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Thiophenes act as dienophiles in novel cycloadditions with masked *o*-benzoquinones

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Abstract—Highly selective Diels–Alder reactions of masked *o*-benzoquinones with thiophenes are described. © 2001 Elsevier Science Ltd. All rights reserved.

Thiophene, unlike furan and pyrrole has been shown to be a rather inefficient diene in Diels–Alder reactions or other cycloaddition reactions.[1] Such inertness could be attributed to the fact that thiophene is of higher aromaticity in comparison with furan and pyrrole. It was also shown that there exists an equilibrium between thiophene and its Diels–Alder adducts, which is unfavorable towards the latter due to the loss of aromaticity that is originally present in thiophene.[2] However, thiophenes can participate in Diels–Alder reactions as dienes but under harsh conditions.[3] Thiophenes were reported to act as dienophiles in their reactions with hexachlorocyclopentadiene,[4a] dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate,[4b] tetrachlorothiophene-1,1-dioxide[4c] and *o*-quinone monoimides,[4d] but the reactions are limited to two or three examples and lack generality.

Masked *o*-benzoquinones (MOBs) are the most easily accessible 2,4-cyclohexadienones and have been shown to be of great synthetic potential.[5] They undergo Diels–Alder reactions with a variety of dienophiles and dienes in an efficient manner with high regio- and stereoselectivities.[6–10] Quite recently, MOBs were shown to undergo facile Diels–Alder reactions with furans[11] and pyrroles[12] in which the heterocycles acted as dienophiles. One of the important observations from our studies involving furans is that MOBs bearing electron-withdrawing substituents react quite readily with furans carrying electron-donating groups.[11] In the light of the poor reputation of thiophenes as partners in cycloaddition reactions and known high reactivity of MOBs, it is worth considering the study of reactions between these two types of compounds. We report herein highly chemo-, regio- and stereoselective Diels–Alder cycloaddition reactions of thiophenes **1**–**5** with masked *o*-benzoquinones **7a**–**c** generated from phenols **6a**–**c**, in which thiophenes apparently played the role of dienophiles leading to mono and bis-adducts in acceptable yields (Scheme 1, Table 1).

We have first examined the case of 2-methylthiophene (**2**). MOB **7a** generated via oxidation of phenol **6a** with diacetoxyiodobenzene (DAIB) in dry methanol at 0°C and reacted with an excess of 2-methylthiophene (**2**, 50 equiv.) at reflux for 3 h to afford adduct **8a** in 50% yield as the sole isolable product.[13] To reaffirm the behavior of **2**, it was allowed to react with MOBs **7b** and **7c**. The reaction of **2** with **7c** at reflux furnished the anticipated adduct **8c** as the sole isolable product in 49% yield. On the other hand, **7b** afforded both mono adduct **8b** and bis-adduct **9b** in 51 and 12%, respectively. The bis-adduct **9b** could also be obtained by treating **8b** with **7b**. Encouraged by these results, the parent thiophene (**1**, 50 equiv.) was allowed to react with **7a**–**c** at reflux to give bis-adducts **10a**–**c** albeit in low yields (16–23%). The formation of bis-adducts could be explained in terms of large anticipated difference in the reactivity of aromatic thiophene and electron-rich vinyl sulfide[14] moiety in the mono adduct. The limited lifetime of MOBs **7a**–**c** and the poor tendency of the parent thiophene to undergo cycloaddition reactions reflect in the relatively low yields of **10a**–**c**.

Reactions of 3-methylthiophene (**3**) with MOBs **7a**–**c** furnished the anticipated adducts **11a**–**c** in 16–48% yield

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Keywords: orthobenzoquinone monoketal; hypervalent iodine reagent; 2,4-cyclohexadienones; thiophenes; Diels–Alder reaction; bicyclo[2.2.2]octenones.

