Enantioselective copper catalyzed allylic alkylation using Grignard reagents; Applications in synthesis
Zijl, Anthoni Wouter van
Chapter 5

Straightforward synthesis of α,β-unsaturated thioesters via olefin cross-metathesis with thioacrylate

In this chapter the cross-metathesis reaction of S-ethyl thioacrylate with a range of olefins is described, as well as a new procedure for the preparation of S-ethyl thioacrylate via a Wittig reaction. The metathesis reaction is catalyzed effectively using a commercially available ruthenium benzylidene olefin metathesis catalyst. This new preparative method provides a convenient and versatile route to substituted α,β-unsaturated thioesters; key building blocks in organic synthesis.*

* This chapter has been published in part: van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, 73, 5651-5653.
5.1 Introduction

Thioesters are becoming increasingly important compounds due to their distinctive chemical properties; the reduced electron delocalization provides for enhanced reactivity compared to oxoesters.\(^1\) The importance of thioesters in the cell is well established; biological systems use their relative reactivity in many enzymatic reactions by employing, for example, acetyl coenzyme A, cysteine proteases or polyketide and fatty acid synthases.\(^2\) Their enhanced reactivity compared to oxoesters has been employed successfully in a wide range of synthetic organic transformations, some inspired directly by related biosynthetic pathways. Stereoselective aldol reactions often depend on the distinctive reactivity of thioesters\(^3\) and their synthetic versatility is further illustrated by other well-known transformations including \(\alpha\)-alkylations,\(^4\) selective reductions\(^4,5\) and Pd-catalyzed coupling reactions\(^6\) amongst others.\(^7\) \(\alpha,\beta\)-Unsaturated thioesters show important differences in their reactivity as Michael acceptors compared to oxoesters.\(^3d,8\) They have been found to be excellent substrates in the enantioselective Cu-catalyzed conjugate additions of Grignard reagents\(^9\) and their reactivity has proven exceptionally versatile in the synthesis of several natural products.\(^9b,10\)

Although a highly useful intermediate, occasionally difficulties are encountered in the synthesis of \(\alpha,\beta\)-unsaturated thioesters through classic methods,\(^11\) such as DCC/DMAP-coupling of acids with thiols and trans-esterification with trimethylsilyl thioethers, due to 1,4-addition of thiolate to the product.

![Scheme 5.1](image)

Scheme 5.1: Formation of a by-product in trans-esterification through conjugate addition of thiolate to the thioester product.

For example, a thioester intermediate in the total synthesis of lasiol and faranal was obtained via the trans-esterification of the corresponding oxo methyl ester (Scheme 5.1).\(^12\) Up to 10% of the thiolate adduct was obtained,
which was difficult to separate from the main product. As routine application of α,β-unsaturated thioesters relies on methods that give ready access to these compounds, we were interested in examining whether it was possible to synthesize these compounds via cross-metathesis with a thioacrylate. This is a particularly attractive route, also, because it would be directly applicable to the products of copper catalyzed allylic alkylation, which contain a terminal olefin, as was demonstrated in chapter 4.

5.1.1 Cross-metathesis with sulfur containing compounds

Ruthenium-catalyzed olefin metathesis has emerged as one of the most versatile of synthetic methods over the past decade.\(^\text{13}\) It is frequently the method of choice for the construction of carbon-carbon double bonds. In particular, cross-metathesis allows for the formation of highly complex products from much simpler precursors.\(^\text{14}\) The increased functional group tolerance as a result of the development of new catalysts (Figure 5.1), their commercial availability and the Grubbs model to predict the selectivity\(^\text{15}\) have enhanced greatly the utility of cross-metathesis reactions.

![Ruthenium based metathesis catalysts](image)

Figure 5.1: Ruthenium based metathesis catalysts; Grubbs 1\(^{\text{st}}\) generation (G-1), Hoveyda-Grubbs 1\(^{\text{st}}\) generation (HG-1), Grubbs 2\(^{\text{nd}}\) generation (G-2), Hoveyda-Grubbs 2\(^{\text{nd}}\) generation (HG-2), Grela’s catalyst (Gre-2).

The use of electron deficient terminal olefins as cross-metathesis partners, such as acrylates and vinyl ketones, which are type II or type III olefins according to the Grubbs model, is now relatively widespread. The application of sulfur containing alkenes has been described previously, also. The earliest reports of metathesis reactions with thioethers and disulfides featured molybdenum and tungsten catalysts.\(^\text{16}\) In 2002 the ruthenium based
Grubbs second generation catalyst (G-2) was found to catalyze metathesis reactions with thioethers and disulfide compounds, for which the Grubbs first generation catalyst was not applicable. The first report of the use of a thioester compound in metathesis, i.e. propargylic thiol benzoates and acetates for ethylene / alkyne metathesis (Scheme 5.2), was disclosed in the same year.

