Diels–Alder Reactions of Substituted Cyclohexa-2,4-dienones with Alkenes and Alkynes

Dimitris Gabrilidis,[1] Christos Kalogiros, Lazaros P. Hadjiarapoglou*

Section of Organic Chemistry and Biochemistry, Department of Chemistry, University of Ioannina, 45110 Ioannina, Greece
Fax +30(265)1098799; E-mail: lxatziar@cc.uoi.gr

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Abstract: Substituted cyclohexa-2,4-dienones, generated in situ by pyrolysis of the appropriate dimer, participated in Diels–Alder reactions with various dienophiles to afford bicyclo[2.2.2]octenone and bicyclo[2.2.2]octadienone derivatives in high yields.

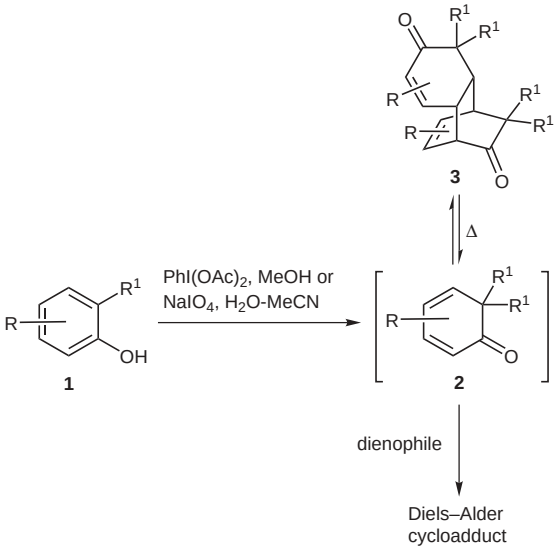
Key words: masked *o*-benzoquinone, spiroepoxycyclohexa-2,4-dienone, retro-Diels–Alder reaction, Diels–Alder reaction, tandem reaction

The structural complexity of natural products demands the development of new and efficient strategies to construct complex polycyclic frameworks from simple starting materials with high selectivities.[2] Occasionally, tandem,[3] cascade,[4] or multicomponent reactions[5] are developed to achieve this objective.

Substituted cyclohexa-2,4-dienones,[6] i.e. **2**, constitute a synthetically useful class of compounds. These compounds can be generated by in situ oxidation of the readily available *o*-alkoxy phenols using hypervalent iodine reagents[7] in the presence of an alcohol or a salicyl alcohol using the Adler–Baker oxidation ($NaIO_4$).[8] Alternatively, when the substituted cyclohexa-2,4-dienones dimerized faster than trapped, thermolysis[9] of dimer **3** is a convenient source of **2** (Scheme 1).

Substituted cyclohexa-2,4-dienones have been shown to be efficient 4π-components in Diels–Alder reactions undergoing regio- and stereoselective cycloaddition processes with electron-poor as well as electron-rich dienophiles.[10] Other 2π-components used in these reactions have been heteroaromatic compounds such as furan,[11] pyrrole,[12] and thiophene[13] derivatives. The resulting bicyclo[2.2.2]octenone derivatives have been used as starting materials for the synthesis of different targets, including polysubstituted cyclohexenes,[14] *cis*-decalins,[15] bicyclo[2.2.2]derivatives,[16] and triquinanes,[17] as key steps in several complex total syntheses of natural products.[18]

We report herein our results of utilizing dimers **3**, as a source of substituted cyclohexa-2,4-dienones **2**, to synthesize various bicyclo[2.2.2]octenone and bicyclo[2.2.2]octadienone derivatives. The required dimer **3a** was obtained in 50–62% yield by the oxidation of *o*-eugenol[19] with (diacetoxy)iodobenzene in MeOH at room temperature, while, dimer **3b** was obtained in 65–70% yield when



Scheme 1

salicyl alcohol **1b** was subjected[8] to sodium *meta*-periodate oxidation in aqueous acetonitrile.