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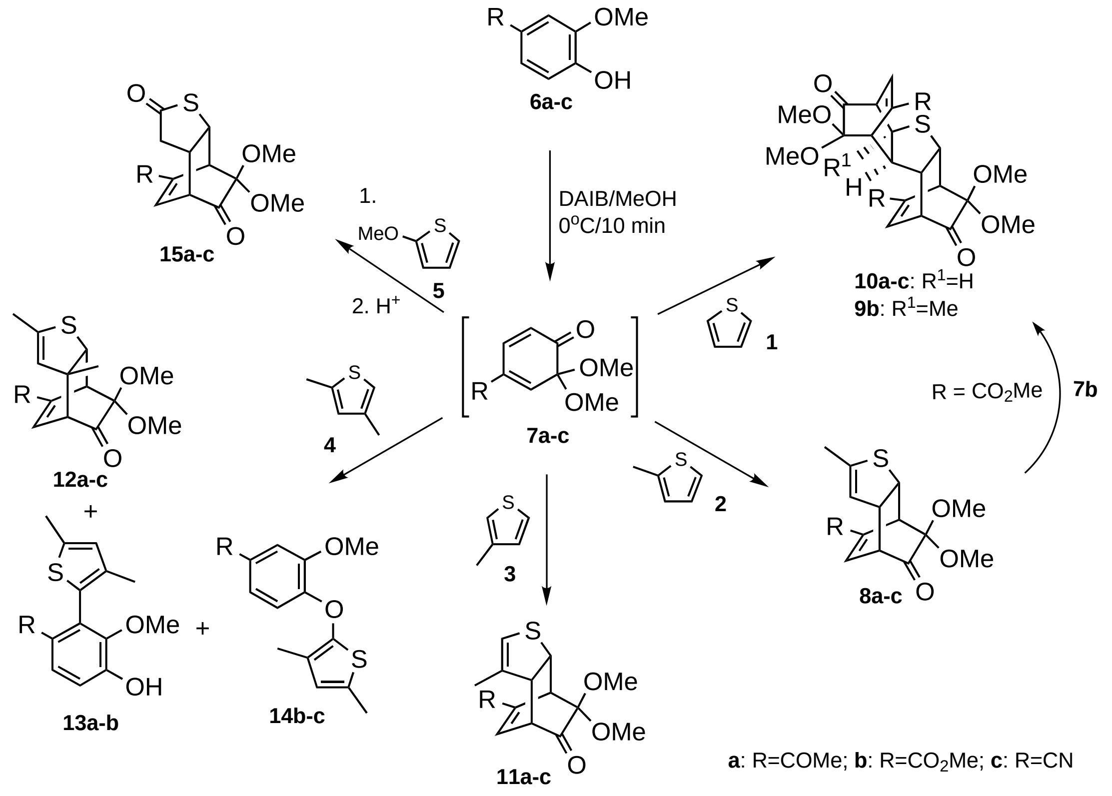

Scheme 1.

Table 1. Diels–Alder cycloadditions of thiophenes **1**–**5** with masked *o*-benzoquinones **7a**–**c**[a]

Entry	Thiophene (equiv.)	Phenol	MOB	Temp. (0°C)	Time[a] (h)	Product(s)/yield (%)[b]
1	**1** (50)	**6a**	**7a**	Reflux	5	**10a**/16
2		**6b**	**7b**	Reflux	5	**10b**/23[c]
3		**6c**	**7c**	Reflux	5	**10c**/17
4	**2** (50)	**6a**	**7a**	Reflux	3	**8a**/50
5		**6b**	**7b**	Reflux	6	**8b**/51; **9b**/12[c]
6		**6c**	**7c**	Reflux	1	**8c**/49
7	**3** (50)	**6a**	**7a**	Reflux	3	**11a**/48
8		**6b**	**7b**	Reflux	3	**11b**/31[c]
9		**6c**	**7c**	Reflux	3	**11c**/16
10	**4** (50)	**6a**	**7a**	Reflux	5	**12a**/21; **13a**/33
11		**6b**	**7b**	Reflux	5	**12b**/32; **13b**/12; **14b**/6
12		**6c**	**7c**	Reflux	5	**12c**/40; **14c**/3
13	**5** (5)	**6a**	**7a**	0	1	**15a**/67
14		**6b**	**7b**	0	1	**15b**/59[c]
15		**6c**	**7c**	rt	0.4	**15c**/36

[a] Time taken for the reaction between MOB and thiophene derivative.

[b] Yields are of pure and isolated products.