Scheme 5.2: Ethylene metathesis with propargylic thioesters; i) 5 mol% G-2, ethylene (60-80 psi), CH₂Cl₂, 97% (PG = Ac), 99% (PG = Bz).

Reports of the application of vinyl sulfides, dithianes and also non-conjugated unsaturated thioesters have followed. However, to the best of our knowledge the use of thioacrylate compounds has so far not been described.
5.2 Results and Discussion

Thioacrylates are not commercially available and the current preparative methods are either unsafe or expensive. Standard procedures for the preparation of thioesters were explored to obtain S-ethyl thioacrylate. However, the reactions of acryloyl chloride with ethane thiol, DCC/DMAP-coupling of acrylic acid and transesterification of methyl acrylate did not give satisfactory results. The reactions led to the formation of the 1,4-adduct of EtSH to thioacrylate as the major product or to complex mixtures, probably due to polymerisation of the product.

However, it was found that compound 2 (Scheme 5.3) could be prepared from Wittig reagent 1, which is readily available from bromoacetic acid, through DCC/DMAP-coupling with ethanethiol followed by reaction with PPh3. Thioacrylate 2 could be obtained in 73% yield after refluxing 1 in CH2Cl2 with 5 equiv. of paraformaldehyde. The reaction could be performed on a synthetically useful scale, yielding up to 25 mL of pure thioacrylate. This new method provides an excellent protocol to prepare thioacrylates on a multigram scale.

Scheme 5.3: Preparation of S-ethyl thioacrylate 2 through a Wittig reaction with reagent 1 and paraformaldehyde.

5.2.1 Optimization of metathesis reaction conditions

With a new route to thioacrylate 2 in hand, the compound was studied in a cross-metathesis reaction with a type I cross-metathesis partner, 1-octene, and five well-known catalysts (Figure 5.1). The results are summarized in Table 5.1, entries 1-5. As expected according to the Grubbs model, both the Grubbs and the Hoveyda-Grubbs 1st generation catalyst (G-1 and HG-1)
were found to be unsuitable for the reaction, since only dimerisation of the 1-octene was observed.

When using 2 mol% of the Grubbs 2\textsuperscript{nd} generation catalyst (G\textsubscript{-}2) and 2.5 equivalents of 1-octene, full conversion of the thioacrylate was observed after 20 h at room temperature and product (\textit{E})-3 could be isolated in 76\% yield. However, the Hoveyda-Grubbs 2\textsuperscript{nd} generation catalyst (HG\textsubscript{-}2\textsuperscript{24}) gave a cleaner reaction and under the same conditions (\textit{E})-3 was obtained in 93\%. The Gre\textsubscript{-}2 catalyst, reported by Grela and co-workers,\textsuperscript{25} was tested also, due to its known potential in metathesis reactions with electron deficient olefins. This catalyst did not provide full conversion, however, and (\textit{E})-3 was obtained in only 72\% yield. In all cases, only traces of the Z-isomer of 3 were detected, which were removed readily by column chromatography.

Table 5.1: Cross-metathesis reactions with S-ethyl thioacrylate and 1-octene.\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>cat</th>
<th>T</th>
<th>time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G\textsubscript{-}1 (2 mol %)</td>
<td>rt</td>
<td>20 h</td>
<td>nd\textsuperscript{b}</td>
</tr>
<tr>
<td>2</td>
<td>HG\textsubscript{-}1 (2 mol %)</td>
<td>rt</td>
<td>20 h</td>
<td>nd\textsuperscript{b}</td>
</tr>
<tr>
<td>3</td>
<td>G\textsubscript{-}2 (2 mol %)</td>
<td>rt</td>
<td>20 h</td>
<td>76%</td>
</tr>
<tr>
<td>4</td>
<td>HG\textsubscript{-}2 (2 mol %)</td>
<td>rt</td>
<td>20 h</td>
<td>93%</td>
</tr>
<tr>
<td>5</td>
<td>Gre\textsubscript{-}2 (2 mol %)</td>
<td>rt</td>
<td>20 h</td>
<td>72%</td>
</tr>
<tr>
<td>6</td>
<td>HG\textsubscript{-}2 (2 mol %)</td>
<td>reflux</td>
<td>60 min</td>
<td>94%</td>
</tr>
<tr>
<td>7</td>
<td>HG\textsubscript{-}2 (1 mol %)</td>
<td>reflux</td>
<td>120 min</td>
<td>94%</td>
</tr>
<tr>
<td>8</td>
<td>HG\textsubscript{-}2 (0.5 mol %)</td>
<td>reflux</td>
<td>24 h</td>
<td>42%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 2 (1.0 mmol), 1-octene (2.5 equiv), catalyst (0.5-2.0 mol%), CH\textsubscript{2}Cl\textsubscript{2} (c = 0.4 M); \textsuperscript{b} Only formation of tetradec-7-ene was observed.
Straightforward synthesis of $\alpha,\beta$-unsaturated thioesters via olefin cross-metathesis with thioacrylate

