Diels-Alder Reaction of 3-Methylthiofuran and Transformation of the Cycloadducts to Substituted Cyclohexenols

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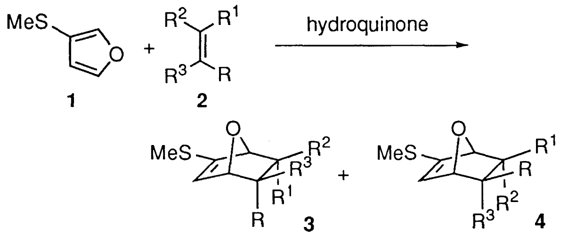
7-Oxabicyclo[2.2.1]hept-2-ene derivatives are prepared by the Diels-Alder reaction employing 3-methylthiofuran as a diene component. A chiral titanium catalyst promotes the Diels-Alder reaction in good enantioselectivity. The cycloadducts are converted to highly functionalized cyclohexenols by treatment with silyl enol ethers and *t*-butyldimethylsilyl trifluoromethanesulfonate.

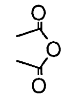
7-Oxabicyclo[2.2.1]heptene derivatives are useful building blocks for the synthesis of many biologically active compounds, such as carbohydrates, prostaglandins, and indolizine alkaloids,[1] since the ring opening reaction of 7-oxabicyclo[2.2.1]heptenes produces highly functionalized cyclic compounds.[2] In this regard, the development of asymmetric synthesis of 7-oxabicyclo[2.2.1]hept-2-ene derivatives would provide a useful method for the preparation of optically active ones.[3] In general, 7-oxabicyclo[2.2.1]hept-2-ene system has been constructed by Diels-Alder reaction between furan and suitable dienophiles. However, reactivity of furan is not sufficiently high as a diene component. The reaction is usually sluggish and the yield is generally low.[4] As introduction of alkylthio group at the 3-position of furan was supposed to enhance the reactivity of furan toward dienophiles,[5] we examined the Diels-Alder reaction of 3-methylthiofuran with various dienophiles. Moreover, the transformation of the Diels-Alder adducts, 2-methylthio-7-oxabicyclo[2.2.1]hept-2-enes, was studied for obtaining highly functionalized cyclohexenol derivatives by regioselective ring opening.

Although a few examples of the Diels-Alder reaction of 3-alkylthio or 3-arylthiofuran derivatives have been reported,[6] only maleic anhydride was employed as a dienophile. Therefore, the Diels-Alder reaction of 3-methylthiofuran with various dienophiles was studied firstly. 3-Methylthiofuran (**1**)[7] was treated with excess amounts of dienophiles **2** (2-5 molar amounts) at room temperature in the presence of 1 wt % of hydroquinone[9] under the conditions shown in Table 1. The reaction with methyl acrylate and methyl vinyl ketone gave the *endo* products **3** predominantly, while the reaction with 2-chloro and 2-acetoxyacrylonitriles or maleic anhydride gave the *exo* products **4** preferentially.



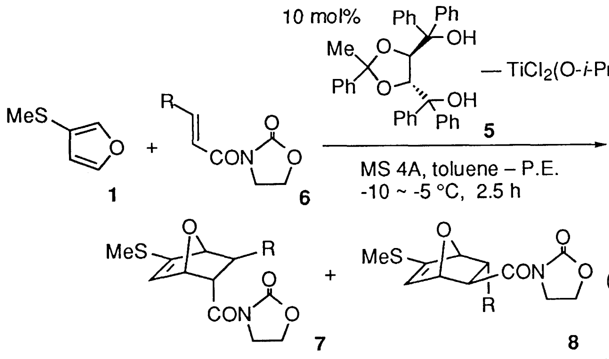
(1)

Table 1. Diels-Alder reaction of 3-methylthiofuran (**1**) with dienophiles **2**

R	R^1	R^2	R^3	Solvent	Time/day	Yield/%[a]	**3** : **4**
CO_2Me	H	H	H	neat	3	74	85 : 15
COMe	H	H	H	Et_2O	2	89	90 : 10
CHO	H	H	H	Et_2O	2	69	62 : 38
CN	H	H	H	neat	3	78	66 : 34
CN	H	H	Cl	neat	1	86	21 : 79
CN	H	H	OAc	neat	7	40	10 : 90
CO_2Me	H	CO_2Me	H	H_2O-MeOH	3	67	57 : 43
					10	81	58 : 42
		H	H	Et_2O	3	54[b]	<1: >99

[a] Isolated yield. [b] The product was isolated as its diol after hydride reduction.

