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Thio Diels–Alder reactions of α,β-unsaturated 1,3-oxathiolanes with aliphatic olefins and 1,3-dienes

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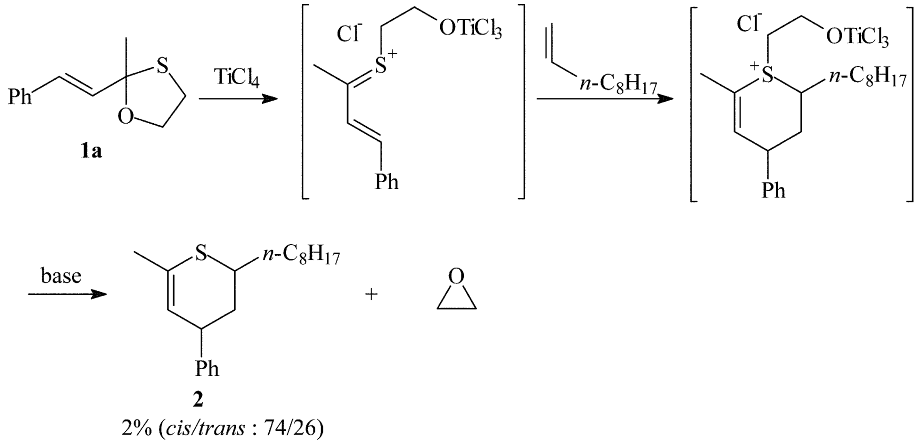
Abstract—A series of α,β-unsaturated 1,3-oxathiolanes reacted with aliphatic olefins such as norbornene and with various 1,3-dienes in the presence of $TiCl_4$ leading to dihydrothiapyrans, via a cycloaddition-type reaction. The unsaturated oxathiolanes acted as masked heterodienes in this thio Diels–Alder reaction.

Thio Diels–Alder reactions have been widely applied in organic chemistry,[1,2] providing useful methodology for the synthesis of natural products through the formation of thiapyran structures.[3–5] These heterocycles can be prepared by the cycloaddition of a thiocarbonyl compound with a conjugated diene,[6] or by that of an α,β-unsaturated thiocarbonyl derivative with an olefin.[7] However, thioketones or thioaldehydes are generally unstable, even at low temperature.[8,9] These highly reactive thio-compounds are generally not isolated, but generated and trapped in situ.[10] α,β-Unsaturated oxathioacetals have also been used as masked heterodienes to achieve a thio Diels–Alder cycloaddition.[11,12] However, these cycloadditions have only been reported with styrene derivatives as the dienophiles.

We present here new examples of the reactions of α,β-unsaturated oxathiolanes[13] with aliphatic olefins and 1,3-dienes. To the best of our knowledge, this is the first report dealing with the thio Diels–Alder reactions of oxathiolanes with aliphatic olefins, such as norbornene, or with 1,3-dienes, reacting as dienophiles.

Non-activated terminal aliphatic olefins demonstrated a low reactivity in the thio Diels–Alder reactions with



Scheme 1. Reaction of oxathiolane **1a** with 1-decene.

Keywords: thio Diels–Alder; cycloaddition; heterodienes; dihydrothiapyrans; titanium tetrachloride.

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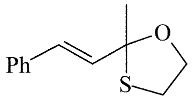
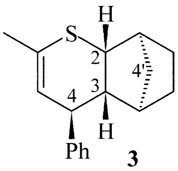
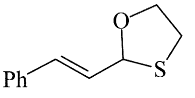
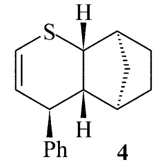
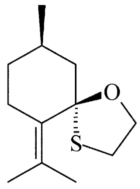
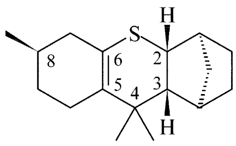
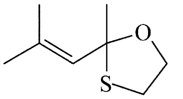
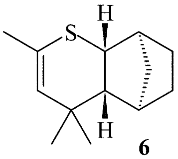
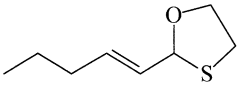
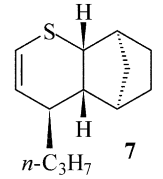
α,β-unsaturated oxathiolanes. Thus, the cycloaddition performed with oxathiolane **1a** and 1-decene in the presence of $TiCl_4$ (Scheme 1) afforded the thiapyran **2** in only 2% isolated yield, with a *cis–trans* ratio of 74:26. Thiapyran **2** was obtained regioselectively: according to the NMR analysis, the *n*-octyl group was located at the 2-position of **2** (α to the S) in both stereoisomers.

