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SITE SELECTIVE CYCLOADDITION REACTION OF 1-METHOXY-1-TRIMETHYLSILOXY-1,3,5-HEXATRIENE WITH DIENOPHILE

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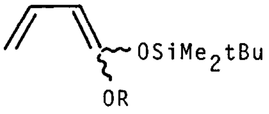
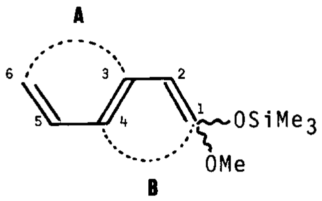
Abstract: The Diels-Alder reaction of the title triene occurred at the site of C-3-C-6 rather than of intuitively favored C-1-C-4, as the result of the prevailing steric effect over the orbital effect.

The Diels-Alder reaction of siloxy-substituted 1,3-dienes has been one of the growth areas of silyl enol ether chemistry in the last five years.[1] The main advantages of siloxybutadienes as Diels-Alder dienes are high reactivity and regioselectivity. The electron-donating nature of a siloxy group raises the HOMO energy and increases the size of coefficient at the termini of the silyl enol ether.[2] Disiloxy-substituted dienes enjoy these characteristics more effectively and are fruitfully utilized in the syntheses of six-membered carbo- and heterocycles.[1] Among them, parent 1-alkoxy-1-siloxybutadiene 1 has recently been prepared and shown to be a vinylketene equivalent in [4+2] cycloaddition reactions.[3] As one of the vinylogous system of this diene 1, namely, extender triene system, we found the interesting site selective cycloaddition reaction of 1-methoxy-1-trimethylsiloxy-1,3,5-hexatriene 2, in which an elongation of 1,4-addition was observed; the reaction took place at C-3 and C-6 rather than at C-1 and C-4 which were expected positions based on the simple orbital theory.



1



2

The 1,1-dioxy-triene 2 was prepared by the silylation of the lithium enolate obtained from deconjugated methyl sorbate (3)[4] with lithium diisopropylamide (LDA). The direct treatment of methyl sorbate itself with LDA followed by the silylation failed.[5]

Typically, the Diels-Alder reaction of 2 was carried out by mixing with maleic anhydride (4a) in benzene at room temperature, and the reaction was completed within 15 min. The cycloadduct 5a was obtained in 76% yield after chromatographic separation during which desilylation occurred. The structure was elucidated by the spectral data; in the IR spectrum, the absorption of the carbonyl group appeared at 1715 cm^{-1}, evidencing the absence of conjugation with an alkene, and in the ^{1}H-NMR spectrum, the ester methyl group was observed as a sharp singlet at δ 3.72 instead of vinyl protons in addition to the olefinic protons due to cyclohexene. These inspections apparently indicate that the cycloaddition is involving the C-3 and C-6 carbons (**A**) rather than the C-1 and C-4 carbons (**B**). As for the relative reactivity with 4a, the triene 2 cycloadded more readily than the diene 1 (30 min, 70° C).[3] The regio- and stereoselectivity was exemplified in the reaction with methacrolein (4d), an unsymmetrical dienophile; the cycloadduct 5d was ortho-directed and formed in the cis/trans ratio with 85/15, which was determined by ^{1}H-NMR spectral comparison with the authentic sample.[4] These results and the other examples are summarized in the Table.

The CNDO/2 calculation for 1,1-dimethoxy-1,3,5-hexatriene suggested that the size of the HOMO coefficient is the largest at C-4 (Fig 1), and therefore, the cycloaddition reaction of 2 with an electron-defficient dienophile should proceed through C-1-C-4 site selection if it is controlled by the orbital effect. However, actually, the cycloadduct 5 resulted from C-3-C-6 site selection; which is the second choice between the two possibilities **A** and **B** . This is attributed to the steric hindrance of either a siloxy or a methoxy group, which significantly reduced diene reactivity at the 1-position.[6] The above cycloaddition reaction sets one of the remarkable examples that the orbital effect is overwhelmed by the steric effect.

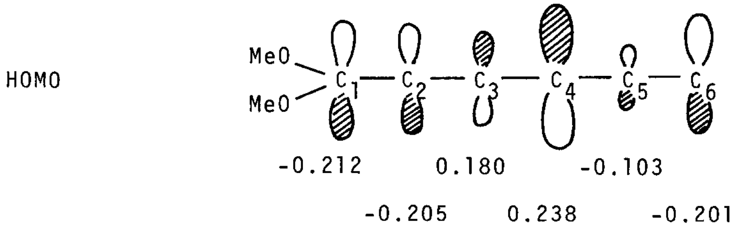
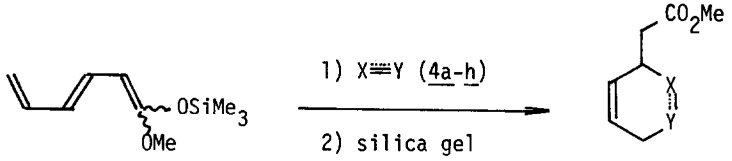


Fig 1. HOMO coefficient of 1,1-dimethoxy-1,3,5-hexatriene

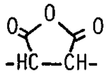
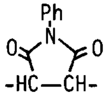
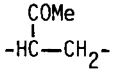
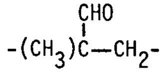
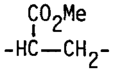
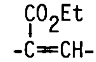
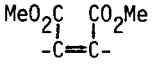
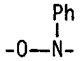
From the synthetic points of view, the triene 2 undergoes thermal [4+2] cycloaddition reaction more smoothly than 3, although both of them give the same product.[4,7] Then, 2 is suitable for thermally unstable dienophiles; for example, with nitrosobenzene (4h), the dihydrooxazine 5h was obtained in good yield. The neighbouring substituents of the cycloadducts can be further used

Table Cycloaddition reaction of the triene 2 with a variety of dienophiles.



