



Diels–Alder reactions of halogenated masked *o*-benzoquinones: synthesis of halogen-substituted bicyclo[2.2.2]octenones

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Dedicated to Professor Chun-Chen Liao for his outstanding contributions to the development of 'masked *o*-benzoquinone chemistry'

ABSTRACT

Intermolecular Diels–Alder reactions of 4-halo masked *o*-benzoquinones generated from hypervalent iodine-mediated oxidation of 4-halo-2-methoxyphenols, with electron-deficient dienophiles—methyl acrylate, methyl methacrylate and methyl vinyl ketone—leading to halo-substituted bicyclo[2.2.2]octenones, are described. The halo-benzoquinone monoketals can be isolated and characterized. The dimerization of these intermediates is not observed under the reaction conditions.

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Orthoquinone monoketals or masked *o*-benzoquinones (MOBs), a class of linearly conjugated cyclohexadienones, are very useful intermediates in organic synthesis.¹ These highly reactive building blocks often undergo self-dimerization via a Diels–Alder reaction in the absence of an external reactant. The MOBs can be easily generated in situ in methanol with hypervalent iodine reagents.^{2,3} Owing to their high reactivity, the in situ generated MOBs can be trapped with dienophiles in the Diels–Alder reaction. The pioneering work by Liao and co-workers disclosed the substituent effect on the reactivity and stability of MOBs.^{1a,c} His research group generated a wide variety of these intermediates and evaluated their potential in inter- and intramolecular Diels–Alder reactions to furnish synthetically useful bicyclo[2.2.2]octenone derivatives.

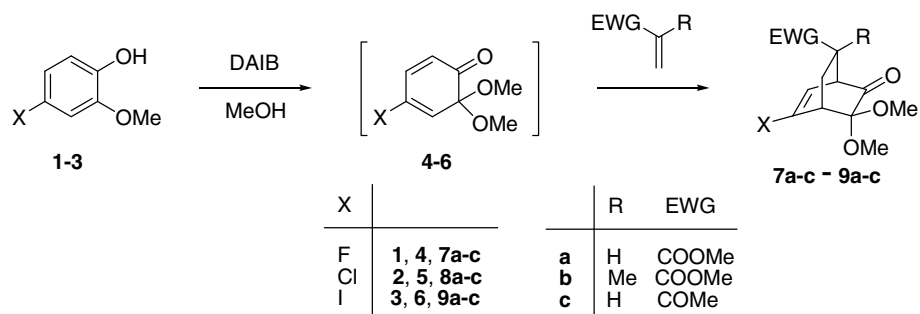
The extent of dimerization of linearly conjugated cyclohexadienones is governed by the nature and pattern of substituent(s) on the phenolic moiety. Several appropriately substituted cyclohexa-2,4-dienones have been generated and some of them have been isolated.⁴ It occurred to us that the introduction of halo substituents such as fluorine, chlorine and iodine at position-4 of the MOBs, not only offers stability for these cyclohexa-2,4-dienones, but also facilitates their isolation and characterization. The halo substituents of Diels–Alder adducts resulting from the corresponding MOBs may be employed as handles for further synthetic manipulations. Accordingly, we selected 4-fluoro-2-methoxyphenol, 4-chloro-2-methoxyphenol and 4-iodo-2-methoxyphenol⁵ as precursors for the generation of 4-halo-MOBs. Herein, we disclose our preliminary results on the Diels–Alder reactions of 4-halo MOBs with electron-deficient dienophiles.

Initially, the oxidation of halo-guaiacols **1–3** with diacetoxyiodobenzene (DAIB) was carried out in methanol to ascertain the stability of 4-halo-MOBs. After 10 min of stirring of a mixture of halo-guaiacol and DAIB in methanol at 0 °C, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography on a silica gel column to obtain pure halo-MOBs in very good yield. The thus obtained intermediates **4–6** were characterized by IR, ¹H and ¹³C NMR spectral data.⁶ Encouraged by this result, we then proceeded to synthesize halo-substituted bicyclo[2.2.2]octenone derivatives. At the outset, we carried out the Diels–Alder reaction of 4-fluoro MOB (**4**) with methyl acrylate (25 equiv) in methanol for 24 h at room temperature and after usual workup, the adduct **7a** was isolated in overall yield of 59% in two steps. To simplify the process, we then carried out the oxidation of 4-fluoroguaiacol (**1**) with DAIB in methanol in the presence of methyl acrylate at 0 °C and then the contents were allowed to stir at room temperature. The reaction was continued at the same temperature (method A)⁷ for 24 h. After the usual workup followed by silica gel column chromatography, the Diels–Alder adduct **7a** was isolated in 61% yield. Alternatively, the MOB **4** was generated at 50 °C in the presence of methyl acrylate and the reaction was complete in 1 h to furnish the adduct **7a** in 72% isolated yield (method B).⁷ The [4+2] cycloaddition of the in situ generated **4** with methyl methacrylate and methyl vinyl ketone was carried out to furnish fluorinated bicyclo[2.2.2]octenone derivatives **7b** and **7c**, respectively (Scheme 1 and Table 1). The one-pot oxidative ketalization–Diels–Alder protocol was then extended for chloro- and iodo-guaiacols (**2** and **3**), and the resultant adducts **8a–c–9a–c** were obtained in high yields. The results are summarized in Table 1.

