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A novel tandem [4$^+$+2] cycloaddition–elimination reaction of 4,4-dimethyl-2-styryl-1,3-oxathianes with olefins

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Abstract

A novel tandem [4$^+$+2] cycloaddition–elimination reaction of 1,3-oxathianes **1a**,**b** with olefins promoted by titanium tetrachloride to give 3,4-dihydro-2*H*-thiopyrans **3** was developed. 4,4-Dimethyl-2-styryl-1,3-oxathiane (**1a**) was used as a synthetic equivalent of a highly reactive thiocinnamaldehyde. Geminal dimethyl substituents at the 4-position of 1,3-oxathianes **1** are an intrinsic part of this cycloaddition–elimination reaction.

Keywords: oxathianes; tandem [4$^+$+2] cycloaddition–elimination reaction; thiocarbonyl compounds; thiopyrans.

The hetero Diels–Alder reaction of α,β-unsaturated thioketones is an important method for the synthesis of six-membered heterocycles containing a sulfur atom.[1] The α,β-unsaturated thioketones used in this cycloaddition[2] and its asymmetric versions[3] are, however, limited to relatively stable phenyl thioketone derivatives (such as thiochalcone) in most cases. On the other hand, α,β-unsaturated thioaldehydes and aliphatic thioketones are known to be highly reactive to polymerization or dimerization. For example, thioacrolein generated by pyrolysis of diallyl sulfide polymerizes even at low temperature[4] and methyl vinyl thioketone readily dimerizes through a hetero Diels–Alder reaction.[5] A little attention has been directed to the Diels–Alder trapping of α,β-unsaturated thioaldehydes.[6] Therefore, the challenge lies in controlling their chemical reactivity for utilization in organic synthesis. We report herein a novel tandem [4$^+$+2] cycloaddition–elimination reaction of 1,3-oxathianes **A** as synthetic equivalents of α,β-unsaturated thioaldehydes with olefins to give 3,4-dihydro-2*H*-thiopyrans **D**, as shown in Scheme 1.

Thienium cations can be subjected to cationic [2$^+$+4] polar cycloadditions as hetero dienophiles[7] or to cationic [4$^+$+2] polar cycloadditions as 2-heterodienes.[8] Consequently, if the alkyl moiety on the sulfur atom were designed to be eliminated from the sulfonium cation intermediate **C**, the α,β-unsaturated thienium cation **B**, as a 1-heterodiene, would open a new type of reaction, a [4$^+$+2] cycloaddition with an olefin to give a 3,4-dihydro-2*H*-thiopyran **D**. The thienium cation **B** must therefore be readily generated by coordination of a hard Lewis acid with the monothioacetal **A**, which can control polymerization of

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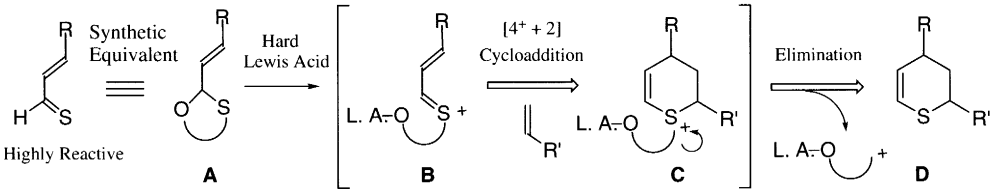
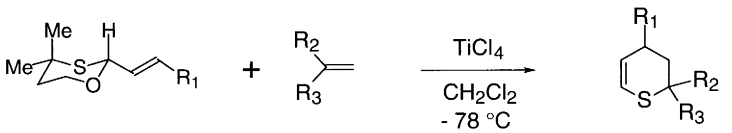


Scheme 1.

the α,β-unsaturated thioaldehyde. For the above strategy to work, the selective coordination of a Lewis acid to the oxygen of monothioacetal **A** and the subsequent elimination of the exocyclic substituent on the sulfur atom from the cationic cycloadduct **C** were required. Accordingly, we designed 1,3-oxathianes **1a**,**b** with dimethyl substituents at the carbon adjacent to the sulfur atom. The methyl groups would retard the coordination of the Lewis acid to the sulfur atom because of steric hindrance and would facilitate the elimination of the exocyclic substituent due to the stability of the carbocation to be removed.