The cycloaddition involving **1** is proposed to proceed by ring-opening of the oxathiolane by the strong Lewis acid, followed by addition of the olefin and elimination of an epoxide to furnish the expected thiapyran **2** (Scheme 1).

The use of norbornene, as a more reactive olefin gave an increased yield of the cycloaddition product. Table 1 summarizes the isolated yields of thiapyrans resulting from the reaction of various oxathiolanes **1** with norbornene. The Table only presents the structures of the major diastereomer of the thiapyrans **3**–**7** obtained. The determination of the relative stereochemistry of these compounds was achieved by NOESY and COSY ^1H NMR correlations.

The reaction of **1a** with norbornene led to the thiapyran **3** in a 77% isolated yield, as a 98:2 mixture of stereoisomers (entry 1). Only the major diastereomer was isolated and characterized. The NOESY ^1H NMR spectrum showed a correlation between the two protons H-2 and H-3 located at the ring junctions, indicating the *cis* ring fusion. A correlation was also observed between H-4 and H-4′ of the bridging methylene group

Table 1. Thio Diels–Alder reactions with oxathiolanes **1** and norbornene[a]

Entry	Oxathiolane **1**	Thiapyran Major diastereomer	Isolated yield (%) (Isomer ratio)[b]
1	 **1a**	 **3**	77 (98:2)
2	 **1b**	 **4**	56 (90:10)
3	 **1c**	 **5**	64 (50:50)[c]
4	 **1d**	 **6**	9 single isomer
5	 **1e**	 **7**	10 (94:6)

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[a] *General procedure*: To a vigorously stirred solution of **1** (1.0 mmol) in dichloromethane (10 mL) at −45°C under an inert atmosphere was added a CH_2Cl_2 solution of titanium tetrachloride (1.0 mmol). After formation of an orange precipitate, norbornene (3.0 mmol) was added. After the complete disappearance of the orange precipitate, the solution was quenched with an aqueous solution of potassium hydroxide (1.0 mol/L). 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 silica-gel column chromatography with a mixture of hexane/CH_2Cl_2 (100/0 to 80/20) as the eluent.

[b] Calculated by GC (except for entry 3). The structure of the minor isomer was not determined.

[c] Estimated by ^{13}C NMR. The structure of the other isomer presents H-2 and H-3 (*cis*) in a *trans* position relative to the methylene bridge but now *trans* to Me-8 which keeps its absolute stereochemistry.

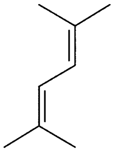
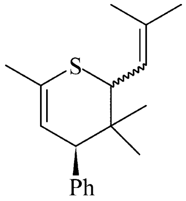
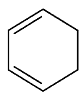
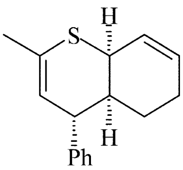
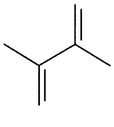
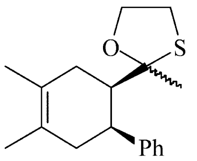
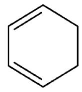
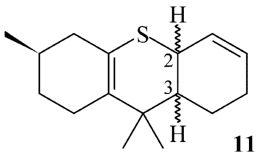
of the norbornene substructure. It is noteworthy that three new chiral centers were created in **3**, indicating that the reaction proceeded with excellent stereoselectivity. The oxathiolane **1b**, an equivalent of thio-cinnamaldehyde, reacted with norbornene to afford **4** in 56%, yield with a 90:10 ratio of two diastereoisomers (entry 2). As observed for adduct **3**, the major isomer of **4** also presented a *cis*-ring junction and the phenyl group in a *cis* position with respect to H-3.

