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Synthesis of α,β-unsaturated oxathiolanes

Sébastien Kerverdo,[a] Louisette Lizzani-Cuvelier[a] and Elisabet Duñach[b,*]

[a]*Laboratoire Arômes, Synthèses, Interactions, Université de Nice Sophia-Antipolis, Parc Valrose, 06108 Nice, Cedex 2, France*
[b]*Laboratoire de Chimie Bio-organique, UMR CNRS 6001, Université de Nice Sophia-Antipolis, Parc Valrose, 06108 Nice, Cedex 2, France*

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Abstract—The formation of α,β-unsaturated oxathiolanes **2** from α,β-unsaturated carbonyl derivatives was achieved selectively and in high yields using the heterogeneous catalyst APSG·HCl.

1. Introduction

Acetals, oxathioacetals and dithioacetals are frequently used for the protection of aldehydes or ketones in multi-step syntheses.[1] Acetals are also used to protect diols and hydroxy groups.[1] On the other hand, Corey and Seebach reported that carbanions stabilized by an adjacent sulfur atom such as 2-lithio-1,3-dithianes were appropriate acyl anion equivalents.[2] Since, the use of dithioacetals and later of oxathioacetals, as masked acyl anion equivalents for carbon–carbon bond formation, has been well documented.[3–5] Furthermore, the oxathioacetal heterocycles have been shown to be very useful for the synthesis of chiral synthons: for example, Eliel has described the use of a chiral oxathiane moiety to induce chirality in the addition reaction to carbonyl compounds.[6–8] Oxathianes were also used as chiral ylides for the epoxidation of carbonyl derivatives.[9,10] In addition, some five-membered ring oxathiolanes present interesting biological properties as nucleoside analogues, as those displayed by (−)-2-deoxy-3′-thiacytidine (3TC®, Epivir) against HIV.[11]

We have been interested in the oxathiolane ring, and particularly in α,β-unsaturated oxathiolanes. The most commonly used way leading to cyclic 1,3-oxathioacetals is the condensation of a mercaptoalcohol with an aldehyde or a ketone, catalyzed by Brönsted or Lewis acids.[12–15] Their synthesis can also be achieved by transoxathioacetalisation between an acetal and a mercaptoalcohol or a carbonyl derivative.[16,17] These methods allow the formation of simple oxathianes or oxathiolanes in good yields.

However, some problems are encountered when reactions are performed with α,β-unsaturated carbonyl derivatives. Indeed, the thiol moiety being a soft nucleophile, it can undergo both 1,2 and 1,4 addition. Double addition of the mercapto alcohol is also possible. To the best of our knowledge, only two references deal briefly with oxathioacetalisation of α,β-unsaturated carbonyl derivatives.[14,17] In the first one, cinnamaldehyde was reacted with 2-mercaptoethanol in presence of $ZrCl_4$ as the catalyst to afford the 1,2 adduct in good yield.[14] In the second case, the reaction proceeded by exchange of the $O-(CH_2)_2-S$ moiety between 2,2-dimethyloxathiolane and a carbonyl compound; however, when crotonaldehyde was used, polymerization of the substrate was observed.[17] Therefore, there is, up to now, no general method described allowing the clean and efficient synthesis of α,β-unsaturated oxathiolanes.

Recently, we reported the use of unsaturated-1,3-oxathiolanes as masked heterodienes for thio Diels–Alder reactions,[18] showing that these derivatives have potential synthetic interest. We present here our results on the selective formation of oxathiolanes from α,β-unsaturated carbonyl derivatives or from the corresponding acetals.

2. Results and discussion

For the synthesis of unsaturated oxathiolanes, we examined three strategies based on the coupling of α,β-unsaturated carbonyl compounds with 1,2 thioalcohols. Thus, we screened the use of conventional Bronstëd and Lewis acids; we further examined the transoxathioacetalisation method between acetals and mercaptoalcohols. Finally, we successfully applied heterogeneous catalysis using an acid-supported silica gel reagent.

2.1. Formation of α,β-unsaturated oxathiolanes catalyzed by conventional Bronstëd and Lewis acids

Our first attempts to prepare α,β-unsaturated oxathiolanes **2** from α,β-unsaturated carbonyl compounds **1** and

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* Corresponding author. Fax: +33-4-92-07-61-51;
e-mail: dunach@unice.fr

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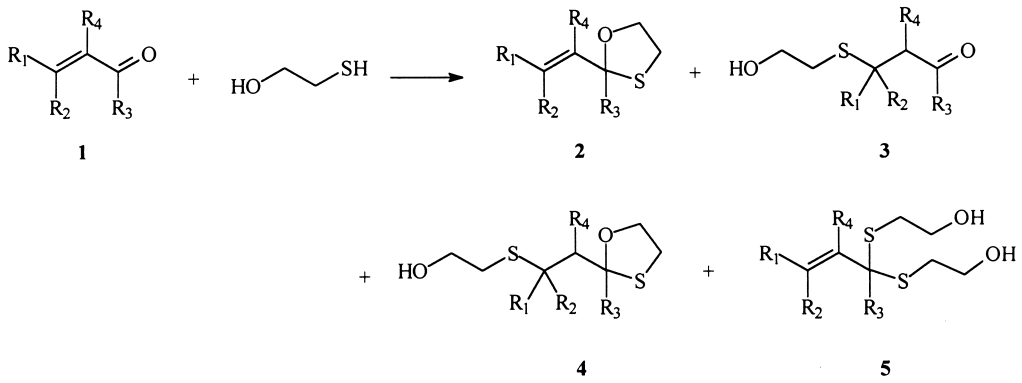


a R_1= Ph, R_2= H, R_3= Me, R_4= H

b R_1= Ph, R_2= R_3= R_4= H

c R_1= R_2= R_3= Me, R_4= H

d R_1= Me, R_2= R_3= R_4= H

e R_1= *n*-Pr, R_2= R_3= R_4= H

f R_1= Ph, R_2= H, R_3= Ph, R_4= H

g R_1= Et, R_2= H, R_3= H, R_4= Me

Scheme 1. Formation of α,β-unsaturated oxathiolanes **2** and by-products.