[c] In these reactions dimer of **7b** was also obtained.

with no trace of bis-adducts. On the other hand, the reactions of 2,4-dimethylthiophene (**4**) with **7a**–**c** provided rather unexpected results. MOB **7a** reacted with **4** to furnish the thienylphenol **13a** (33%) in addition to cycloadduct **12a** (21%). Interestingly, the reaction of **7b** and **4** afforded three products, **12b** (32%), **13b** (12%) and **14b** (6%). While the reaction of **7c** with large excess of **4** (50 equiv.) furnished the adduct **12c** (40%) along with unexpected **14c** (3%). 2-Methoxythiophene (**5**, 5 equiv.) reacted quite rapidly with **7a**–**c**, but provided a complex mixture probably due to the sensitive cyclic ketene acetal moiety.[11b] Consequently, the crude reaction mixtures were subjected to hydrolysis with *p*TSA and water to afford the corresponding thiolactones **15a**–**c** in good yields. We also noticed that the reactions of **7a**,**b** with **4** for longer periods did not alter the ratio of the products. No change was observed when methanolic solutions of **12a**,**b** and AcOH (2 equiv.) were heated at reflux temperature, thus ruling out the possibility of formation of **13a**,**b** from **12a**,**b** under the reaction conditions.

The regiochemistry of all the cycloadducts was determined by ^{1}H–^{1}H decoupling NMR experiments. The assigned structures of **8b** (Fig. 1)[15] and **9b** (Fig. 2)[16] were further confirmed by single X-ray diffraction method. The regioselectivity of these reactions is consistent and similar to that of reactions of furans with MOBs. Even the second addition of MOB to the primary adduct proceeded in highly regioselective manner just as a reaction between vinyl sulfide and MOB.[14] The unsubstituted double bond of thiophenes **2**, **3** and **5** always participated in the cycloaddition indicating that these reactions are highly chemoselective. The stereochemical assignments of all the adducts except **12** were based on the observed long-range coupling between the vinylic protons on the cyclohexenone ring and the nearest methine proton on the heterocycle.

Note that the cycloaddition reactions proceed smoothly only when MOBs bearing electron-withdrawing groups at position-4 with thiophenes containing electron-donating groups. For example, the reaction of MOB **7d** (6,6-dimethoxy-4-methyl-2,4-cyclohexadienone) with 2-methylthiophene did not furnish any cycloadduct. Methyl 2-thiophenecarboxylate and 2,5-dimethylthiophene did not react with MOB **7a**. The mechanism of these cycloaddition reactions appears to be interesting but unclear. Scheme 2 outlines the possible pathways (thiophene **4** is taken as an example): A concerted cycloaddition of thiophene as a 2π partner to MOB (4π); and a step-wise reaction involving nucleophilic attack by thiophene on electron-deficient MOB leading to zwitterionic species **16**, which would then either undergo ring-closure to furnish the desired adduct or suffer loss of MeOH to give aromatized product. Our earlier work on the Diels–Alder reactions of MOBs with furans[11] and pyrroles[12] suggests that these heteroaromatics prefer to play the role of dienophiles in a concerted pathway. In the present study, thiophenes apparently act as dienophiles in the Diels–Alder reactions with MOBs in a highly regio- and stereoselective manner to provide a single isomer in each case. However, in view of the formation of thienyl-phenol **13a**, the possibility of a step-wise cycloaddition may not be ruled out. It is noteworthy that the formation of **13** was observed only from the reaction of sterically hindered thiophene **4**. Furthermore, it will be difficult to explain the observed high regio- and stereoselectivities via the ring closure of zwitterionic species **16** in a step-wise cycloaddition.

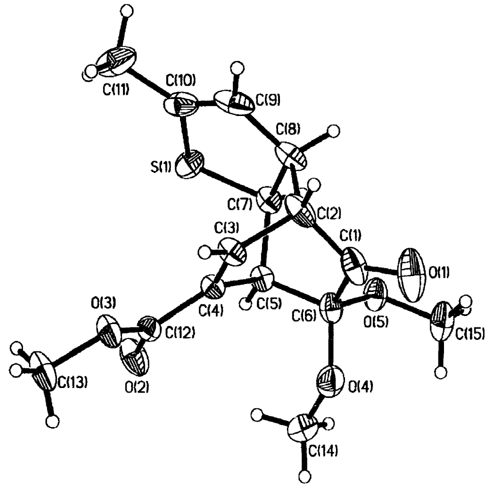

Figure 1. ORTEP plot of **8b** (numbering is arbitrary).