The results of this tandem [4+2] cycloaddition–elimination reaction of 1,3-oxathianes **1a,b**[9] with olefins **2** are summarized in Table 1. Treatment of **1a** and 1,1-diphenylethylene (**2a**) with titanium tetrachloride in dichloromethane at −78°C gave the desired 3,4-dihydro-2*H*-thiopyran **3aa** in 88% yield (entry 1). The reactions of **1a** with α-alkylstyrenes **2b**–**e** afforded **3ab**–**3ae** in lower yields than those with **2a** (entries 2–5). The moderate yields are attributable to competitive polymerization of the α-alkylstyrenes **2b**–**e** promoted by titanium tetrachloride. Although the reaction of 4′-bromo-α-methylstyrene **2f** gave the 3,4-dihydro-2*H*-thiopyran **3af** (entry 6), the *o*-bromo- and *o*-methoxy substituents on the phenyl group of α-methylstyrene resulted in unreacted starting material. Allyltrimethylsilane (**2g**) also afforded the desired 3,4-dihydro-2*H*-thiopyran **3ag**, along with the γ-allylated alcohol (*trans*-3,3-dimethyl-7-phenyl-4-thia-5,9-decadien-1-ol) (entry 7). The reactions of **1b** having the 4-methoxyphenyl substituent as R_1

Table 1



1a: R_1 = Ph
1b: R_1 = 4-MeOPh

2

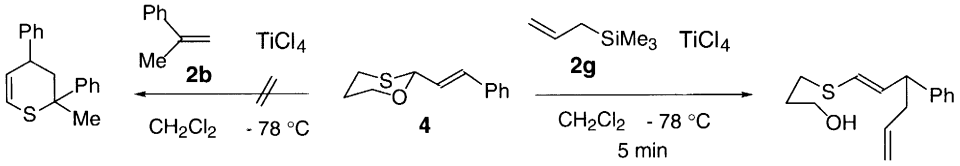
3

Entry	Oxathiane	Olefin **2**				$TiCl_4$ (eq.)	Time	Product **3**		
			R_2	R_3	eq.				Yield [a]	Ratio [b] *cis* : *trans*
1	**1a**	**2a**	Ph	Ph	4	1.2	15 h	**3aa**	88 %	—
2	**1a**	**2b**	Ph	Me	4	1.0	1 h	**3ab**	38 %	2 : 1
3	**1a**	**2c**	Ph	Et	4	1.0	1 h	**3ac**	37 %	2 : 1
4	**1a**	**2d**	Ph	Pr	4	1.0	1 h	**3ad**	42 %	2 : 1
5	**1a**	**2e**	Ph	Bn	5	1.0	26 h	**3ae**	48 %	3.3 : 1
6	**1a**	**2f**	4-BrPh	Me	5	1.2	3 h	**3af**	31 %	2.5 : 1
7	**1a**	**2g**	allyltrimethylsilane		4	1.0	40 min	**3ag**	32 % [c]	5 : 1
8	**1b**	**2a**	Ph	Ph	4	1.2	3 d	**3ba**	76 % [d]	—
9	**1b**	**2b**	Ph	Me	5	1.2	3 d	**3bb**	77 %	10 : 1
10	**1b**	**2d**	Ph	Pr	5	1.2	4 d	**3bd**	65 %	1.2 : 1

a) Isolated yields b) Determined by ^{1}H-NMR. c) γ–Allylated alcohol (37%) was obtained.
d) The reaction was conducted at -30 °C.

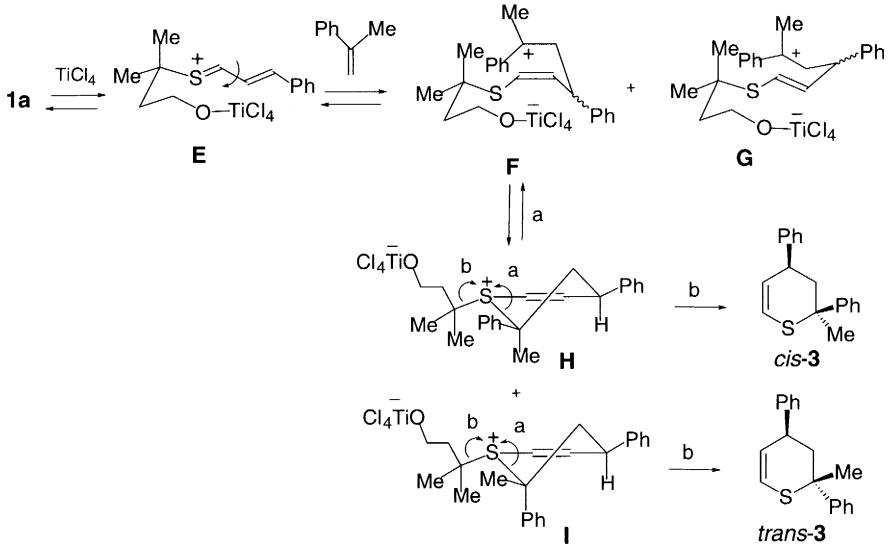
proceeded slowly to give the corresponding dihydrothiopyrans **3ba**, **3bb** and **3bd**, but the yields were higher than those of **3ab** and **3ad** (entries 8–10). The electron donating effect of the *p*-methoxy group on the phenyl substituent was obviously affected by the stability of the α,β-unsaturated thienium cation intermediate (**B**). All these reactions showed *cis* diastereoselectivity[10] varying from 10:1 to 1.2:1.

