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Highly selective and facile Diels–Alder reactions of masked *o*-benzoquinones with pyrroles

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Abstract—The reactions of pyrroles with 2-methoxyphenols, which proceeded smoothly at either 0°C or room temperature via the Diels–Alder reactions of in situ generated masked *o*-benzoquinones are described. © 2001 Elsevier Science Ltd. All rights reserved.

Unlike furan, pyrrole and its derivatives do not undergo cycloadditions efficiently owing to their higher resonance energy than the former. When pyrrole ring is substituted at position-1 by an electron-withdrawing group, it exhibits enhanced dienic character due to reduced aromaticity, and consequently undergoes cycloadditions with dienophiles.[1] However, the Diels–Alder reactions of pyrroles are mostly confined to electron-deficient alkynes. Alkenes generally do not react with *N*-acylated pyrroles at ambient pressure.[2] Even at high pressures, only more reactive dienophiles such as *N*-phenylmaleimide are known to participate in the Diels–Alder cycloadditions with activated pyrroles.[3–5] Added constraint to this is the competing Michael addition of pyrroles as a result of their π-excessive aromatic character. The parent pyrrole and *N*-alkylated pyrroles can undergo Michael-type addition in which the dienophile acts as an electrophile resulting in the substitution at the α-position of the pyrrole ring.[6] At this juncture, the participation of pyrroles as dienophiles in the Diels–Alder reactions appears difficult. However, the dienophilicity of pyrroles in the Diels–Alder cycloadditions was recorded[7] in few cases, albeit it demands high temperatures[8] with prolonged reaction times,[9] which often results in poor yields and unstable adducts. This contribution reports the extremely facile and efficient Diels–Alder reactions of masked *o*-benzoquinones with *N*-acyl pyrroles, which act as 2π-components.

Masked *o*-benzoquinones (MOBs),[10] a class of 2,4-cyclohexadienones, can be easily generated in situ by the oxidation of readily available 2-methoxyphenols with hypervalent iodine reagents in MeOH. Despite the fact that MOBs are electron-deficient homodienes, they readily undergo Diels–Alder reactions with both electron-poor[11] and elelctron-rich dienophiles[12] affording stable bicyclo[2.2.2]octenone derivatives. Very recently, MOBs were shown to drive heteroaromatics such as furans[13] and indoles[14] as 2π-components in the Diels–Alder reaction. The unique properties of MOBs have led us to explore their cycloaddition reactions with pyrroles.

Initially, the reactions of 2-methoxyphenols **2a–c**, with *N*-benzoylpyrrole (**3**) were investigated. Phenols **2a–c** were oxidized to the corresponding MOBs **1a–c** with diacetoxyiodobenzene (DAIB) in methanol at 0°C and the subsequent reaction with pyrrole **3** underwent smoothly at 0°C resulting in the formation of the cycloadducts **8a–c**[15] in very good yields. Encouraged by these results, the reactions of **2a–c** with *N*-benzoylpyrroles **4–6** were studied. Gratifyingly, the reactions of MOBs **1a–c** with **4–6** proceeded efficiently at either 0°C or room temperature to afford cycloadducts **9a–c**, **11a–c** in good to excellent yields (Scheme 1, Table 1). To evaluate the effect of electron-withdrawing group in the pyrrole ring, reactions of **2a–c** with *N*-acetylpyrrol-2-yl acetate (**7**) were tested. While the reactions of methyl vanillate (**2a**) and acetovanillone (**2b**) with *N*-acetylpyrrol-2-yl acetate (**7**) furnished the corresponding adducts **12a,b**, respectively, in low yields; the reaction of vanillonitrile (**2c**) did not provide the cycloadduct **12c**. These results are summarized in Table 1.