2-mercaptoethanol (Scheme 1), rapidly raised the problem of selectivity: a mixture of sulfur derivatives **2**–**5** was obtained. The reactions were generally carried out using an initial 1:1 mixture of **1** and 2-mercaptoethanol in diethyl ether or dichloromethane in the presence of dehydrating agent such as $MgSO_4$ or 4 Å molecular sieves. As catalysts, we used *p*-TsOH or Lewis acids such as $BF_3{\cdot}Et_2O$, $ZnCl_2$, $ZrCl_4$, $MgBr_2$ and $LiBF_4$. Table 1 summarizes the main results obtained. Thus, the reaction of 4-phenylbutenone **1a** in refluxing ethyl ether in the absence of catalyst afforded a mixture of oxathiolane **2a** and Michael adduct **3a** with a poor conversion after 24 h (entry 1). The rate of the reaction was enhanced with acid catalyst (*p*-TsOH, 5%, entry 2), but the selectivity for **2a** was only of 20%. In this case, the major compound was the 1,4-addition product **3a**, obtained with 56% of selectivity. The adduct **4a**, issued from a double 1,2 and 1,4 addition was also obtained in 24% selectivity. The same reaction run at room temperature with either $MgSO_4$ or molecular sieves afforded a good selectivity towards **2a**, respectively of 98 and 84% (entries 3, 4), though with a low conversion. A better conversion could not be obtained without loss of selectivity and it was accompanied by an increasing formation of **3a** and **4a**.

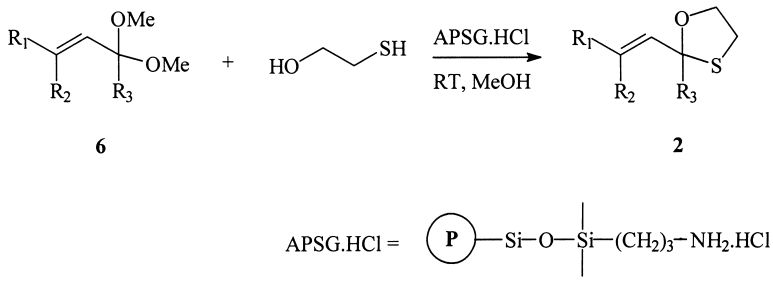
The use of trimethylorthoformate as the desiccant (entry 5) in dichloromethane led to a rapid conversion of **1a**, but with a poor selectivity for **2a** of 47%. The loss of selectivity was attributed to the enhancement of the polarity of the solvent by the presence of methanol, formed during the reaction. In comparison, dehydrating agents such as magnesium sulfate or 4 Å molecular sieves led to lower conversions, but **2a** could be obtained with better ratios (compare entries 3–5).

Different Lewis acids were tested as catalysts for the reaction of **1a** in order to orientate the addition of the mercapto ethanol in a 1,2 fashion (entries 6–10). The best catalyst concerning selectivity towards **2a** was $BF_3{\cdot}Et_2O$ (entry 6). $ZnCl_2$ led almost exclusively to the Michael

Table 1. Reaction of 2-mercaptoethanol with α,β-unsatured carbonyl derivatives **1**

Entry	Carbonyl derivate **1**	Desiccant	Solvent	*T* (°C)	Acid (molar %)	Time (h)	Conversion of **1**[a] (%)	Selectivity[a] **2/3/4/5**
1	**1a**	$MgSO_4$	Et_2O	Reflux	–	24	18	58:42:0:0
2	**1a**	$MgSO_4$	Et_2O	reflux	*p*-TsOH (5%)	1.5	80	20:56:24:0
3	1a	$MgSO_4$	Et_2O	rt	*p*-TsOH (5%)	4.5	40	98:2:0:0
4	**1a**	MS 4 A	Et_2O	rt	*p*-TsOH (5%)	3	42	84:15:1:0
5	**1a**	$HC(OCH_3)_3$	CH_2Cl_2	rt	*p*-TsOH (5%)	1	85	47:50:3:0
6	**1a**	$MgSO_4$	Et_2O	rt	$BF_3{\cdot}Et_2O$ (10%)	1.5	35	68:32:0:0
7	**1a**	$MgSO_4$	Dioxane	rt	$ZnCl_2$ (1 equiv.)	1.5	75	5:95:0:0
8	**1a**	$MgSO_4$	CH_2Cl_2	rt	$ZrCl_4$ (5%)	0.5	81	2:67:31:0
9	**1a**	$MgSO_4$	CH_2Cl_2	rt	$MgBr_2$ (10%)	4	2	50:50:0:0
10	**1a**	$MgSO_4$	CH_2Cl_2	rt	$LiBF_4$ (10%)	6	40	52:48:0:0
11	**1b**	$MgSO_4$	Et_2O	rt	*p*-TsOH (5%)	0.5	63	31:0:0:69[b]
12	**1c**	$MgSO_4$	Et_2O	rt	*p*-TsOH (5%)	1	61	14:82:4:0
13	**1d**	$MgSO_4$	Et_2O	rt	*p*-TsOH (5%)	1	65	34:0:30:36

[a] Determined by GC.
[b] Determined by ^{1}H NMR.



Scheme 2. Formation of α,β-unsaturated oxathiolanes **2** by transoxathioacetalisation.

addition product **3a** (entry 7). Similarly, $ZrCl_4$ (5%) did not afford the expected oxathiolane **2a**, but led to **3a** and to **4a** in a 67 and 31% selectivity, respectively (entry 8). The use of $MgBr_2$ did not catalyze the reaction, since after 4 h at room temperature, only 2% conversion was observed (entry 9). $LiBF_4$ was not selective and gave a mixture of oxathiolane **2a** and the Michael addition product **3a** in almost the same amounts (entry 10).

