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α,β-Unsaturated 1,3-oxathiolanes as masked heterodienes in the thio Diels–Alder reaction with styrene derivatives

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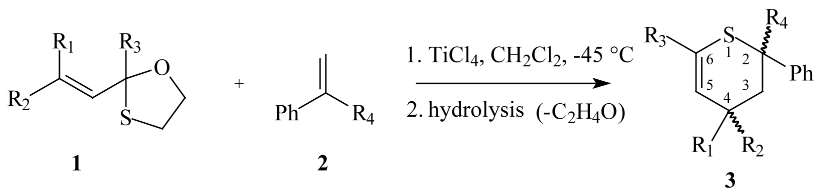
Abstract—The cycloaddition reactions of various alkyl and aryl substituted α,β-unsaturated 1,3-oxathiolanes with styrene derivatives led to dihydrothiapyrans in the presence of $TiCl_4$. Some mechanistic aspects of the cycloaddition are presented. © 2003 Elsevier Science Ltd. All rights reserved.

Thio Diels–Alder reactions provide a useful methodology for the synthesis of thiapyrans, which has been widely applied in organic chemistry,[1,2] particularly for the synthesis of natural products.[3–5] The preparation of six-membered ring sulfur-containing heterocycles can be achieved either by the cycloaddition involving a thiocarbonyl compound and a conjugated diene,[6] or by that of an α,β-unsaturated thiocarbonyl derivative with an olefin.[7] However, in contrast to the homologous oxygenated substrates, thioketones or thioaldehydes generally present very low stability.[8] Indeed, except for conveniently substituted thiocarbonyl compounds, the polymerization or dimerization of these products has been observed.[9] In most cases, these highly reactive thiocompounds are not isolated, but are generated and trapped in situ. For example, Sato has described the generation of thiochalcone from its dimer by a retro Diels–Alder reaction, and its trapping of by various olefins.[10,11] The use of α,β-unsaturated oxathioacetals as masked unsaturated thiocarbonyl derivatives has been recently shown as well to furnish convenient heterodienes.[12,13]

Our work involves the use of α,β-unsaturated 1,3-oxathiolane heterocycles. We present here the extension of our preliminary work[13] to different oxathiolanes, and our first results on the proposed mechanism. We prepared several aliphatic and aromatic substituted α,β-unsaturated oxathiolanes **1**,[14] and studied the cycloaddition with styrene derivatives **2** (Scheme 1). To the best of our knowledge, this is the first report including the use of aliphatic α,β-unsaturated oxathioacetals in the thio Diels–Alder reaction.

In a general procedure, oxathiolanes **1** were vigorously stirred in presence of 1.0 equiv. of $TiCl_4$ and 2.0–3.0 equiv. of styrene derivatives **2** in dichloromethane at –45°C. After completion of reaction, the mixture was hydrolyzed by aqueous KOH to lead, after purification, to the corresponding thiapyrans **3**.[15] Table 1 summarizes the isolated yields of **3**, as well as the regio and stereoselectivities in thio Diels–Alder-type reaction of **1** with olefins **2**.



Scheme 1.

Keywords: thio Diels–Alder; oxathiolane; dihydrothiapyran; Lewis acid; cycloaddition.

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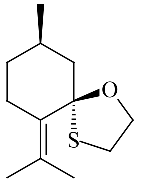
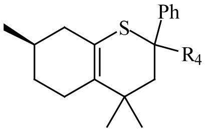
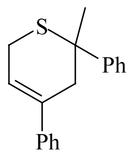
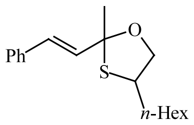
Table 1. Thio Diels–Alder reaction between oxathiolanes **1** and styrene derivatives **2**

Entry	R_1	R_2	R_3	Oxathiolane	R_4	Thiapyran derivative	Isolated yield[a] (*cis*/*trans* ratio)
1	H	Ph	Ph	**1a**	Me	**3a**	70 % (46/54)
2	”	”	”	**1a**	H	**3a’**	48 % (62/38)
3	Me	Me	Me	**1b**	Me	**3b**	32 %
4	”	”	”	**1b**	H	**3b’**	15 %
5				**1c**	Me	 **3c**	71 % (55/45)[b]
6		”		**1c**	H	**3c’**	52 % (63/37)[b]
7	H	Ph	H	**1d**	Me	 **4d**	13 %[c]
8	H	Ph	Me	**1e**	Me	**3e**	76 % (45/55)
9				**1f**	Me	**3e**	74 % (45/55)

[a] Purified by silica gel chromatography using a mixture of hexane and CH_2Cl_2 as the eluents.

[b] The attribution of each diastereomer was not effected.

[c] The reaction was quenched by a solution of sodium methanoate.

The reactions were completely regioselective in all the examples that we examined. The aryl group of the styrene derivative **2** was always located at the 2-position, α to S in compounds **3**.