With the best catalyst, HG-2, the reaction temperature and catalyst loading were varied (entries 6-8). The reaction can be accelerated substantially by elevating the reaction temperature; heating the mixture in CH$_2$Cl$_2$ at reflux for 60 min yielded 94% of compound 3. With only 1 mol% catalyst, the same excellent yield was obtained in 120 min, but the use of 0.5 mol% of HG-2 led to incomplete conversion after 1 d and only 42% yield of 3.

These optimised conditions for the cross-metathesis reaction can be applied to a wide range of substrates to provide various $\alpha,\beta$-unsaturated thioesters (Table 5.2). The reactions were performed in CH$_2$Cl$_2$ heated to reflux with 2 mol% HG-2. Most cross-metathesis partners, which contain a terminal olefin and are not branched at the allylic position led to fast reactions, which provided the products in excellent yields (Table 5.2, entries 1-4). Thioesters with a phenyl ring or trimethylsilyl group at the $\gamma$-position (products 4 and 5) or a more remote oxoester group (products 6 and 7) were thus obtained.

Table 5.2: Cross-metathesis reactions with S-ethyl thioacrylate and a range of olefins.$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>CM-partner</th>
<th>product</th>
<th>time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph-Ph</td>
<td>1 h</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td>Me$_3$Si</td>
<td>Me$_3$Si</td>
<td>2 h</td>
<td>92%</td>
</tr>
<tr>
<td>3</td>
<td>AcO</td>
<td>AcO</td>
<td>4 h</td>
<td>86%</td>
</tr>
<tr>
<td>4</td>
<td>MeO$_2$C</td>
<td>MeO$_2$C</td>
<td>4 h</td>
<td>91%</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>18 h</td>
<td>72%</td>
</tr>
</tbody>
</table>

$^a$
Chapter 5

| 6<sup>b</sup> | HO₂C\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)OEt | 9 | 24 h | 83% |
| 7<sup>b</sup> | HO\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)OEt | 10 | 24 h | 93% |
| 8<sup>b</sup> | O\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)OEt | 11 | 24 h | 75% |
| 9<sup>b</sup> | Br\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)OEt | 12 | 24 h | 75% |
| 10<sup>b</sup> | OH\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)OEt | 13 | 24 h | 66% |
| 11<sup>b</sup> | OH\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)OEt | 14 | 24 h | 71% |
| 12<sup>b</sup> | TsHN\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)OEt | 15 | 24 h | 59% |
| 13<sup>b,c</sup> | AcO\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)OAc | 16 | 24 h | 65% |
| 14<sup>b,c</sup> | Br\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)CH₂\(-\)Br | 17 | 24 h | 64% |

<sup>a</sup> Reaction conditions: 2 (1.0 mmol), CM-partner (2.5 equiv), HG-2 (2.0 mol%), CH₂Cl₂ (c = 0.4 M), reflux; <sup>b</sup> HG-2 (4.0 mol%) added in 2 portions; <sup>c</sup> CM-partner (1.5 equiv).

Reaction with styrene, featuring a conjugated double bond, required an extended reaction time (Table 5.2, entry 5) providing the cinnamic acid thioester 8 in 72% yield after 18 h. In the case of linear terminal olefins with a carboxylic acid, an unprotected alcohol, an aldehyde or a bromide functionality, a second portion of catalyst was needed to bring the reaction to completion (entries 6-9); the same held for secondary and tertiary unprotected allylic alcohols and allyl tosylamide (entries 10-12). The products 9-15 were all obtained in good yield after 24 h.

Reactions with olefins containing an internal double bond, such as 1,4-diacetoxy-cis-but-2-ene or 1,4-dibromo-trans-but-2-ene, were performed
Straightforward synthesis of \( \alpha, \beta \)-unsaturated thioesters via olefin cross-metathesis with thioacrylate

with only 1.5 equivalents of the cross-metathesis partner and again two portions of the catalyst were needed (Table 5.2, entries 13 and 14). Crotonic acid thioesters with an acetoxy or bromo substituent at the \( \gamma \)-position (products 16 and 17, respectively) were obtained in good yield after 24 h. Cross-metathesis with 3,3-dimethyl-1-butene was attempted but product formation was not observed. The reaction was performed under the standard conditions employed in this chapter (as specified in Table 5.2), although with 3,3-dimethyl-1-butene as cosolvent.
5.3 Conclusions