The conditions for the best selectivity obtained in entry 3 were extended to other α,β-unsaturated carbonyl compounds. Thus, the reaction of cinnamaldehyde **1b** led to the corresponding oxathiolane **2b** and to the dithioacetal **5b** in a 31:69 ratio, respectively (entry 11). Formation of **5b** was attributed to a second addition of 2-mercaptoethanol on the hemithioacetal intermediate, rather than to the attack of the mercapto alcohol on **2b** to re-open the cycle. This fact was confirmed by stirring 2-mercaptoethanol and **2b** with *p*-TsOH (5%), which did not lead to **5b** in any significant ratio.

The comparison between entries 3 and 11 indicated that the reaction was very strongly dependent on the nature of the substrate: cinnamaldehyde preferentially formed **5b**, whereas the corresponding methyl ketone afforded selectively **2a**. An aliphatic ketone such as **1c** gave preferentially the 1,4-addition product **3c**, with a selectivity of 82% (entry 12). However, the aliphatic aldehyde **1d** led to a mixture of **2d**, **4d** and **5d** in almost the same proportions (entry 13). Under the same reaction conditions, differently substituted unsaturated ketones and aldehydes afforded different reaction products: either **2**, **3** or **5** could be obtained as main reaction products, respectively with **1a**, **1c** or **1b**.

2.2. Formation of oxathiolanes from α,β-unsaturated acetals

We also considered the possibility to prepare compounds **2** more selectively by a transoxathioacetalisation reaction. The exchange of the alkoxy groups of acetals by other alcohols in presence of an acidic catalysis is known to proceed smoothly.[19] This exchange reaction has been recently applied to mercapto alcohols for the formation of oxathiolanes and oxathianes.[16] The reaction proceeded in good yields without solvent under microwave irradiation, with Montmorillonite clay K10 as the catalyst.

However, the reactivity of unsaturated acetals with mercapto alcohols has, to our knowledge, not yet been reported.[20] We thus decided to apply this methodology to the formation of α,β-unsaturated oxathiolanes. Indeed, the main advantage of acetals for the synthesis of **2** (Scheme 2) is the decrease in electrophilicity of the β-carbon, due to the absence of conjugated system, thus limiting the 1,4-addition reaction leading to derivatives **3** and **4**.

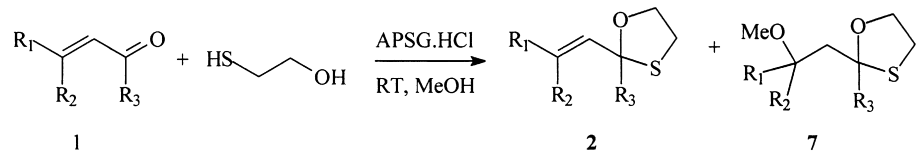
The synthesis of the acetals from the corresponding carbonyl derivatives **1** has been reported to proceed efficiently in the case of unsaturated aldehydes,[21–23] but is less common in the case of unsaturated ketones. Indeed, only a few examples of unsaturated ketones have been described: 2-cyclohexenone has been reported to reacted with alkoxytrimethylsilane and TMSOTf as the catalyst, leading to its corresponding acetal.[24] Aromatic α,β-unsaturated ketones such **1a**[25] and chalcone **1f**[26] were also readily converted into the corresponding acetals. Following these examples, we prepared several dimethyl acetals **6** from α,β-unsaturated carbonyl derivatives **1** in quantitative yields. We carried out the exchange reaction between **6** and 2-mercaptoethanol using the aminopropylated silica gel hydrochloride (APSG·HCl) as supported catalyst (Scheme 2) for the transoxathioacetalisation step. This catalyst is known to be efficient under mild conditions.[25] The reactions were run in methanol at room temperture, with 5% catalyst,[27] and led to the oxathiolane **2** in modest to good yields (Table 2).

The transoxathioacetalisation reaction of methyl acetals of α,β-unsaturated carbonyl compounds was less selective than expected. Starting acetals **6a** and **6f** gave the best results concerning the selectivity towards **2**, **2a** and **2f** were isolated in yields of 71 and 72%, respectively (entries 1, 5). Reaction of acetals **6b**, **6d** and **6e**, derived from aldehydes, led to a poor selectivity and to modest yields of **2** (entries

Table 2. Formation of oxathiolanes **2** by transoxathioacetalisation catalyzed by APSG·HCl

Entry	Acetals **6**	Conversion[a]	Selectivity **2/3/4/5**[a]	Isolated yields of **2**[b]
1	**6a**	85	94:6:0:0	71
2	**6b**	85	68:0:0:32	53
3	**6d**	88	21:12:0:44	16
4	**6e**	72	25:0:61:0	25
5	**6f**[c]	89	92:8:0:0[d]	72[e]

[a] Determined by GC.
[b] Isolated after silica gel column chromatography.
[c] The reaction was performed in dichloromethane.
[d] Ratio determined by ^1H NMR.
[e] Isolated yield after alumina oxide gel column chromatography.



1 2 7

Scheme 3. Formation of α,β-unsaturated oxathiolanes **2** and by-product **7**.

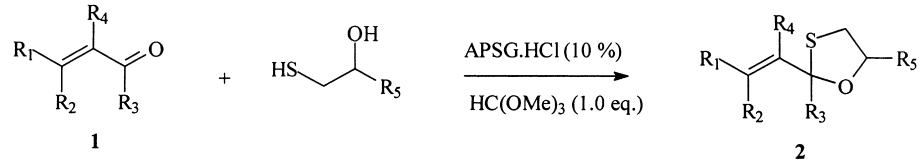
2–4). In the case of **6d**, the formation of the dithioacetal **5d** was predominant with 44% of selectivity. The formation of **5b** in 32% selectivity was also observed with **6b**. Acetal **6e** led preferentially to the Michael-type addition product **4e**. These results were attributed to the low steric hindrance of the acetals derived from aldehydes. Some attempts to work in diluted solution or at lower temperature did not allow significant improvement of the selectivities.