The reaction of norbornene with aliphatic oxathiolanes **1c–e** afforded the cycloadducts **5–7**. The optically pure thio-pulegone analogue **1c**[13] led to a mixture of two diastereomers of **5** in 64% isolated yield (entry 3). The ratio of the two isomers was estimated by ^{13}C NMR to be close to 50:50. The thiapyrans **6** and **7** were obtained in 9 and 10% yields, respectively (entries 4 and 5). These low yields could be explained by the poor stability of the corresponding aliphatic oxathiolanes **1d** and **1e** in the presence of $TiCl_4$, even at low temperature (−45°C). The stereochemistry of **6** was determined by NOESY and by comparison with the data for **3** and **4** with the results indicating that a single stereoisomer was present. In the case of **7**, the main stereoisomer obtained had the same stereochemical arrangement as found in structures **3** and **4**.

It is noteworthy that the reactions presented in Table 1 constitute the first examples of a successful cycloaddition of aliphatic and aromatic unsaturated oxathiolanes, as masked heterodienes, with aliphatic olefins.

We then examined the reactivity of some 1,3-dienes in the thio Diels–Alder reaction with oxathiolanes **1a** and **1c** under our standard conditions. The results and yields of the cycloadducts are presented in Table 2 and indicated that the 1,3-dienes could act, with substrates **1**, as electron-rich dienophiles. Thus, the cycloaddition of **1a** and 2,5-dimethylhexadiene gave a 47% isolated yield of the thiapyran **8** with a 60:40 ratio of the two diastereomers (entry 1). The reaction proceeded regioselectively, with the remaining double bond of the diene located α to the S atom in **8**. The relative stereochemical assignment for each isomer was not established. The reaction of **1a** with 1,3-cyclohexadiene led to the formation of **9** in 20% yield, with very good stereoselectivity, 99:1 (entry 2). By NMR analogy, the main stereoisomer corresponded to the structure represented shown. In this case, the formation of adducts (12%) resulting from the Diels–Alder cycloaddition of 1,3-cyclohexadiene and the double bond of the oxathiolane **1a** was also observed. Thus, there is competition between the thio Diels–Alder and the normal Diels–Alder reactions, and the nature of the major product seems to depend on the structure of the 1,3-diene. In the case of 2,3-dimethylbutadiene, we did not observe the formation of the thio Diels–Alder adducts, but only the normal Diels–Alder cycloadduct **10** in 43% isolated yield (entry

Table 2. Cycloaddition of oxathiolanes **1** and 1,3-dienes

Entry	Oxathiolane **1**	1,3-Diene	Product	Isolated yield (%) (Isomer ratio)[b]
1	**1a**		 **8**	47 (60:40)
2	**1a**		 **9**	20 (99:1)
3	**1a**		 **10**	43 (52:48)
4	**1c**		 **11**	37 (63:37)[a]

[a] H-2 and H-3 are *cis* to one another and, *cis* or *trans* with respect to the chiral methyl group.

[b] Calculated by GC.

3). In contrast, the cycloaddition of the aliphatic oxathiolane **1c** with 1,3-cyclohexadiene afforded the tricyclic thiapyran **11** in a 37% yield via a thio Diels–Alder process, as a 63:37 mixture of two diastereoisomers, both with a *cis*-ring junction (entry 4).

In conclusion, the cycloaddition of aliphatic and aromatic α,β-unsaturated oxathiolanes, as precursors of thioketones or thioaldehydes, with norbornene and conjugated 1,3-dienes is reported herein for the first time. The use of masked heterodienes seems to be a useful methodology to generate these unstable thiocarbonyl derivatives for the thio Diels–Alder reactions.

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