To prove the significance of geminal dimethyl substituents on 1,3-oxathiane **1a**, we tested the reactivity of 2-styryl-1,3-oxathiane (**4**), as shown in Scheme 2. The tandem reaction of **4** with α-methylstyrene **2b** (4 equiv.) activated by titanium tetrachloride (1 equiv.) in dichloromethane at −78°C did not take place. Furthermore, the reaction of **4** with allyltrimethylsilane (4 equiv.) gave only the γ-allylated alcohol in low yield (25%). The above results indicate that the geminal dimethyl substituents at the 4-position of 1,3-oxathianes **1a**,**b** are an intrinsic part of this tandem [4⁺+2] cycloaddition–elimination reaction.



Scheme 2.

The formation of 3,4-dihydro-2*H*-thiopyran **3** can be formally interpreted as being the result of a hetero Diels–Alder reaction of an α,β-unsaturated thioaldehyde with an olefin. Although we cannot rule out the mechanism of the concerted process (hetero Diels–Alder reaction) at present, we believe that this [4+2] cycloaddition proceeds via a stepwise process for the following reasons: (1) using normal olefins such as 1-hexene, 3-phenyl-1-propene, 2-hexyl-1-octene, and methyl acrylate did not give 3,4-dihydro-2*H*-thiopyrans in this reaction; and (2) the reactive olefins were limited to α-substituted styrenes and allylsilane, which generate stable cations by the attack of an electrophile. Furthermore, the generation of free thiocinnamaldehyde from the thienium cation **E** can probably be excluded, because the starting 1,3-oxathiane **1a** was recovered in 87% yield when **1a** without α-methylstyrene was treated with titanium tetrachloride (1.0 equiv.) in dichloromethane at −78°C for 1 h. A plausible reaction mechanism of **1a** with α-methylstyrene (**2b**) is illustrated in Scheme 3.



Scheme 3. A plausible reaction mechanism

The selective coordination of titanium tetrachloride to the oxygen of 1,3-oxathiane **1a** would initially generate the α,β-unsaturated thienium cations **E**. Electrophilic attack of **E** on α-methylstyrene would give the carbocation intermediates **F** and **G**. The subsequent cyclization by sulfur in the (*Z*)-vinyl sulfide **F** would form the sulfonium intermediates **H** and **I**, but the (*E*)-vinyl sulfide **G** could not cyclize because of the strong strain in the six-membered ring and would be transformed into **F** via reversion to **E**. The cleavage of the carbon–sulfur bond of the sulfonium intermediates **H** and **I** in path b furnished the cationic [4^++2] cycloaddition reaction to give 3,4-dihydro-2*H*-thiopyrans **3**, while the cleavage of the other carbon–sulfur bond, via path a, led back to the intermediate **F**. The *cis* selectivity might be attributed to the stability of the sulfonium intermediates **H** and **I**. The sulfonium intermediate **H** should be more stable than **I** because the two phenyl substituents assume the equatorial position in the half chair conformation.

In summary, we have exploited a novel tandem [4^++2] cycloaddition–elimination reaction using 1,3-oxathianes **1a**,**b** as synthetic equivalents of α,β-unsaturated thioaldehydes to give 3,4-dihydro-2*H*-thiopyrans. It is worth noting that, because of their high reactivity, it is difficult to synthesize of α,β-unsaturated thioaldehydes; however, α,β-unsaturated 1,3-oxathianes, as substrates in this reaction, can be easily prepared from the corresponding aldehydes by monothioacetalization using mercaptoalcohol. This tandem reaction therefore offers a new method of controlling the high reactivity toward polimerization of α,β-unsaturated thioaldehydes. Further studies on the chemistry of 4,4-dimethyl-1,3-oxathianes are in progress.

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9. 1,3-Oxathianes **1a**,**b** were easily prepared from 3-mercapto-3-methyl-1-butanol and the corresponding aldehydes catalyzed by boron trifluoride etherate in high yields.
10. The stereochemistry was determined by NOE experiments between the methyl proton and the methine proton adjacent to the phenyl ring of the diastereomer *cis*-**3ab** (Table 1, entry 2) isolated by silica gel chromatography. The *cis* and *trans* stereochemistry of the other compounds was determined by comparison of the chemical shifts of the olefinic protons of 3,4-dihydro-2*H*-thiopyran **3**.