Although the two step synthesis produced the expected oxathiolanes **2a**, **2b** and **2f** in moderate to good yields, substrates such as **6d** and **6e** did not react selectively and **2d** and **2e** were obtained in low yields. This lack of generality led us to undertake further studies, particularly on the use of mild and efficient APSG·HCl as the catalyst.

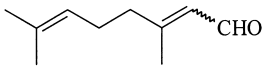
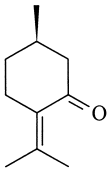
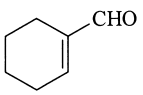
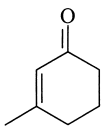
2.3. Formation of α,β-unsaturated oxathiolanes via heterogeneous catalysis

The silica gel supported catalyst, APSG·HCl, resulted to be efficient for the selective synthesis of oxathiolanes **2** directly from α,β-unsaturated carbonyl derivatives **1** and 2-mercaptoalcohol, in reactions performed in the presence of 10% of the catalyst and 1 equiv. of trimethylorthoformate. For

Table 3. Formation of oxathiolanes **2** catalyzed by APSG·HCl



1 2

Entry	Carbonyl derivative **1**	R_5	Conditions	Product **2**	Yield[a]
1	**1a**	H	MeOH, 0°C, 1 h	**2a**	77
2	**1b**	H	CH_2Cl_2 refluxing, 1 h	**2b**	91[b]
3	**1c**	H	MeOH, −15°C, 5 h	**2c**	60
4	**1d**	H	CH_2Cl_2 refluxing, 1 h	**2d**	56
5	**1e**	H	CH_2Cl_2 refluxing, 1 h	**2e**	73
6	**1g**	H	CH_2Cl_2 refluxing, 2 h	**2g**	42
7	**1b**	Me	CH_2Cl_2, rt, 1 h	**2h**	76[c]
8	**1a**	*n*-hex	MeOH, 0°C, 2 h	**2i**	73[d]
9	 **1j** (*cis*/*trans* mixture)	H	CH_2Cl_2 refluxing, 1.5 h	**2j**	72
10	 **1k**	H	MeOH, 0°C, 6 h	**2k**	53
11	 **1l**	H	CH_2Cl_2 refluxing, 2 h	**2l**	77
12	 **1m**	H	MeOH, −15°C, 5 h	**2m**	54

[a] Isolated yields after silica gel column chromatography.
[b] Reaction was carried out using 1% of catalyst, and purified by distillation in a bulb to bulb oven.
[c] A 70:30 mixture of diastereoisomeres was obtained.
[d] A 55:45 mixture of diastereoisomeres was obtained.

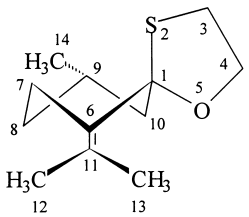
unsaturated aldehyde derivatives, reactions were best carried out in refluxing methylene chloride, and in cold methanol (−15 to 0°C) for α,β-unsaturated ketones. In methanol reactions at higher temperatures, we could observed the formation of an oxathiolane derivative **7**, in which MeOH was added in a 1,4-fashion on the product **2** (Scheme 3). Thus, in the case of the reaction of mesityl oxide **1c**, the by-product **7c** was obtained in a 55% selectivity after 2 h at room temperature. When operating in methanol at 0°C to −15°C, adducts **7** were formed in less than 5% yield, and under optimized conditions, oxathiolanes **2** were obtained selectively and in good isolated yields, as summarized in Table 3.

The reaction of aromatic carbonyl derivatives such as 4-phenylbutenone **1a** or cinnamaldehyde **1b**, readily afforded the corresponding oxathiolanes **2a** and **2b** in isolated yields of 77 and 91%, respectively (entries 1, 2). Aliphatic substrates **1c**–**1e** and **1g** were less selective toward the addition of the mercapto alcohol, but led to **2** in moderate to good yields (entries 3–6). Crotonaldehyde **1d** led to oxathiolane **2d** in a 56% yield. This yield was low compared to that obtained for the analogous substrate **1e** (compare entries 4, 5), and this fact could be attributed to the low boiling point of **2d**, and to its partial evaporation during removal of solvent upon treatment. In the case of **1g**, the presence of an alkyl group at the α position of the carbonyl group of **1** increasing the steric hindrance may explain the lower yield of **2g** (42%, entry 6).

When the 2-mercaptoalcohol had an alkyl group such as methyl or *n*-hexyl[28] at the 1-position, the reaction proceeded without significant loss of reactivity, and **2h** and **2i** could be obtained in 76 and 73% yields, respectively from **1b** or **1a** (entries 7, 8).

The reaction was also performed successfully on natural terpenic products. For example, citral **1j** (mixture *cis*/*trans* of geranial and neral) led after 1.5 h to the corresponding oxathiolane **2j** in good yield (72% of *cis*/*trans* mixture, entry 9). Moreover, reaction occurred without isomerization of the α double bond, and the unsaturation of the terminal chain of **1j** remained unaffected under the reaction conditions.

The reaction of pulegone **1k** afforded **2k** in fairly good yield (53%, entry 10). Interestingly, this reaction proceed with excellent stereoselectivity, and a diastereomeric excess of 98% was obtained, as determined by GC/MS. The stereochemistry of the main diastereoisomer of **2k** was examined by ^{1}H NMR (Scheme 4). The coupling constants of H_7, H_8, and of two H_{10} were calculated. The signals of H_9 and of the second H_7 and H_8 were superimposed. One H_8 has three coupling constants of 13.0 Hz, which correspond to one ^2J coupling and two axial–axial couplings. This indicates that H_9 is in an axial position, and thus, that the methyl-14 is in an equatorial position. This fact was confirmed by the W type long range coupling ^4J=2.1 Hz between the equatorial H_{10} and the second H_8, necessarily in an equatorial position. Moreover, the NOESY spectrum showed a correlation spot between one H_4 α to oxygen and the protons of methyl-13. We could therefore, conclude that one H of the methylene group at the 4-position should be in an equatorial position close to the methyl-13, and that the oxygen and the methyl-14 are on a relative *cis* position.