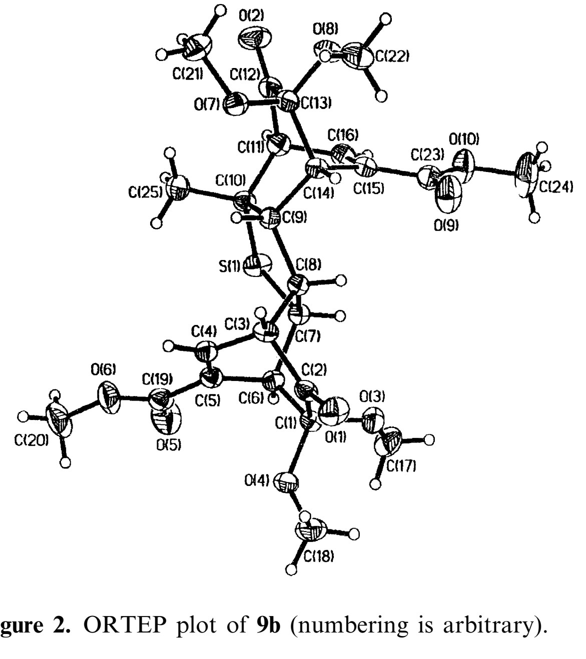

Figure 2. ORTEP plot of **9b** (numbering is arbitrary).

The stereochemical outcome of these cycloadditions is presumably due to the secondary orbital interactions. We have computed the energies of transition-state structures for the reaction of 2-methylthiophene (**2**) and MOB **7c** by ab initio RHF/3-21G* method. Among 16 possible transition-state structures[17] (**2** as dienophile – 8 structures and **2** as diene – 8 structures) computed, the transition-state structure **17** (MOB **7c** as diene and **2** as dienophile) (Fig. 3) has the lowest energy supporting the procured regio- and stereoselectivities. These calculations also suggest the highly asymmetric nature of the transition-state and thereby reaction proceeding through a non-synchronous concerted pathway.[18]

In conclusion, in the reactions described herein, thiophenes were shown to behave as dienophiles with considerable generality in Diels–Alder reactions. It is also important to mention that in these processes aromaticity of two compounds was broken to achieve synthesis of compounds with a high degree of structural complexity.

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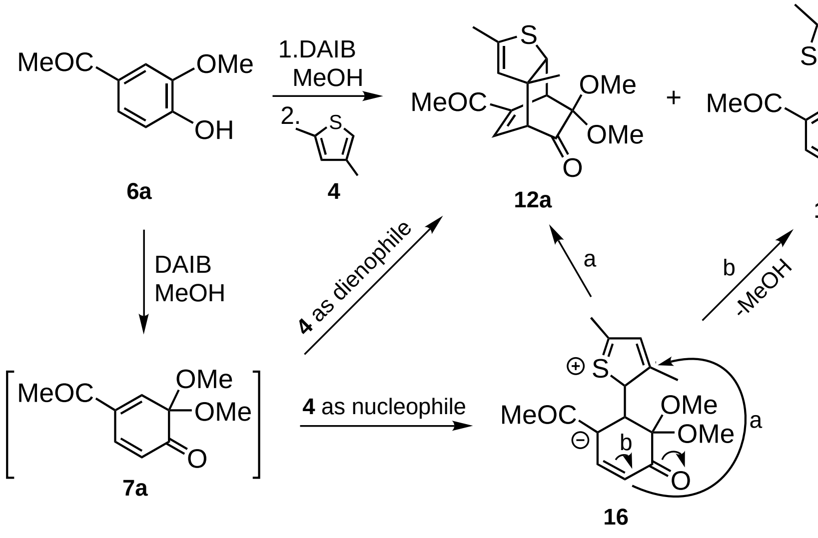

Scheme 2.

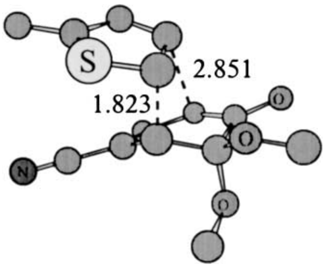

Figure 3. The transition-state structure **17** (distances are in Å).