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

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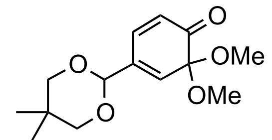
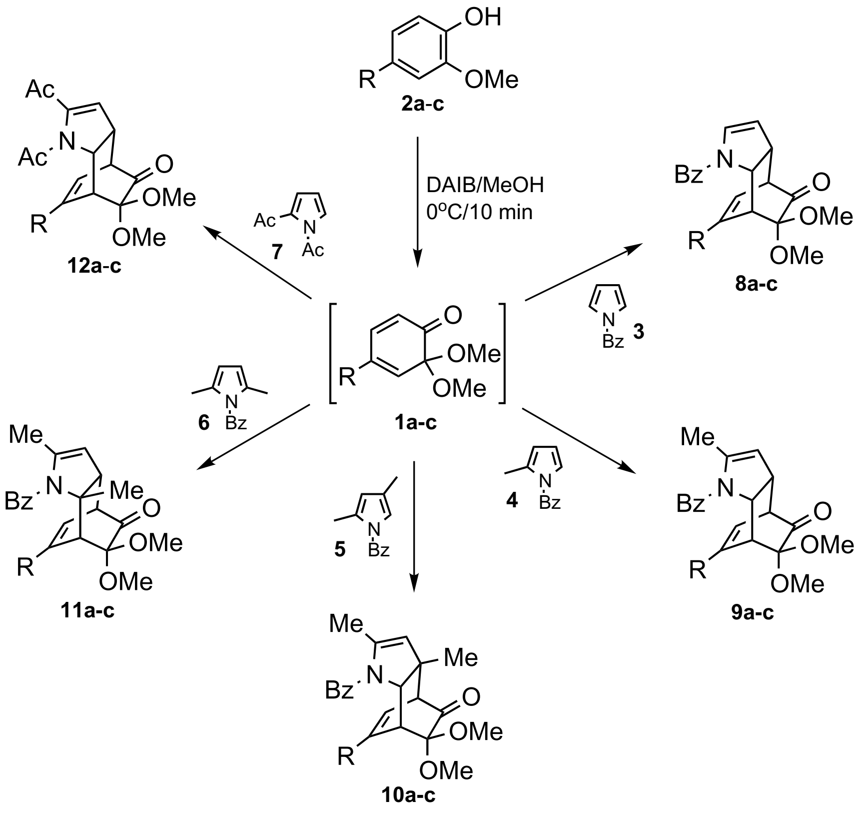
This diminished reactivity of MOBs with **7** could be due to the fact that these processes being inverse-electron-demand Diels–Alder reactions, require electron-rich dienophiles for facile cycloadditions.[12c] The moderately stable MOB **1d** did not react with pyrrole **4**. Therefore, it appears that an electron-withdrawing group at C-4 of MOB is necessary for the cycloaddition to occur.



1d

The regiochemistry of these cycloadducts was determined from ^1H–^1H decoupling NMR experiments. The stereochemical assignments of all the adducts except **10**



a: R = CO_2Me; **b**: R = COMe; **c**: R = CN

Scheme 1.

Table 1. Diels–Alder cycloadditions of pyrroles **3**–**7** with masked *o*-benzoquinones **1a**–**c**[a]

Entry	Pyrrole (equiv.)	Phenol	MOB	Temp. (°C)	Adduct/Yield (%)[b]
1	**3** (5)	**2a**	**1a**	0	**8a**/85
2		**2b**	**1b**	0	**8b**/83
3		**2c**	**1c**	0	**8c**/56
4	**4** (3)	**2a**	**1a**	0	**9a**/92
5		**2b**	**1b**	0	**9b**/84
6		**2c**	**1c**	0	**9c**/49
7	**5** (5)	**2a**	**1a**	0	**10a**/83
8		**2b**	**1b**	0	**10b**/82
9		**2c**	**1c**	0	**10c**/47
10	**6** (20)	**2a**	**1a**	rt	**11a**/64
11		**2b**	**1b**	rt	**11b**/66
12		**2c**	**1c**	rt	**11c**/55
13	**7** (20)	**2a**	**1a**	rt	**12a**/40
14		**2b**	**1b**	rt	**12b**/25
15		**2c**	**1c**	rt	**12c**/-

[a] All reactions were carried out for 1 h after the addition of pyrrole derivative.

[b] Yields are of pure and isolated products.

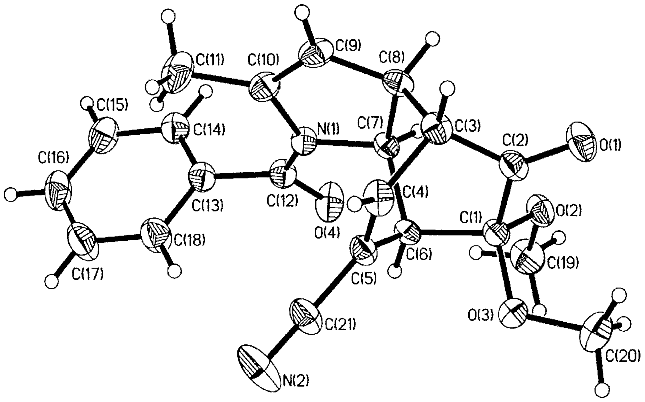
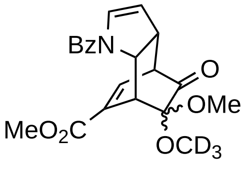