Scheme 4. Configuration of main isomer of **2k**.

The reaction proceeded well when the double bond was in a cycle such as in aldehyde **1l**, which led to the corresponding oxathiolane **2l** in a 77% yield (entry 11). The reaction of 3-methylcyclohexenone **1m** led to the spiro derivative **2m** in 54% yield (entry 12). We could notice that the substitution at the 3-position of the unsaturated ketone avoided Michael addition products. Indeed, under the same conditions, the reaction of cyclohexenone did not provide **2**, but exclusively the Michael addition product **3** in quantitative yield.

This α,β-unsaturated oxathiolane formation method was shown to be very versatile. A large variety of carbonyl derivatives and mercapto alcohols reacted in good isolated yields. Moreover, the double bond of the α,β-unsaturated carbonyl compounds (aldehydes or ketones) could either be in a linear chain (entries 1–9), or in a cycle (entries 11, 12) or in an exocyclic position (entry 10).

Except for **2b**,[14] all other oxathiolanes **2a**–**m** were prepared and characterized for the first time.

The reaction described here with the use of APSG·HCl as the supported catalyst was clean and the workup procedure was very simple. Filtration of the catalyst was followed by removal of the solvent in vacuo. Crude products were purified by silica gel column. The catalyst could be further reused after washing with no significant loss of activity. Thus, the reaction of **1b** under the same conditions as entry 2 led, with the regenerated catalyst, to the oxathiolane **2b** in an isolated yield of 90%.

3. Conclusion

In summary, we have shown that the formation of various unsaturated oxathiolanes from α,β-unsaturated aldehydes or ketones could be easily effected in good yields with supported APSG·HCl as the catalyst. The workup of the reaction was achieved by filtration of the catalyst and removal of the solvent. Most of the oxathiolanes are new compounds and were obtained in isolated yields of 53–91%.

4. Experimental

4.1. General

All solvents used were dried and distilled according to the standard procedures. ^{1}H and ^{13}C NMR data were recorded

on a Bruker AC 200 FT spectrometer with TMS as internal reference. 2D ^{1}H NMR spectra were recorded on a Bruker AC 500 spectrometer. GC analysis was carried out using an HP-5890 gas chromatograph. GC/MS analysis was accomplished by using an HP-5890 chromatograph coupled to a 5970A mass selective detector. Mass spectra were obtained by electron ionization at 70 eV and source temperature of 250°C. Elemental analysis were performed at the service of ICSN at Gif sur Yvette, France. Infrared spectra were recorded neat, as KBr pellets, on a Mattson infrared spectrophotometer.

Chromatographic separations were performed using 70–260 mesh (SDS) silica gel eluted with hexane/dichloromethane mixtures by changing the gradient from 95/5 to 80/20. Thin-layer chromatography was carried out on SDS precoated silica plates (60/15 m layer thickness).

4.2. General procedure for the synthesis of α,β-unsaturated oxathiolanes by conventional catalysis

The reactions were performed with **1a**–**d** (10 mmol) and 2-mercaptoethanol (10 mmol) under nitrogen atmosphere in dry solvent. The temperature, the catalyst and the desiccant are indicated in Table 1. $MgSO_4$ was heated at 120°C before use and 4 Å molecular sieves were heated under vacuum. The monitoring of the reaction was made by GC, and the conversions were determined by comparison with dodecane, used as internal standard. Compounds **2a**–**4a** and **2b**–**2d** were isolated by silica gel column chromatography. **5b** was purified by crystallization in dichloromethane. The other by-products from **1c** and **1d** were not isolated and were analysed by their MS spectra.

4.3. General procedure for the synthesis of α,β-unsaturated oxathiolanes from acetals

Acetals **6a**, **6b** and **6d**, **6e** were prepared according to the reported procedure,[25] from **1** (50 mmol) in methanol (100 ml) at room temperature, using APSG·HCl (1.0 g) and trimethylorthoformate (50 mmol). The reaction was stopped when the disappearance of **1** was complete as checked by GC. The mixture was filtered off and the solvent was removed in vacuo. Derivatives **6** were obtained in 95% to quantitative yields.

Acetal **6f** was obtained according to Ref. 26 from chalcone **1f** (50 mmol) in trimethylorthoformate as the solvent (150 ml) catalyzed by Dowex 50W-X4 cation-exchange resin (8.0 g) at room temperature. The completion of the reaction was monitored by GC. After filtration of the mixture and evaporation of the solvent, **6f** was obtained in 93% yield. All the acetals were used with any further purification.

The exchange reaction was performed with acetals **6** (10 mmol) and 2-mercaptoethanol (10 mmol) in methanol at room temperature with APSG·HCl (0.2 g) as the catalyst. The reactions were stopped when the disappearance of **6** was complete as monitored by GC. The mixture was then filtered off and the solvent was evaporated in vacuo. The crude product was purified by silica gel column chromatography using a gradient of hexane and dichloromethane as the eluents.

4.4. General procedure for the synthesis of α,β-unsaturated oxathiolane via heterogeneous catalysis

A mixture of a carbonyl derivative **1** (10 mmol), of 2-mercaptoalcohol (11 mmol), and of trimethylorthoformate (10 mmol) catalyzed by APSG·HCl (1.0 g) in the solvent and at the temperature given in Table 3 was stirred under nitrogen atmosphere. After complete consumption of **1** according to GC analysis, the mixture was filtered off and the solvent evaporated in vacuo. The crude product was purified by silica gel column chromatography using a gradient of hexane and dichloromethane as the eluents.

4.5. Synthesis and regeneration of APSG·HCl

The procedure was followed according to Gasparrini:[25] Lichroprep-NH_2™ 25–40 μm, Merck (10.0 g) was suspended in methanol (50 ml), and 10 ml HCl (37%) were added. After 15 min stirring at room temperature, the mixture was filtered off and the collected precipitate was washed successively with methanol (100 ml) and dichloromethane (10 ml), and dried under vacuum. Regeneration of the catalyst: the filtered solid was washed with methanol, water and again with methanol and treated as described.