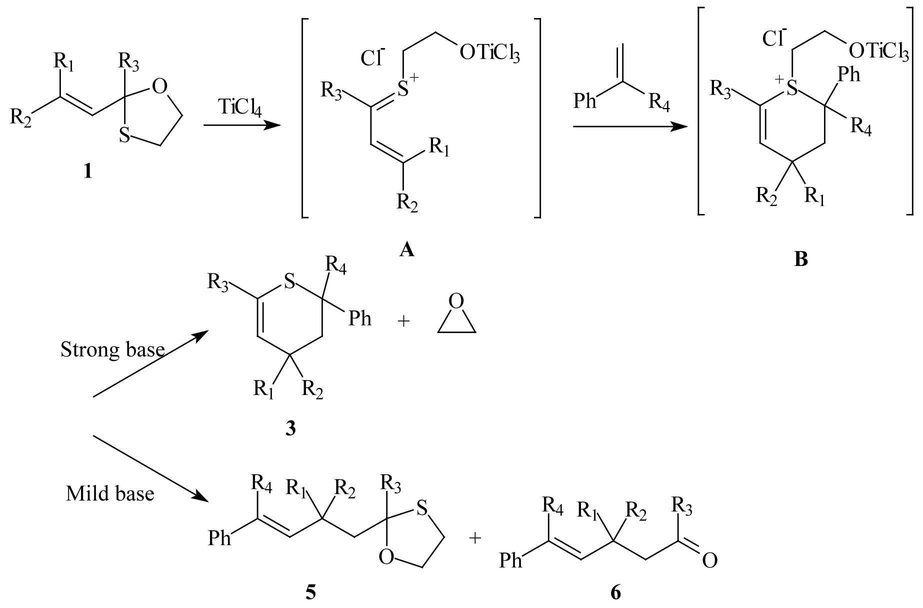
The oxathiolane **1a**, an equivalent of thiochalcone, on reaction with α-methylstyrene led to the thiapyran **3a** in 70% isolated yield. A 46/54 mixture of *cis–trans* stereoisomers (according to the relative positions of Ph-2 and Ph-4) was obtained for **3a** (entry 1). The *cis–trans* ratio was calculated by ^{1}H NMR and GC. The diastereomeric assignment was based on NOESY ^{1}H NMR correlations. The cycloaddition of **1a** with styrene (entry 2) gave 48% isolated yield of **3a′** with a *cis–trans* ratio of 62/38.

The oxathiolane **1b**, substituted by aliphatic groups, is the thio equivalent of mesityl oxide. Its reaction with α-methylstyrene or styrene furnished cycloadducts **3b** and **3b′** in 32 and 15% isolated yields, respectively (entries 3 and 4). These low yields could be explained by the poor stability of **1b** in presence on $TiCl_4$, even at low temperature (−45°C).

However, the reaction of chiral aliphatic **1c**[16] (masked thio-pulegone analogue) allowed the cycloaddition with α-methylstyrene and styrene in yields of 71 and 52%, for **3c** and **3c′**, respectively (entries 5 and 6). It is noteworthy that these reactions constitute the first examples of a successful utilization of an aliphatic oxathiolane as a masked thio-heterodiene.

The reaction of **1d** as an analogue of an α,β-unsaturated thioaldehyde did not lead to the formation of the expected thiapyran **3d**, after KOH hydrolysis, due to the degradation of the reactants. However, when the reaction was quenched with a solution of sodium methanoate, the thiapyran **4d** was isolated with a yield of 13% (entry 7). This compound was probably formed through the isomerisation of the double bond of the expected thiapyran **3d**. The change of reactivity could be attributed to the difference of stability of the intermediate species, particularly during the hydrolysis step (see Scheme 2).

The cycloaddition of oxathiolane **1e** led to **3e** in a 76% isolated yield with a *cis–trans* ratio of 45/55 (entry 8).[17]



Scheme 2.

A plausible reaction mechanism of oxathiolanes **1** with olefins **2** is illustrated in Scheme 2. The coordination of $TiCl_4$ to **1** could induce the cleavage of the C–O bond of the oxathiolane heterocycle to generate a thienium cation of type **A**. The cycloaddition of **A** with an electron-rich olefin would lead to the regioselective formation of a sulfonium cation of type **B**. We could observe that the reaction products were different, depending on the hydrolysis conditions. When an strong base such KOH or NaOMe was used, the thiapyrans **3** were obtained (excepted for **1d**, entry 7), with the loss of ethylene oxide.

The formation of the epoxide during the fragmentation process was evidenced by the reaction of oxathiolane **1f** with α-methylstyrene. The cycloaddition led to **3e** in 74% isolated yield in a *cis–trans* ratio of 46/54 (entry 9). Indeed, we could observe, by GC and GC/MS analysis, the presence of octene oxide in the crude product by its comparison with the commercial standard. When the crude reaction was hydrolysed by a by a mild base such aqueous K_2CO_3 or by the addition of MeOH, no formation of **3e** was observed.

