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SODIUM 6-METHOXY-(E,E)-3,5-HEXADIENOATE: A USEFUL DIENE IN THE AQUEOUS DIELS-ALDER REACTION

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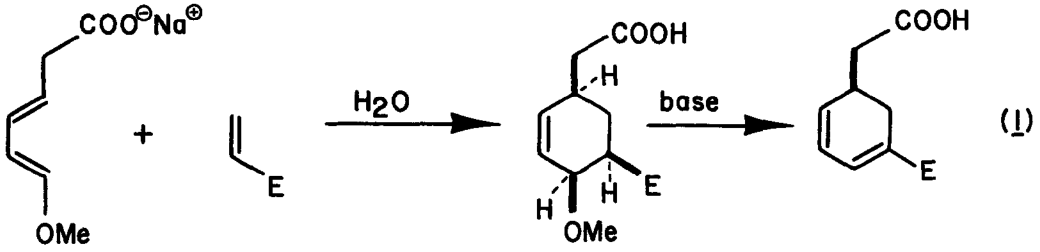
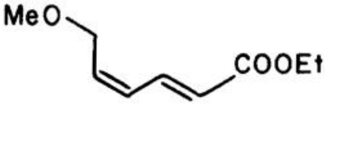
Summary: The sensitive dienol ether functionality in sodium 6-methoxy-(E,E)-3,5-hexadienoate has been shown to be compatible with the conditions of the aqueous Diels-Alder reaction.

In connection with a variety of synthetic objectives and our interest in developing the potential of the aqueous Diels-Alder reaction,[1] we set out to examine the transformation generalized in equation 1 in which the initially formed adduct **3** is capable of either directly undergoing, during the course of the Diels-Alder reaction, or in a separate operation, β-elimination of methoxide with formation of **4**. Of major concern to us was the compatibility of the sensitive dienol ether with the aqueous, often acidic, conditions[2] of the reaction and the regiochemical consequences of bringing **1** and **2** together in water.



1 2 3 4

Diene **1** was generated in situ from 6-methoxy-(E,E)-3,5-hexadienoic acid (**7**) which was prepared from 4-methoxy-(Z)-2-buten-1-ol (**5**).[3] Oxidation [$(COCl)_2$, DMSO, i-Pr_2NEt, CH_2Cl_2] of **5** and subsequent condensation with the sodium salt of triethylphosphonoacetate in tetrahydrofuran afforded ethyl 6-methoxy-2(E),4(Z)-hexadienoate (**6**). Treatment of **6** with potassium hydroxide in aqueous methanol provided in 95% yield the corresponding acid which was quantitatively deconjugated (2.2 equiv. LDA, THF, -78°C) to **7**.[4] Deconjugation of the 6-methoxy-(E,E)-



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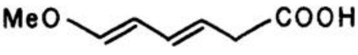

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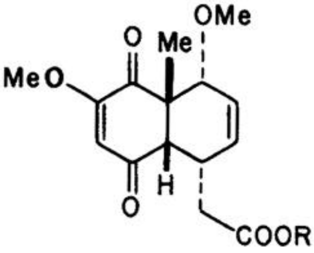
2,4-hexadienoic acid, readily available from 4-methoxy-(E)-2-buten-1-ol, provided mainly the undesired 6-methoxy-3(E)-5(Z)-hexadienoic acid.

The compatibility of diene **1** with the aqueous Diels-Alder reaction and the regiochemical question were initially addressed by examining the condensation of 1 with substituted benzoquinones. Reaction of 2-methyl-6-methoxybenzoquinone with 4.75 equivalents of sodium 6-methoxy-(E,E)-3,5-hexadienoate (**1**) [generated in situ from 5.0 equiv of **1** and 4.75 equiv of sodium bicarbonate]^2 in water (ca. 2.0 M in diene) gave rise after 10 min to a 93% yield of an adduct **8** (R=H) which was characterized as its methyl ester **8** (R=Me), mp 114-116°C, by treatment of the acid with ethereal diazomethane. The regiochemical issue was readily resolved by examination of the ^{1}H NMR (360 MHz) spectra of adduct **8** (R=Me). For comparison purposes we examined the reaction of 2-methyl-6-methoxybenzoquinone with methyl 6-methoxy-(E,E)-3,5-hexadienoate in benzene at room temperature and 80°C. No reaction occurred at room temperature after 4 h. In contrast a 69% yield of **8** (R=Me) was isolated after 12 h at 80°C. Diene **1** is capable of surviving long reaction times. For instance, the condensation of **1** with the sluggish dienophile 2-methyl-1,4-naphthoquinone in water at ambient temperature required 40 h to realize a > 95% yield of adduct **9**, mp 128-129°C, after esterification.^{5}