4.6. Spectral data

4.6.1. 2-Methyl-2-styryl-1,3-oxathiolane (2a). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.80 (3H, s), 3.15 (2H, m), 4.20 (2H, m), 6.30 (1H, d, J=15.8 Hz), 6.60 (1H, d, J=15.8 Hz), 7.2–7.4 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.0 (CH_3), 34.4 (C-4), 71.0 (C-5), 93.4 (C-2), 126.8, 128.7, 127.4, 127.8, 133.7, 136.6. MS, *m/z* (%): 77 (43.6), 103 (71.5), 131 (100), 145 (67.0), 146 (40.0), 191 (17.2), 206 (M^+, 19.1), 208 (1.0). Elemental analysis: found C, 69.78; H, 6.84; O, 7.94; S, 15.43. $C_{12}H_{14}OS$ requires C, 69.85; H, 6.85; O, 7.75; S, 15.54%.

4.6.2. 2-Styryl-1,3-oxathiolane (2b). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.12 (2H, m), 3.88 (1H, m), 4.38 (1H, m), 5.68 (1H, d, J=7.4 Hz), 6.28 (1H, dd, J=7.4, 15.8 Hz), 6.65 (1H, d, J=15.8 Hz), 7.2–7.4 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.6 (C-4), 71.6 (C-5), 86.2 (C-2), 126.7, 127.1, 128.0, 128.5, 132.0, 135.8. MS, *m/z* (%): 77 (19.6), 104 (54.8), 115 (21.6), 131 (100), 132 (25.8), 192 (M^+, 88.9), 194 (4.5). Elemental analysis: found C, 68.55; H, 6.58; O, 8.52; S, 16.33. $C_{11}H_{12}OS$ requires C, 68.70; H, 6.30; O, 8.32; S, 16.68%.

4.6.3. 2-Methyl-2-[2-methylpropenyl]-1,3-oxathiolane (2c). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71 (3H, d, J=1.4 Hz), 1.72 (3H, s), 1.78 (3H, d, J=1.2 Hz), 3.12 (2H, dd, J=6.3, 5.8 Hz), 4.05 (1H, dt, J=9.2, 6.5 Hz), 4.19 (1H, dt, J=9.2, 5.5 Hz), 5.50 (1H, sept., J=1.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.9, 26.6, 30.2, 34.0 (C-4), 69.9 (C-5), 93.4 (C-2), 130.9, 133.4. MS, *m/z* (%): 43 (34.6), 55 (24.2), 83 (100), 98 (14.6), 99 (14.3), 113 (5.5), 143 (18.6), 158 (M^+, 10.8), 160 (0.6). Elemental analysis: found: C, 60.58; H, 8.88; O, 10.29; S, 20.24. $C_8H_{14}OS$ requires C, 60.70; H, 8.93; O, 10.11; S, 20.26%.

4.6.4. 2-Propenyl-1,3-oxathiolane (2d). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.72 (3H, dd, J=6.4, 1.3 Hz), 3.05 (2H, m), 3.80 (1H, ddd, J=9.1, 8.2, 6.4 Hz), 4.34 (1H, J=9.1, 5.7, 3.5 Hz), 5.45 (1H, d, J=7.7 Hz), 5.59 (1H, ddq, J=14.8, 7.6, 1.4 Hz), 5.82 (1H, dq, J=14.8, 6.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5, 33.6 (C-4), 71.4 (C-5), 86.3 (C-2), 129.3, 129.8. MS, *m/z* (%): 39 (39.1), 45 (35.3), 59 (47.1), 60 (100), 61 (41.2), 69 (50.6), 85 (18.8), 130 (M^+, 66.7), 132 (3.4). Elemental analysis: found: C, 57.88; H, 8.07; O, 11.91; S, 21.96. $C_6H_{10}OS$ requires C, 58.27; H, 8.40; O, 11.09; S, 22.23%.

4.6.5. 2-Hexenyl-1,3-oxathiolane (2e). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.3 Hz), 1.40 (2H, sex., J=7.3 Hz), 2.04 (2H, qd, J=7.3, 1.1 Hz), 3.09 (2H, m), 3.81 (1H, ddd, J=9.1, 8.2, 6.4 Hz), 4.35 (1H, ddd, J=9.1, 5.7, 3.5 Hz), 5.46 (1H, d, J=7.7 Hz), 5.57 (1H, ddt, J=14.7, 7.6, 1.1 Hz), 5.80 (1H, dt, J=14.7, 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 21.9, 33.6, 34.0, 71.4 (C-5), 86.4 (C-2), 128.0, 134.9. MS, *m/z* (%): 41 (39.1), 59 (37.8), 60 (100), 61 (42.9), 85 (17.4), 97 (33.6), 98 (88.7), 115 (62.6), 129 (15.0), 158 (M^+, 37.3), 160 (2.0). Elemental analysis: found C, 60.35; H, 8.89; O, 10.52; S, 19.86. $C_8H_{14}OS$ requires C, 60.70; H, 8.93; O, 10.11; S, 20.26%.

4.6.6. 2-Phenyl-2-styryl-1,3-oxathiolane (2f). White solid, Mp 54–55°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.14 (2H, m), 4.11 (1H, dt, J=9.0, 6.4 Hz), 4.27 (1H, dt, 9.0, 5.8 Hz), 6.50 (2H, s), 7.1–7.4 (8H, m), 7.5–7.6 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.4 (C-4), 70.7 (C-5), 97.3 (C-2), 126.2, 126.7, 127.7, 127.8, 128.1, 128.4, 129.5, 132.6, 136.1, 143.0. MS, *m/z* (%): 77 (57.1), 105 (31.4), 131 (27.9), 165 (17.5), 180 (25.1), 207 (100), 208 (38.0), 268 (M^+, 39.3), 270 (2.5). Elemental analysis: found C, 75.74; H, 6.01; O, 5.94; S, 11.82. $C_{17}H_{16}OS$ requires C, 76.07; H, 6.02; O, 5.96; S, 11.95%.