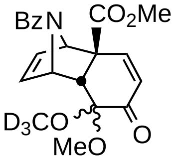
Figure 1. ORTEP plot of the crystal structure of adduct **9c** (numbering is arbitrary).

were based on the observed long-range coupling between the vinylic protons on the cyclohexenone ring and the nearest methine proton on the heterocycle. The stereochemistry of cycloadducts **10** was confirmed by comparing their ^{1}H NMR chemical shift values with that of adducts **8**, **9**, and **11**–**12**. In addition, the structure of **9c** was confirmed by the single-crystal X-ray diffraction method (Fig. 1).[16] The reactions of MOBs and pyrroles are highly chemoselective. While the unsubstituted double bond of substituted pyrroles **4** and **7** participated in the cycloaddition, α-unsubstituted double bond of pyrrole **5** took part in the reaction.

The reactions of MOBs and pyrroles can occur in one of the three possible pathways (Scheme 2). (1) Path A: a tandem process involving (i) [4+2] cycloaddition of pyrrole and MOB, where the pyrrole participates as the diene and C_4–C_5 double bond of MOB as dienophile followed by (ii) a Cope rearrangement, (2) path B: [4+2] cycloaddition of MOB and pyrrole where MOB acts as diene and pyrrole as dienophile, and (3) path C: (i) an electrophilic attack of C-5 of MOB at α-carbon of pyrrole followed by (ii) an electrophilic attack of β-carbon of pyrrole at C-2 of MOB in a double Michael-type addition. Path A is highly improbable under the reaction conditions as pyrroles (4π) cannot undergo cycloadditions at ambient pressures[3] with alkenes (2π) (vide supra). Furthermore, the reaction of MOB **1a** with pyrrole **3** was carried out in deuterated methanol in an NMR tube at 0–5°C and monitored by NMR spectroscopy. As expected, a mixture of adducts **8a′** was found during the entire course of the reaction; and the adducts **13′** were not observed providing no evidence for path A.

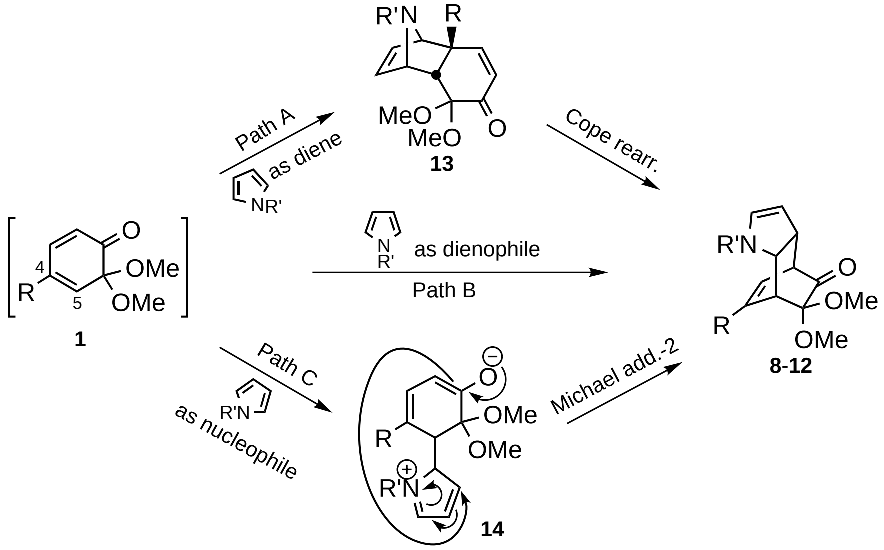


8a'

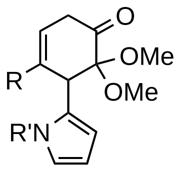


13'

Though pyrroles can also undergo Michael addition, there are no such reports on pyrroles bearing electron-with-drawing group on nitrogen in the absence of Lewis-acid. This may be due to the fact that these pyrrole derivatives are not electron-rich enough to act as Michael donors. If MOB attacks pyrrole derivatives in Michael-type addition, products of type **15** should also be formed after transfer of a proton from AcOH (produced during the oxidation with DAIB)/MeOH to the intermediate **14**. In fact, such products were not observed from MOB **1a** and **3**–**7**. To probe the influence of acetic acid present in the reaction medium, the reaction of **1a** with **3** was carried out in the presence of $KHCO_3$; the reaction provided only the cycloadduct **8a** indicating that Michael-type addition was not taking place. Thus, path C seems to be improbable; however, it cannot be completely excluded. As there is no indication for paths A and C, probably the path B involving *N*-acyl pyrroles as dienophiles is in operation.

