**18a**/64
18		**11**	**7**	reflux	120	**18b**/45
19		**12**	**8**	reflux	30	**18c**/64
20		**13**	**9**	reflux	300	**18d**/5

[a] Of oil bath. [b] During which DAIB in MeOH was added. [c] Yields are of isolated products and unoptimized. [d] Reflux 5 h after addition. [e] Observed in ^{1}H NMR spectrum of the crude reaction mixture. [f] Only dimer of **9** was produced.

It is pertinent to mention that in prior studies, furans required activation by strong electron-releasing or electron-demanding groups to act as dienophiles.[8,9] In contrast, the present reactions do not require activation of furan and tolerate the presence of both electron-releasing and electron-demanding groups on the furan ring (Scheme 2). On the other hand, the position of an electron-demanding group on masked *o*-benzoquinones seems to be very important for their reactions with furans (Table 1). For example, masked *o*-benzoquinone **9** with the methoxycarbonyl group on C_3 exhibited poor reactivity (entries 4, 12, and 20). On the other hand, masked *o*-benzoquinone **7** with an additional electron-releasing methoxy group on C_2 is found to be less reactive (entries 6, 10, 14, and 18) when compared to **6**.

In reactions of **2** and **4**, the unsubstituted double bond of the furan ring participated in the reaction, showing that the cycloaddition is highly site-selective. The regiochemistry has remained identical throughout and was clearly established by ^{1}H−^{1}H decoupling experiments in all the cases. The fact that in all of the cases only the adducts resulting from *endo* addition were produced clearly shows that these reactions follow all of the ground rules of Diels−Alder reactions.[18]

It is important to note that in these processes two aromatic compounds were employed to generate highly complex and potentially useful multifunctional compounds. These Diels−Alder reactions make it clear that masked *o*-benzoquinones prefer to play the role of dienes and force the furans to play the role of dienophiles.[11,12] In light of the mild conditions and considerable generality, these reactions are certainly note-worthy. They clearly show that there exists a possibility for using furan and its derivatives as 2π partners in thermal Diels−Alder reactions.

Acknowledgment. We thank National Science Council (NSC) of the Republic of China for financial support. P.D.R. thanks NSC for a postdoctoral fellowship.

Supporting Information Available: Characterization data for all of the Diels−Alder adducts described in this paper (10 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA982974L

---

(17) Adducts **16b** and **23b** were produced in traces along with the dimer of **7**. They were only observed in the ^{1}H NMR spectrum of the corresponding crude reaction mixtures and were not isolated.

(18) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley: New York, 1975.