References

1. (a) Rajappa, S.; Natekar, N. V. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Pergamon: Oxford, 1996; Vol. 2, pp. 491–606; (b) Joule, J. A.; Mills, K.; Smith, G. F. In *Heterocyclic Chemistry*; Chapman & Hall: London, 1995; (c) Benders, P. H.; Reinhoudt, D. N.; Trompenaars, W. P. In *Thiophene and its Derivatives*; Wiley-Interscience: New York, 1985; pp. 671–744.
2. (a) Lert, P. W.; Trindle, C. *J. Am. Chem. Soc.* **1971**, *93*, 6392–6395; (b) Jursic, B. S.; Coupe, D. *J. Heterocycl. Chem.* **1995**, *32*, 483–489; (c) Jursic, B. S. *J. Heterocycl. Chem.* **1995**, *32*, 1445–1455.
3. Corral, C.; Lissavetzky, J.; Manzanares, I. *Synthesis* **1997**, 29–31 and references cited therein.
4. (a) Hamadait, H.; Neeman, M. Israel Patent 9749, 1957; *Chem. Abstr.* **1958**, *52*, 1263e; (b) Seitz, G.; Kaempchen, T. *Arch. Pharm.* **1978**, *311*, 728–735; (c) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856–867; (d) Heine, H. W.; Williams, D. K.; Rutherford, J. L.; Ramphal, J.; Williams, E. A. *Heterocycles* **1993**, *35*, 1125–1140.
5. (a) Liao, C.-C. In *Modern Methodology in Organic Synthesis*; Shono, T., Ed.; Kodansha: Tokyo, 1992; pp. 409–424; (b) Quideau, S.; Pouysegu, L. *Org. Prep. Proc. Int.* **1999**, *31*, 619–680.
6. (a) Hsiu, P.-Y.; Lee, Y.-C.; Liao, C.-C. *Tetrahedron Lett.* **1998**, *39*, 659–662; (b) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102–4110.
7. Gao, S.-Y.; Ko, S.; Lin, Y.-L.; Peddinti, R. K.; Liao, C.-C. *Tetrahedron* **2001**, *57*, 297–308.
8. (a) Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Song, L.-D.; Liao, C.-C. *J. Org. Chem.* **1999**, *64*, 4111–4118; (b) Hsu, P.-Y.; Liao, C.-C. *Chem. Commun.* **1997**, 1085–1086; (c) Chen, Y.-K.; Peddinti, R. K.; Liao, C.-C. *Chem. Commun.* **2001**, 1340–1341.
9. (a) Rao, P. D.; Chen, C.-H.; Liao, C.-C. *Chem. Commun.* **1998**, 155–156; (b) Hsu, D.-S.; Rao, P. D.; Liao, C.-C. *Chem. Commun.* **1998**, 1795–1796.
10. (a) Chu, C.-S.; Liao, C.-C.; Rao, P. D. *Chem. Commun.* **1996**, 1537–1538; (b) Lee, T.-H.; Liao, C.-C. *Tetrahedron Lett.* **1996**, *37*, 6869–6872; (c) Liu, W.-C.; Liao, C.-C. *Synlett* **1998**, 912–914; (d) Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1995**, *117*, 10889–10904; (e) Carlini, R.; Higgs, K.; Older, C.; Randhwa, S.; Rodrigo, R. *J. Org. Chem.* **1997**, *62*, 2330–2331.
11. (a) Chen, C.-H.; Rao, P. D.; Liao, C.-C. *J. Am. Chem. Soc.* **1998**, *120*, 13254–13255; (b) Rao, P. D.; Chen, C.-H.; Liao, C.-C. *Chem. Commun.* **1999**, 713–714.
12. Hsieh, M.-F.; Peddinti, R. K.; Liao, C.-C. *Tetrahedron Lett.* **2001**, *42*, 5481–5484.
13. All the new compounds were characterized by IR, ^{1}H (400 MHz), and ^{13}C NMR (100 MHz), DEPT, and low and high resolution MS analyses and elemental analyses.
14. Gao, S.-Y.; Lin, Y.-L.; Rao, P. D.; Liao, C.-C. *Synlett* **2000**, 421–423.
15. CCDC deposition No. 159663.
16. CCDC deposition No. 159664.
17. We were able to locate total 14 transition-state structures.
18. Details will be published in a full account.