4.6.7. 2-[1-Methylbutenyl]-1,3-oxathiolane (2g). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.5 Hz), 1.68 (3H, d, J=1.0 Hz), 2.06 (2H, Quint., J=7.5 Hz), 3.07 (2H, m), 3.76 (1H, m), 4.43 (1H, m), 5.49 (1H, s), 5.58 (1H, t, J=7.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.9, 13.7, 21.0, 33.6 (C-4), 74.0 (C-5), 91.2 (C-2), 131.1, 131.9. MS, *m/z* (%): 41 (91.5), 55 (37.6), 60 (100), 69 (75.3), 83 (35.5), 89 (21.5), 98 (85.7), 129 (72.8), 143 (16.0), 158 (M^+, 33.4), 160 (1.7).

4.6.8. 2-Styryl-5-methyl-1,3-oxathiolane (2h). The two diastereoisomers could not be separated after silica gel column chromatography. Analysis was made on a 70:30 mixture. Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ Minor diastereoisomer: 1.39 (3H, d, J=6.1 Hz), 2.76 (1H, t, J=10.1 Hz), 3.21 (1H, dd, J=10.1, 5.0 Hz), 4.50 (1H, Hept., J=5.0 Hz), 5.81 (1H, d, J=7.2 Hz), 6.29 (1H, dd, J=15.8, 7.2 Hz), 6.59 (1H, d, J=15.8 Hz), 7.2–7.5 (5H, m). Major diastereoisomer: 1.47 (3H, d, J=5.9 Hz), 2.79 (1H, t, J=9.8 Hz), 3.15 (1H, dd, J=4.12 (1H, Hept. d, J=5.4, 1.0 Hz), 5.70 (1H, d, J=7.7 Hz), 6.29 (1H, dd, J=15.8, 7.7 Hz), 6.66 (1H, d, J=15.8 Hz), 7.2–7.4 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0 (CH_3), 39.6+40.0 (C-4), 78.5+80.2 (C-5), 84.0+85.7 (C-2), 126.7, 126.8, 127.1, 128.0, 128.1, 128.5, 128.6, 131.0, 132.5, 135.9, 136.5. MS, *m/z* (%): Minor: 74 (34.4), 77 (30.3), 104 (98.1), 115 (32.8), 131 (100), 132 (24.9), 161 (3.3), 206 (M^+, 68.6), 208 (3.8). Major: 74 (32.9), 77 (30.5), 104 (97.1), 115 (32.7), 131 (100), 132 (22.9), 161 (3.4), 206 (M^+, 64.1), 208 (3.5). Elemental analysis: found C, 69.85; H, 6.83; O, 8.05; S, 15.36. $C_{12}H_{14}OS$ requires C, 69.85; H, 6.85; O, 7.75; S, 15.54%.

4.6.9. 2-Methyl-2-styryl-5-hexyl-1,3-oxathiolane (2i). The two diastereoisomers could not be separated after silica gel column chromatography. Analysis was made on a 55:45 mixture. Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89+0.90 (3H, dt, J=7.2 Hz), 1.2–1.6 (10H, m), 1.80+1.81 (3H, s), 2.85 (1H, t, J=10.0 Hz), 3.11 (ddd, J=10.0, 4.5, 2.6 Hz), 4.25 (1H, m), 6.30+6.39 (1H, d, J=15.9 Hz), 6.61 (1H, d, J=15.9 Hz), 7.1–7.4 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 22.6, 26.4, 29.0, 29.3, 30.0, 31.8, 34.1, 34.2, 39.1 (C-4), 82.9+83.7 (C5), 92.0+92.7 (C-1), 126.7, 126.8, 127.0, 127.6, 127.7, 128.1, 128.5, 128.6, 134.6. Elemental analysis: found C, 74.20; H, 9.02; O, 5.64; S, 11.09. $C_{18}H_{26}OS$ requires C, 74.41; H, 9.04; O, 5.51; S, 11.04%.

4.6.10. 2-[2,6-Dimethylhepta-1,5-dienyl]-1,3-oxathiolane (2j). Colorless oil. Analysis was made on a 55:45 mixture of *cis*/*trans* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) δ minor isomer: 1.60 (3H, m), 1.68 (3H, m), 1.76 (3H, d, J=1.4 Hz), 2.0–2.2 (4H, m), 3.76 (2H, m), 4.37 (2H, m), 5.08 (1H, m), 5.41 (1H, quint., J=1.1 Hz), 5.79 (1H, d, J=3.0 Hz). Major isomer: 1.60 (3H, m), 1.68 (3H, m), 1.71 (3H, d, J=1.2 Hz), 2.0–2.2 (4H, m), 3.76 (2H, m), 4.37 (2H, m), 5.08 (1H, m), 5.36 (1H, quint., J=1.2 Hz), 5.75 (1H, d, J=3.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.9, 17.7 (×2), 23.5, 26.2 (×2), 26.7, 32.0, 33.7, 33.8, 39.4, 71.3 (×2, C-5), 82.3+82.6 (C-2), 122.7, 123.5, 123.6, 123.7, 131.9, 132.3, 141.1 (×2). MS, *m/z* (%): Minor: 41 (75.4), 55 (44.9), 69 (100), 84 (33.4), 109 (32.5), 123 (7.2), 143 (14.4), 184 (28.9), 197 (2.5), 212 (M^+, 11.6). Major: 41 (57.5), 55 (35.5), 69 (100), 84 (39.2), 109 (14.0), 123 (11.7), 143 (26.0), 184 (9.8), 197 (1.0), 212 (M^+, 2.7). Elemental analysis: found C, 67.57; H, 9.43; O, 7.87; S, 14.98. $C_{12}H_{20}OS$ requires C, 67.86; H, 9.51; O, 7.53; S, 15.10%.