The substituted cyclohexa-2,4-dienones **2** generated in situ by the pyrolysis of dimer **3** in *o*-xylene in a sealed tube at 230 °C (sand bath), furnished Diels–Alder cycloadducts in the presence of appropriate dienophile as shown in Table 1. Cycloadduct **4a**,[20] as a single isomer, was obtained in 95% yield, when styrene was allowed (at 230 °C in a sealed tube) to undergo reaction with masked *o*-benzoquinone (**2a**), generated in *o*-xylene by thermolysis of dimer **3a** (Scheme 2). The oxidation of *o*-eugenol with (diacetoxy)iodobenzene in the presence of styrene at room temperature was found to be sluggish, it produced substantial amounts of dimer **3a** and some desired product **4a**. Similarly, cycloadduct **4b**, as a single isomer, was produced in 52% yield when styrene was allowed (at 230 °C in sealed tube) to react with spiroepoxycyclohexa-2,4-dienone (**2b**), generated by thermolysis of dimer **3b** (Scheme 3). In the past, it has been reported[6a] that pyrolysis of dimer **3b** in the presence of dienes/olefins failed to yield Diels–Alder adducts due to thermal rearrangement of the oxirane ring followed by a retro Diels–Alder reaction and aromatization.

The reaction with an electron-rich dienophile, such as phenylthioethylene, was also considered. The substituted cyclohexa-2,4-dienones **2**, generated by pyrolysis of

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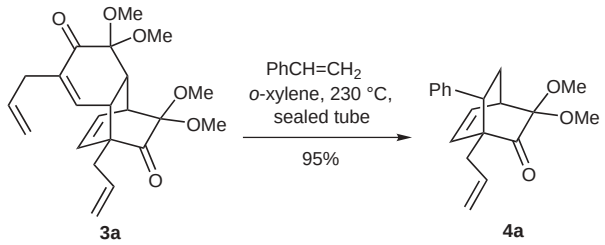
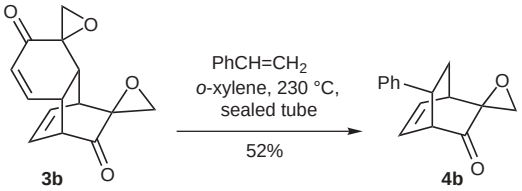


Scheme 2



Scheme 3

dimers **3**, reacts with phenylthioethylene to give the corresponding cycloadducts **4c**,**d** as single diastereomers and in acceptable yields (Table 1). Even if acetylenic dienophiles are expected to be less reactive, bicyclo[2.2.2]octadienones **5** and **6** were isolated in good yields when substituted cyclohexa-2,4-dienones **2** were generated in the presence of an acetylenic dienophile. Methyl propiolate gave two regioisomers **5a** and **6a** (75:25) upon reaction with masked *o*-benzoquinone (**2a**) and **5b**, **6b** (83:17) upon reaction with spiroepoxycyclohexa-2,4-dienone (**2b**), whereas dimethyl acetylenedicarboxylate afforded cycloadducts **5c** and **5d** as single isomers. It may be noted that the dimer **2b** and dicyclopentadiene provided the cycloadduct **7**, used as starting material in the total synthesis[21] of (±)-hirsutene, via the Diels–Alder reaction of their in situ generated monomers.

The Diels–Alder cycloadducts thus obtained, could be easily isolated after column chromatography on silica gel. Their structures were deduced by spectral studies. By comparison of the yields of these cycloadditions, it is clear that the Diels–Alder reactivity of masked *o*-benzoquinone (**2a**) is better than the corresponding spiroepoxycyclohexa-2,4-dienone (**2b**).

In summary, we have demonstrated that a tandem retro-Diels–Alder sequence employing dimers **3** provides an effective route to bicyclo[2.2.2]octenone and bicyclo[2.2.2]octadienone derivatives, which are valuable starting materials for the total synthesis of various natural products. We are currently examining the optimization and applications of this useful synthetic sequence.

Table 1 Synthesis[a] of Bicyclo[2.2.2]octenone and Bicyclo[2.2.2]octadienone Derivatives **4**–**7**