2

5a-h

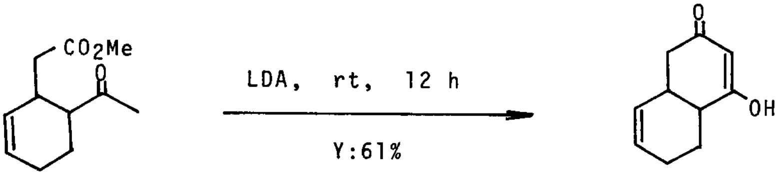
	-X═Y-
a	
b	
c	 $-\overset{COMe}{HC}-CH_2-$
d	 $-(CH_3)\overset{CHO}{C}-CH_2-$
e	 $-\overset{CO_2Me}{HC}-CH_2-$
f	 $-\overset{CO_2Et}{C}=CH-$
g	 $-\overset{MeO_2C}{C}=\overset{CO_2Me}{C}-$
h	 $-O-\overset{Ph}{N}-$

Dienophile	Reaction conditions[a] temp.	time	Product[b]	yield
4a	rt	15 min	5a	76%
4b	rt	1 hr	5b	100%
4c	90°C	30 hr	5c	98%
4d	110°C	9 hr	5d	36%
4e	90°C	40 hr	5e	89%
4f	90°C	70 hr	5f	35%
4g	100°C	5 hr	5g	62%
4h	rt	30 min	5h	82%

[a] The solvent used was benzene except for 4d (toluene).

[b] The products were obtained in a crystal for 5a (mp 97-98°C) and in oils for all others, and their cis/trans ratio ranged from 8/2 to 9/1 (^{1}H- and ^{13}C-NMR spectra).

for the condensation reaction to a bicyclic compound as demonstrated below as an example. Thus, readily obtainable 1-methoxy-1-siloxy-hexatriene 2 is useful as a novel building block in the Diels-Alder chemistry.



5c

6

General Procedure for cycloaddition reaction of 2 --- The starting triene 2 was prepared as follows; to a solution of LDA (35 mmol) in THF (70 ml) was added 3 (3.0g, 23 mmol) in THF (30 ml) at -78°C under a nitrogen atmosphere and the solution was stirred for 30 min. Then trimethylsilyl chloride (7.6 ml, 60 mmol) was added and the mixture was stirred for 2 h and for further 30 min at room temperature. After exchange of the solvent, filtration of the precipitates and evaporation of the solvent, the resulting oil was subjected to trap-to-trap distillation to give 2 (4.0g, 88%). A solution of thus prepared 2 (198 mg, 1 mmol) and a dienophile (1 mmol) in benzene (2 ml) was stirred in a capped glass cylinder under an atmosphere of argon at room or elevated temperature. After an appropriate time (Table 1), evaporation of the solvent left the residue which was chromatographed on a silica gel column (Fuji-Davison BW-300, hexane/ethyl acetate=10/1) to give the product 5. For spectral data, see footnote 8.

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8. Spectral data for the cycloadduct 5.[a]

Compd.	IR (cm^{-1})[b]	^{1}H-NMR (δ)[c]
5a	1840, 1760, 1715	5.6-6.2 (2H, m), 3.72 (3H, s), 2.3-3.7 (7H, m).
5b	1720, 1700, 1595	7.0-7.5 (5H, m), 5.7-6.2 (2H, m), 3.67 (3H, s), 2.3-3.6 (7H, m).
5c	1730, 1705	5.6-6.7 (2H, m), 3.60 (3H, s), 2.13 (3H, s), 1.5-3.2 (8H, m).
5e	1735	5.6-5.7 (2H, m), 3.61 (6H, s), 1.6-3.2 (8H, m).
5f	1730, 1700, 1630	6.98 (1H, t, J=4 Hz), 5.6-5.8 (2H, m), 4.18 (2H, q, J=7 Hz), 3.61 (3H, s), 3.3-3.6 (1H, m), 2.6-3.0 (2H, m), 2.71 (1H, dd, J=16 and 4 Hz), 2.18 (1H, dd, J=16 and 9 Hz), 1.30 (3H, q, J=7 Hz).
5g	1730, 1700, 1645	5.7-5.8 (2H, m), 3.74 (6H, s), 3.66 (3H, s), 3.4-3.7 (1H, m), 3.13 and 2.78 (each 1H, ABq, J=14 Hz), 2.70 (1H, dd, J=16 and 9 Hz), 2.23 (1H, dd, J=16 and 9 Hz).
5h	1730, 1600, 1490	6.8-7.4 (5H, m), 5.89 (2H, s), 4.82 (1H, dd, J=7 and 6 Hz), 3.6-3.8 (2H, m), 3.66 (3H, s), 2.86 (1H, dd, J=16 and 7 Hz), 2.49 (1H, dd, J=16 and 6 Hz).

a. The structure of 5d was confirmed by the independent synthesis.[4]
b. All the samples were scanned in neat except for 5a (KBr).
c. The solvent used was CCl_4 except for 5a ($CDCl_3$).

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