The structures of bicyclo[2.2.2]octenones **7a–c–9a–c** were assigned on the basis of their IR, ¹H (500 MHz) and ¹³C (125 MHz) NMR, DEPT and GC–MS/ESI–MS spectral analysis. Of the possible

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Scheme 1.

Table 1
Diels-Alder reactions of halo-MOBs **4–6** generated from 4-halo-guaiacols **1–3**^a

Entry	4-Halo-2-methoxyphenol	MOB	Dienophile	Method ^b /time ^c (h)	Product	Yield ^d (%)
1 2				A/24 h B/1 h		61 72
3 4	1	4		A/24 h B/1 h		50 61
5 6	1	4		A/24 h B/1 h		89 91
7 8				A/24 h B/1 h		77 92
9 10	2	5		A/24 h B/1 h		64 72
11 12	2	5		A/24 h B/1 h		70 78
13				A/44 h		80
14	3	6		A/47 h		81
15	3	6		A/28 h		76

^a The reactions were carried out with 1 mM of halo-guaiacol, 25 mM of dienophile and 1.1 mM of DAIB in 10 mL of MeOH.^b Method A: room temperature; method B: 50 °C (see Ref. 7).^c Represents the reaction time after the addition of DAIB.^d Yield of pure and isolated products.

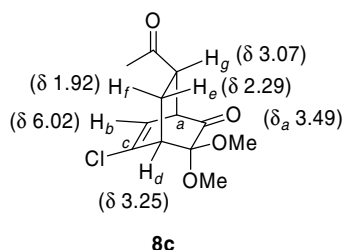


Figure 1.

four isomers, only the one possessing *ortho* regiochemistry (EWG is adjacent to octenone carbonyl function) and *endo* stereochemistry (EWG is *anti* to octenone carbonyl function) was formed in this study. The regiochemistry of these cycloadducts was deduced from ^1H – ^1H decoupling NMR experiments. The assigned stereochemistry is based on the coupling constants between H_e – H_g and H_f – H_g . For instance, these J values for the adduct **8c** are 10.0 and 6.0 Hz, respectively. The larger J value for H_e – H_g reveals the *cis* orientation of the protons, H_e and H_g , thus confirming the *endo* stereochemistry of the [4+2] cycloadduct (Fig. 1). The *endo* stereochemistry of cycloadduct **9c** was further confirmed by the two-dimensional rotational frame nuclear Overhauser effect spectroscopy (ROESY) measurements.⁸ The observed regio- and stereoselectivities are in accordance with the literature precedents.^{3,4b,9}

In conclusion, bicyclo[2.2.2]octenones derivatives bearing halogen substituents are accessed in a highly regio- and stereoselective manner from the corresponding 4-halo-guaiacols. We have demonstrated for the first time that the title 4-halo-orthobenzoquinone monoketals ($\text{X} = \text{F}, \text{Cl}, \text{I}$) are sufficiently stable for isolation and characterization.

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- Spectral data for MOB **4**: ^1H NMR (CDCl_3 , 500 MHz): δ 6.82 (d, $J = 8.5$ Hz, 1H), 6.49 (d, $J = 3.0$ Hz, 1H), 6.39 (dd, $J = 8.5, 3.0$ Hz, 1H), 3.81 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 187.4, 181.6, 158.6, 137.2, 134.4, 107.6, 56.2. MOB **5**: ^1H NMR (CDCl_3 , 500 MHz): δ 6.78 (dd, $J = 10.5, 2.0$ Hz, 1H), 6.44 (d, $J = 2.0$ Hz, 1H), 6.05 (d, $J = 10.5$ Hz, 1H), 3.39 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 192.8, 141.3, 131.0, 130.7, 126.5, 92.1, 50.1. MOB **6**: ^1H NMR (CDCl_3 , 500 MHz): δ 6.99–6.96 (m, 2H), 5.80 (d, $J = 9.5$ Hz, 1H), 3.37 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 192.8, 146.9, 143.9, 126.3, 93.3, 91.1, 50.2.
- General procedure: Method A: To a solution of 4-halo-2-methoxyphenol (1 mM) and dienophile (25 mM) in anhydrous methanol (4 mL) was added a solution of DAIB (1.1 mM) in anhydrous methanol (6 mL) over a period of 30 min at 0 °C under nitrogen atmosphere. After 10 min, the ice bath was removed and the contents were allowed to stir at room temperature for the time specified in Table 1. After the reaction was complete, the reaction mixture was concentrated using a rotary evaporator under reduced pressure, and the residue was purified by silica gel column chromatography with 10% ethyl acetate in hexanes to furnish the cycloadduct.
- Method B: To a solution of 4-halo-2-methoxyphenol (1 mM) and dienophile (25 mM) in anhydrous methanol (4 mL) was added a solution of DAIB (1.1 mM) in anhydrous methanol (6 mL) over a period of 1 h at 50 °C under nitrogen atmosphere. The stirring was continued for 1 h at 50 °C for the reaction to reach completion, and then the products were purified as in method A.
- Details will be published in full account.
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