With a catalytic amount (0.1 molar amount) of a titanium reagent prepared *in situ* from dichlorodiisopropoxytitanium and a tartrate-derived chiral 1,4-diol **5**, 3-methylthiofuran reacted with 3-acryloyl-1,3-oxazolidin-2-one (**6a**) or 3-[3-(methoxycarbonyl)-propenoyl]-1,3-oxazolidin-2-one (**6b**) in a toluene-petroleum ether (P.E.) mixture (1:1) at -10 ~ -5 °C for 2.5 h in the presence of Molecular Sieves 4A (MS 4A).[10] As shown in eq 2, the *endo* adducts **7a** and **7b** were obtained in good yields with good enantioselectivity.[11] The absolute configuration of the cycloadduct **7a** was decided as depicted in eq 2,[12] and the sence of the asymmetric induction was consistent with that of the asymmetric Diels-Alder reaction previously reported.[10] The asymmetric reaction was also tried by using 3-methoxyfuran instead of **1**. The *endo* cycloadducts were obtained in good yields but with low ee.



(2)

	R	Yield/%	**7** : **8**	Ee of **7**/%
6a	H	97	85 : 15	87
6b	CO_2Me	99	78 : 22	86

Since the Diels-Alder adducts, 2-methylthio-7-oxabicyclo[2.2.1]hept-2-enes, possess a vinyl sulfide moiety, it was expected that treatment with Lewis acid would cleave the bicyclic framework regioselectively to generate 4-carbocationic intermediates. Triisopropylsilyl (TIPS) ether **9** was prepared from the adduct **3** ($R=CO_2Me$, $R^1=R^2=R^3=H$) by a 2-step procedure ($LiAlH_4$/THF, TIPSCl/imidazole/DMF), and the reaction with *t*-butyldimethylsilyl (TBS) enol ether **10a** was attempted in the presence of Lewis acids. As shown in Table 2, screening of Lewis acids revealed that *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) is suitable for this transformation. The ring opening product **11a** was obtained in high regioselectivity and high stereoselectivity without a concomitant aromatization. Addition of MS 4A slightly improved the yield of the cyclohexenol **11a**. Under the similar conditions, the reaction of a ketene silyl acetal **10b** with **9** gave **11b** in 91% yield. The 5-TIPSO-methyl group sterically prevents the attack of the enol ethers from the α-side, giving the 4,5-*trans* isomers **11** almost exclusively.

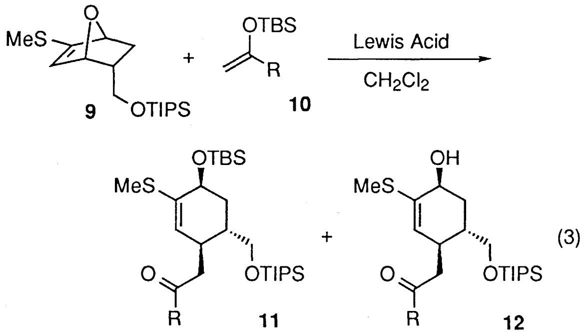


Table 2. Lewis acid promoted regioselective ring opening reaction of **9** with silyl enol ethers **10a, b**

	R	Lewis acid	Temp/°C	Time/h	Yield/%^{a}	
					11	12
10a	Ph	$ZnCl_2$	0	24	68	–
		$TiCl_4$	-30 ~ -20	2	37	15
		BF_3-Et_2O	-30 ~ -20	2	–	68
		$EtAlCl_2$	-30	0.8	80	–
		$SnCl_4$	-30	1	81	–
		TBSOTf	0	1	87	–
		TBSOTf + MS 4A	0	1	89	–
10b	OEt	TBSOTf + MS 4A	0	1	91^b	–

^{a} Isolated yield. ^{b} A trace amount of the stereo isomer was contained.

In summary, 3-methylthiofuran was found to be utilized as a useful diene component in the Diels-Alder reaction. The products, 2-methylthio-7-oxabicyclo[2.2.1]hept-2-ene derivatives, could be cleaved regioselectively to highly functionalized chiral cyclohexenols, which are versatile building blocks in organic synthesis.[13]

References and Notes

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5 For a review on the Diels-Alder reaction of hetero-substituted 1,3-dienes, see: M. Petrzilka and J. I. Grayson, *Synthesis*, **1981**, 753.

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7 3-Methylthiofuran was prepared from commercially available 3-bromofuran by a modification of the literature procedure[8] in 76% yield.

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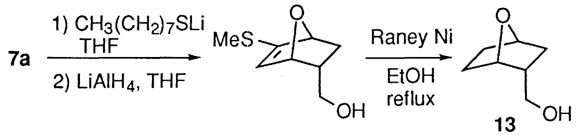
9 Hydroquinone was added to prevent the polymerization of **1** and dienophiles under the reaction conditions. In the absence of hydroquinone, **1** reacted with methyl acrylate to afford the adduct in 42% yield.

10 a) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989); b) K. Narasaka, H. Tanaka, and F. Kanai, *Bull. Chem. Soc. Jpn.*, **64**, 387 (1991).

11 The *endo* and *exo* isomers were separated by column chromatography. The optical purity was determined by the HPLC analysis using chiral columns (CHIRALCEL® OD, OJ).

12 The absolute configuration of **7a** was determined by comparison of optical rotation of **13** with that in the literature.[3b]



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