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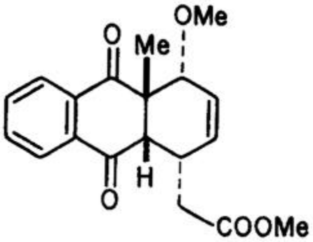

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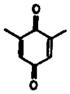
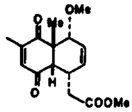
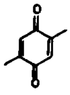
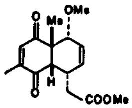
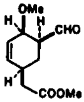
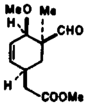
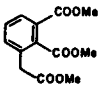
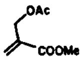
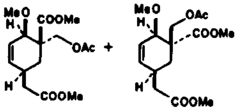
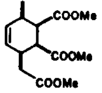
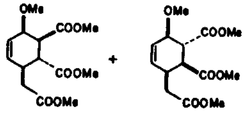
Diene **1** is also compatible with long reaction times at elevated temperatures. For

TABLE I.[a] Reaction of Sodium 6-Methoxy-(E,E)-3,5-hexadienoate in Water with Some Standard Dienophiles.

Entry	Dienophile	Temperature	Time	Product(s)[b]	Yield[c]
1		R.T.	0.5 h		67%
2		R.T.	3 h		66%
3	$CH_2{=}CHCHO$	R.T.	3 h		76%
4	$CH_2{=}C(Me)CHO$	R.T.	4 h		65%[d]
5	$MeOOCC{\equiv}CCOOMe$	R.T.	24 h		50%
6		R.T.	72 h		63%[e]
7	Dimethyl Maleate	50°C	48 h		62%
8	Dimethyl Fumarate	50°C	24 h		71%[f]

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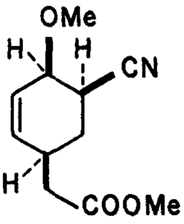
[a] ALL REACTIONS WERE CARRIED OUT 2.0 M IN DIENE. A FIVE-FOLD EXCESS OF DIENE WAS EMPLOYED. [b] PRODUCTS WERE CHARACTERIZED AS THEIR METHYL ESTERS. [c] YIELDS REPORTED ARE FOR CHROMATOGRAPHICALLY PURE MATERIALS. [d] APPROXIMATELY 3% OF THE CORRESPONDING EXO ADDUCT WAS ISOLATED. [e] THE ENDO:EXO RATIO WAS 2:1. [f] THE PRODUCT RATIO WAS 1:1.

example, condensation of diene **1** with the sluggish dienophile, acrylonitrile, required heating at 50°C for 72 h in order to realize an 80% yield of Diels-Alder adduct **10.** Additional examples appear in the Table. It will be noted that all the reactions cited in the Table give rise to endo Diels-Alder adducts. In the case of methyl acetoxymethylacrylate (entry 6), a 2:1 endo:exo ratio was observed. The sensitive endo adduct isolated from the reaction of 1 with acrolein underwent β-elimination with the formation of **11** upon exposure to silica gel. In the reaction of 1 with dimethyl acetylenedicarboxylate (entry 5) the endo adduct **12** could not be detected.



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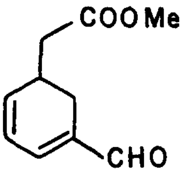

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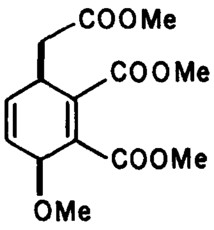

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2. Cf. Grieco, P.A.; Garner, P.; Yoshida,K.; Huffman, J.C. Tetrahedron Lett., **1983**, 24, 3087.
3. Kalinowski, H.-O.; Grass, G.; Seebach, D. Chem. Ber., **1981**, 114, 477.
4. Zimmerman, M.P. Syn Commun., **1977**, 7, 189. Kende, A.S.; Toder, B.H. J. Org. Chem., **1982**, 47, 168.
5. The benzoquinone Diels-Alder adducts with the exception of **8** upon exposure to silica gel undergo isomerization to the trans fused adducts.

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