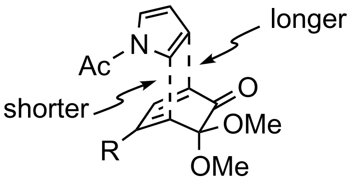


Scheme 2.



15

The stereochemical outcome of these cycloadditions is presumably due to the secondary orbital interactions. To gain better insight into the mechanism, we have computed the energies of transition-state structures for the reaction of *N*-acetylpyrrole and MOBs by ab initio RHF/3-21G method. Among all the transition-states computed, **16** (simplified structure) has the lowest energy supporting the procured regio- and stereoselectivities. The calculations also suggest that the transition-state is highly asymmetric and hence, the reaction proceeds through a non-synchronous concerted pathway.[17]



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In summary, for the first time we have described very efficient and highly selective Diels–Alder cycloadditions of pyrrole derivatives at/below room temperature. Furthermore, multifunctional molecules with a high degree of structural complexity were generated from simple aromatic compounds in a single synthetic operation.

Acknowledgements

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References

1. (a) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: New York, 1977; pp. 256–264; (b) Chadwick, D. J. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon: London, 1984; Vol. 4, pp. 261–264; (c) Toube, T. P. In *Pyrroles*, *part* 2; Jones, R. A., Ed.; John Wiley: New York, 1992; pp. 92–95.
2. (a) Gabel, N. W. *J. Org. Chem.* **1962**, *27*, 301–303; (b) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979–3982.
3. Drew, M. G. B.; George, A. V.; Isaacs, N. S.; Rzepa, H. S. *J. Chem. Soc.*, *Perkin Trans. 1* **1985**, 1277–1284.
4. *N*-Acyl pyrroles do not react with acrylates and maleates at high pressure, see: Ref. 3 and: Kotsuki, H.; Mori, Y.; Nishizawa, H.; Ochi, M.; Matsuoka, K. *Heterocycles* **1982**, *19*, 1915–1920.
5. *N*-Carbomethoxypyrrole bearing activated group (methylthio/phenylthio) at β-position underwent cycloaddition with phenyl vinyl sulfone and methyl acrylate at high pressure: Aben, R. W. M.; Keijsers, J.; Hams, B.; Kruse, C. G.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 1299–1300.
6. (a) Noland, W. E.; Lee, C. K. *J. Org. Chem.* **1980**, *45*, 4573–4582; (b) Bennett, R. A.; Cann, M. C. *J. Heterocyclic Chem.* **1994**, *31*, 293–296.
7. (a) Seitz, G.; Kämpchen, T. *Arch. Pharm. (Weinheim)* **1978**, *311*, 728–735; (b) Cobb, R. L.; Vives, V. C.; Mahan, J. E. *J. Org. Chem.* **1978**, *43*, 931–936; (c) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188–7194; (d) Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1993**, *58*, 516–519.
8. For instance, even the intramolecular Diels–Alder reactions of pyrrole tethered with 1,2,4-triazines required temperatures up to 232°C (Ref. 7d).
9. Reaction times up to 19 days were reported for intermolecular cycloadditions (Ref. 7b).
10. (a) Liao, C.-C. *Modern Methodology in Organic Synthesis*; Kodansha: Tokyo, 1992; pp. 409–424; (b) Quideau, S.; Pouy-segu, L. *Org. Prep. Proced. Int.* **1999**, *31*, 617–680.
11. (a) 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; (b) Yen, C.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2909–2912.
12. (a) Arjona, O.; Medel, R.; Plumet, J. *Tetrahedron Lett.* **1999**, *40*, 8431–8433; (b) Gao, S.-Y.; Lin, Y.-L.; Rao, P. D.; Liao, C.-C. *Synlett* **2000**, 421–423; (c) Gao, S.-Y.; Ko, S.; Lin, Y.-L.; Peddinti, R. K.; Liao, C.-C. *Tetrahedron* **2001**, *57*, 297–308.
13. (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; (c) Avalos, M.; Babiano, R.; Bravo, J. L.; Cabello, N.; Cintas, P.; Hursthouse, M. B.; Jimenez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron Lett.* **2000**, *41*, 4101–4105.
14. Hsieh, M.-F.; Rao, P. D.; Liao, C.-C. *Chem. Commun.* **1999**, 1441–1442.
15. 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; the majority of the adducts provided satisfactory elemental analyses.
16. CCDC deposition No. 151859.
17. Details will be published in a full account.