The influence of the base during the hydrolysis step, was more carefully examined in the reaction of 2-methyl-2-styryloxathiolane **1e** and α-methylstyrene. The results are presented in Table 2. The use of a mild base such as aqueous potassium carbonate or methanol did not led to the expected thiapyran **3e**, but to compounds **5e** and **6e** (entries 1 and 2). The formation of **5e** occurred presumably by a loss of the proton in position 3 of the sulfonium cation **B** to form an enol thioether followed by a ring-closure of the oxathiolane.[18] Compound **6e** is issued from the hydrolysis of **5e**.

On the other hand, when the hydrolysis was performed with a MeOH solution of sodium methanoate or aqueous KOH, the thiapyran **3e** was isolated in 68 and 76% yield, respectively (entries 3 and 4). No change on the diastereoselection of the reaction was observed and the *cis*/*trans* isomers were obtained in a 45/55 ratio in each case. The use of *n*-butyl lithium as a base during the quenching led only to the degradation of the compounds.

Table 2. Effect of the base on the hydrolysis step of the reaction of **1e** with α-methylstyrene

	Base/solvent	Isolated yield (*cis*/*trans* ratio)		
		3e	**5e**	**6e**
1	K_2CO_3/H_2O	0	9	16
2	MeOH	0	8	21
3	MeONa/MeOH	68 (45/55)	0	0
4	KOH/H_2O	76 (45/55)	0	0

The generation of the proposed thienium cation **A** (Scheme 2) from the reaction of 1,3-oxathiolanes **1** and $TiCl_4$ appears to be a useful method to form in situ α,β-unsaturated thiocarbonyl equivalents, which could be successfully used as heterodienes in thio Diels–Alder reactions. Aromatic and aliphatic substituted α,β-unsaturated oxathiolanes are suitable to react with styrene derivatives affording regioselectively dihydrothiapyran derivatives **3** in modest to good yields, as a mixture of *cis–trans* isomers.

Work is in progress to extend the reaction to other olefins, specially to aliphatic ones and to achieve a better comprehension of the reaction mechanism.

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15. *Typical procedure for the synthesis of* **3**: To a vigorously stirred solution of **1** (1.0 mmol) in dichloromethane (10 ml) at −45°C under inert atmosphere was added a CH_2Cl_2 solution of titanium tetrachloride (1.0 mmol). After formation of an orange precipitate, the styrene derivative **2** was added dropwise. After the complete disappearance of the precipitate, the solution was quenched with an aqueous solution of potassium hydroxide (1.0 M). After filtration over celite, the crude mixture was twice extracted with diethyl ether. The organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by silicagel column chromatography with a mixture of hexane/CH_2Cl_2 (100/0 to 80/20) as the eluent.
16. The oxathiolane **1c** was used in an enantiopure form. Its stereochemistry is discussed in Ref. 14.
17. *Representative data. cis*-**3e**: ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 3H), 2.05 (dd, $J=2.0$, 1.4 Hz, 3H), 2.20 (m, 2H), 3.66 (t quint., $J=8.8$, 2.2 Hz, 1H), 5.65 (dq, $J=2.2$, 1.3 Hz, 1H), 7.2–7.4 (m, 8H), 7.6 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 23.6, 27.0, 41.1, 45.7, 48.8, 118.8, 126.0, 126.7, 127.3, 128.0, 128.6, 128.7, 130.4, 145.7, 146.1. MS m/z (relative intensity): 280 (M^+ 26.1), 247 (18.3), 161 (100), 147 (14.0), 129 (21.7), 128 (18.4), 91 (23.2), 77 (14.2).

    trans-**3e**: ^{1}H NMR ($CDCl_3$): δ 1.64 (s, 3H), 2.00 (dd, $J=2.2$, 1.4 Hz, 3H), 2.10 (dd, $J=13.2$, 12.6 Hz, 1H), 2.48 (dd, $J=13.5$, 5.0 Hz, 1H), 2.91 (dd quint., $J=12.5$, 5.0, 2.0 Hz, 1H), 5.42 (m, 1H), 7.11 (d, $J=7.1$ Hz, 2H), 7.15–7.40 (m, 6H), 7.58 (d, $J=7.4$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 23.2, 31.8, 40.4, 46.8, 50.2, 120.6, 126.4, 126.6, 128.8, 128.4, 128.5, 129.4, 145.4, 145.6. MS m/z (relative intensity): 280 (M^+ 20.9), 247 (18.2), 161 (100), 147 (13.2), 129 (19.9), 128 (19.8), 91 (20.4), 77 (12.8). Elemental analysis of mixture *cis*/*trans* $C_{19}H_{20}S$ requires: C, 81.36; H, 7.20; S, 11.43. Found: C, 81.52; H, 7.11; S, 11.37%.

18. This type of ring-closure has already been described. See: Reglier, M.; Ruel, O.; Lorne, R.; Julia, S. A. *Synthesis* **1983**, 624–628.