4.6.11. 6-Isoprenyl-9-methyl-5,2-oxathiospiro[4.5]decane (2k). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (1H, qd; J=13.0, 3.7 Hz), 0.97 (3H, d, J=6.5 Hz), 1.61 (1H, t, J=12.2 Hz), 1.71 (3H, d, J=0.7 Hz), 1.72 (1H, m), 1.85 (2H, m), 1.96 (3H, d, J=1.5 Hz), 2.00 (1H, ddd, J=12.2, 3.9, 2.1 Hz), 2.76 (1H, dt, J=14.2, 3.5 Hz), 2.97 (1H, ddd, J=10.0, 8.4, 5.6 Hz), 3.10 (1H, m), 4.09 (1H, ddd, J=9.0, 8.4, 5.2 Hz), 4.36 (1H, ddd, J=9.0, 5.6, 3.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4, 21.6, 23.3, 30.9, 32.3, 33.1, 35.5, 51.2, 71.1 (C-5), 101.4 (C-2), 120.6, 133.2. MS, *m/z* (%): 41 (38.6), 67 (54.6), 81 (100), 82 (27.3), 109 (44.9), 137 (80.7), 152 (41.8), 197 (77.3), 212 (M^+, 45.5), 214 (2.8). Elemental analysis: found C, 67.61; H, 9.51; O, 7.69; S, 14.92. $C_{12}H_{20}OS$ requires C, 67.86; H, 9.51; O, 7.53; S, 15.10%.

4.6.12. 2-Cyclohexenyl-1,3-oxathiolane (2l). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5–1.7 (4H, m), 1.9–2.2 (4H, m), 3.05 (2H, m), 3.79 (1H, m), 4.40 (1H, m), 5.50 (1H, s), 5.86 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3, 22.9, 25.0, 33.4, 71.9 (C-5), 89.8 (C-2), 128.8, 135.7. MS, *m/z*

(%): 39 (49;5), 53 (45.5), 60 (60.4), 79 (62.1), 81 (82.9), 95 (34.7), 109 (29.8), 110 (68.3), 141 (9.1), 170 (M^+, 100), 172 (4.9). Elemental analysis: found C, 63.21; H, 8.31; O, 9.65; S, 18.68. $C_9H_{14}OS$ requires C, 63.47; H, 8.30; O, 9.39; S, 18.83%.

4.6.13. 7-Methyl-5,2-oxathiospiro[4.5]dec-6-ene (2m). Colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.66 (3H, s), 1.70–2.05 (6H, m), 3.10 (2H, m), 4.12 (1H, ddd, J=9.2, 6.7, 5.7 Hz), 4.24 (1H, ddd, J=9.2, 5.8, 5.3 Hz), 5.53 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 23.4, 29.6, 34.1, 37.5, 69.9 (C-4), 92.8 (C-1), 125.6 (C-6), 137.9 (C-7). MS, m/z (%): 39 (18.9), 60 (13.7), 77 (9.8), 79 (10.9), 82 (79.9), 95 (11.3), 111 (100), 170 (M^+, 34.0), 172 (1.8). Elemental analysis: found C, 63.21; H, 8.33; O, 9.55; S, 18.65. $C_9H_{14}OS$ requires C, 63.47; H, 8.30; O, 9.39; S, 18.83%.

4.6.14. 4-Phenyl-7-hydroxy-5-thiaheptan-2-one (3a). Colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 2.05 (3H, s), 2.45 (2H, t, J=5.9 Hz), 2.90 (2H, dd, J=7.2, 3.1 Hz), 3.55 (2H, m), 4.30 (1H, t, J=7.2 Hz), 7.1–7.3 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.8, 34.2, 43.8, 50.2, 60.8, 127.6, 128.1, 128.9, 142.0, 205.6. MS, m/z (%): 43 (100), 77 (16.3), 103 (22.0), 105 (19.6), 147 (14.4), 179 (6.0), 206 (2.2), 224 (M^+, 3.6), 226 (0.2). IR (cm^{-1}): 1712, 3432.

4.6.15. 2-Methyl-2-[5-hydroxy-2-phenyl-3-thiapentyl]-1,3-oxathiolane (4a). Colorless oil. 50:50 mixture of two diastereoisomers. ^1H NMR (200 MHz, $CDCl_3$) δ 1.39+1.45 (3H, s), 2.45 (4H, m), 3.05 (2H, m), 3.55 (2H, m), 4.08 (3H, m), 7.1–7.3 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.7 (×2), 34.3 (×2), 34.5, 45.6, 45.9, 49.0, 49.3, 60.3 (×2), 70.0, 70.3, 127.4, 128.1, 128.7, 143.2. MS, m/z (%): 43 (92.9), 77 (10.0), 103 (100), 147 (18.3), 167 (7.1), 179 (7.6), 206 (12.7), 239 (3.6), 284 (M^+, 7.0), 286 (0.7).

4.6.16. 4-Styryl-3,5-dithiaheptan-1,7-diol (5b). White solid, Mp 87–88°C. ^1H NMR (200 MHz, DMSO-d) δ 2.70 (4H, td, J=6.4, 3.0 Hz), 3.57 (4H, q, J=6.4 Hz), 4.80 (1H, d, J=9.0 Hz), 4.86 (2H, t, J=5.5 Hz), 6.19 (1H, dd, J=15.6, 9.0 Hz), 6.60 (1H, d, J=15.6 Hz), 7.25–7.55 (5H, m). ^{13}C NMR (50 MHz, DMSO-d_6) δ 33.2, 50.8, 60.5, 126.3, 127.8, 128.0, 128.6, 130.3, 135.7. IR (cm^{-1}): 3298.4. Elemental analysis: found C, 57.74; H, 6.76; O, 11.65; S, 23.61. $C_{13}H_{18}O_2S_2$ requires C, 57.73; H, 6.72; O, 11.83; S, 23.72%.

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