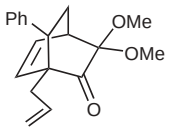
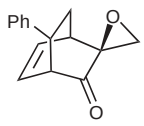
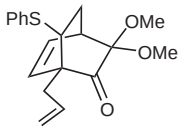
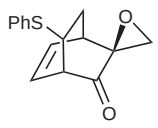
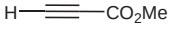
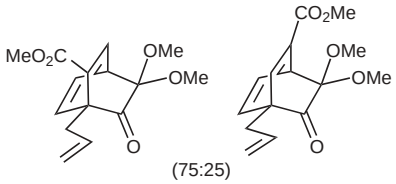
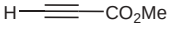
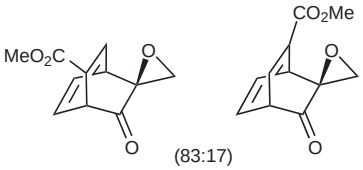
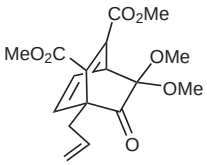
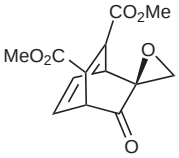
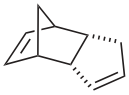
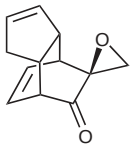
Entry	Dienophile	Dimer	Time (h)	Product	Yield (%)[b]
1		**3a**	43	 **4a**	95
2		**3b**	25	 **4b**	52
3		**3a**	25	 **4c**	77
4		**3b**	46	 **4d**	69
5		**3a**	27	 (75:25) **5a** **6a**	89

Table 1 Synthesis[a] of Bicyclo[2.2.2]octenone and Bicyclo[2.2.2]octadienone Derivatives **4**–**7** (continued)

Entry	Dienophile	Dimer	Time (h)	Product	Yield (%)[b]
6		**3b**	43	 (83:17) **5b** **6b**	78
7		**3a**	21	 **5c**	81
8		**3b**	68	 **5d**	79
9		**3b**	19	 **7**	46

[a] All reactions were carried out by heating at 230 °C in a sealed tube a mixture of dimer **3** (1.0–2.0 mmol), dienophile (10.0 mmol) in *o*-xylene (3 mL) for the given time.
[b] Yield of isolated product after column chromatography on silica gel.

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(20) **Representative Experimental Procedure.**
Synthesis of 4a: A mixture of dimer **3a** (0.39 g, 1.0 mmol), styrene (1.0 g, 9.62 mmol) in *o*-xylene (3 mL) was heated at 230 °C for 43 h in a sealed tube. The solvent was evaporated and the residue was chromatographed on silica gel (CH_2Cl_2 as eluant) to afford cycloadduct **4a** as colorless oil (0.57 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (ddd, *J* = 2.8, 6.6, 13.2 Hz, 1 H), 1.81 (dd, *J* = 8.0, 14.2 Hz, 1 H), 2.35 (dd, *J* = 6.1, 14.2 Hz, 1 H), 2.61 (ddd, *J* = 2.8, 9.6, 10.1 Hz, 1 H), 3.04 (dd, *J* = 6.7, 9.6 Hz, 1 H), 3.19–3.21 (m, 1 H), 3.37 (s, 3 H), 3.42 (s, 3 H), 4.78–4.82 (m, 1 H), 4.91–4.94 (m, 1 H), 5.66–5.78 (m, 1 H), 6.00 (d, *J* = 8.1 Hz, 1 H), 6.62 (dd, *J* = 7.2, 8.1 Hz, 1 H), 7.08–7.19 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.4, 34.4, 38.9, 44.7, 49.7, 50.3, 56.0, 94.0, 117.8, 126.9, 128.3, 128.9, 134.5, 134.6, 143.1, 202.4. Anal. Calcd for $C_{19}H_{22}O_3$ (298.38): C, 76.48; H, 7.44. Found: C, 76.24; H, 7.52.
Synthesis of 4b: A mixture of dimer **3b** (0.48 g, 2.0 mmol), styrene (1.00 g, 9.62 mmol) in *o*-xylene (3 mL) was heated at 230 °C for 43 h in a sealed tube. The solvent was evaporated and the residue was chromatographed on silica gel (CH_2Cl_2 as eluant) to afford cycloadduct **4b** as colorless oil (0.47 g, 52% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.82–1.90 (m, 1 H), 2.61–2.74 (m, 2 H), 2.89 (d, *J* = 6.4 Hz, 1 H), 3.20 (d, *J* = 6.1 Hz, 1 H), 3.42–3.53 (m, 2 H), 6.18–6.24 (m, 1 H), 6.70–6.76 (m, 1 H), 7.16–7.33 (m, 5 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 30.5, 38.9, 40.3, 52.8, 54.9, 126.7, 127.1, 127.5, 128.3, 135.4, 143.4, 204.4. Anal. Calcd for $C_{15}H_{14}O_2$ (226.28): C, 79.62; H, 6.25. Found: C, 79.44; H, 6.40.

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