In summary, a mild and scalable new route to \( S \)-ethyl thioacrylate is presented. The feasibility of the use of this olefin in cross-metathesis reactions with the Hoveyda-Grubbs second generation catalyst is demonstrated. The high functional group tolerance of the reaction allows the preparation of a broad range of versatile functionalized \( \alpha,\beta \)-unsaturated thioesters. The relevance of this new approach to obtain these compounds has been demonstrated in its application in the protocol to obtain vicinal dimethyl arrays, described in chapter 4.
5.4 Experimental Part

General Remarks: For general remarks, see the experimental part of previous chapters. In addition, the following remarks should be taken into account:

Catalyst Gre-2\textsuperscript{25} and Wittig reagent I\textsuperscript{23} were synthesized according to literature procedures. Paraformaldehyde and all cross-metathesis partners were purchased from chemical suppliers and used without further purification, with the exception of methyl 4-pentenoate, which was synthesized from 4-pentenoic acid and trimethylsilyldiazomethane, and allyl tosylamide, which was synthesized from allylamine and tosyl chloride.

\textit{S}-Ethyl thioacrylate (2):

\[ \text{CH}_3\text{CH}=[\text{CH}_2\text{S}]\text{CH}=[\text{CH}_2] \]

A flame dried Schlenk-flask under N\textsubscript{2}-atmosphere was charged with Wittig reagent I (29.8 g, 82 mmol), paraformaldehyde (12.3 g, 410 mmol) and CH\textsubscript{2}Cl\textsubscript{2} (200 mL). The resulting suspension was stirred for 30 min at reflux temperature. The mixture was concentrated in vacuo and the residue was suspended in n-pentane (100 mL) and filtered over silica. The filtercake was washed (10:90 Et\textsubscript{2}O/n-pentane, 250 mL) and the filtrates combined. Hydroquinone (ca. 30 mg) was added to the solution to prevent polymerisation and the solvents were removed by distillation at atmospheric pressure using an efficient fractionating column. The crude thioacrylate was further purified by distillation at reduced pressure (50 mbar, 56-58\degree C), which afforded 2 (6.93 g, 73\% yield) as a colorless oil. The compound was stored without stabilizer and used as such in the metathesis reactions; to prevent decomposition it was shielded from light and stored at 5-8 \degree C. \textsuperscript{1}H-NMR \( \delta \) 6.37 (dd, \( J = 17.2, 9.7 \) Hz, 1H), 6.28 (dd, \( J = 17.2, 1.6 \) Hz, 1H), 5.66 (dd, \( J = 9.7, 1.6 \) Hz, 1H), 2.96 (q, \( J = 7.4 \) Hz, 2H), 1.29 (t, \( J = 7.4 \) Hz, 3H); \textsuperscript{13}C-NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 190.0, 134.9, 125.7, 22.9, 14.4; MS (EI) \( m/z \) 116 (M\textsuperscript{+}, 37), 91 (6), 89 (6), 86 (17), 84 (25), 62 (10), 61 (16), 55 (100); HRMS Calcd. for C\textsubscript{5}H\textsubscript{8}OS 116.0296, found 116.0299.
(E)-S-ethyl non-2-enethioate (3):

A flame dried Schlenk-flask under N₂-atmosphere was charged with S-ethyl thioacrylate 2 (1.0 mmol, 116 mg), 1-octene (2.5 mmol, 395 μl) and CH₂Cl₂ (2.5 mL). Hoveyda-Grubbs 2nd generation catalyst (2 mol%, 20 μmol, 12.5 mg) was added and the resulting solution was stirred for 60 min at reflux temperature. The mixture was then concentrated in vacuo and the residue purified by flash column chromatography (SiO₂, 0.5 : 99.5 to 5 : 95 Et₂O / n-pentane gradient, Rf (2 : 98) = 0.45), which afforded 3 (188 mg, 94% yield) as a colorless oil; ¹H-NMR δ 6.89 (dt, J = 15.5, 7.0 Hz, 1H), 6.10 (dt, J = 15.5, 1.6 Hz, 1H), 2.94 (q, J = 7.4 Hz, 2H), 2.22-2.14 (m, 2H), 1.50-1.38 (m, 2H), 0.88 (t, J = 6.9 Hz, 1H); ¹³C-NMR δ 190.0, 145.3, 128.5, 32.1, 31.5, 28.7, 27.8, 22.9, 22.4, 14.7, 13.9; MS (EI) m/z 200 (M+, 11), 140 (10), 139 (100), 81 (6), 69 (36), 68 (11), 67 (7), 55 (66), 53 (9); HRMS Calcd. for C₁₁H₂₀OS 200.1235, found 200.1236.

(=)-S-ethyl 4-phenylbut-2-enethioate (4):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and allylbenzene (2.5 mmol, 330 μl) following the procedure described for 3 (reaction time: 60 min). Purification by flash column chromatography (SiO₂, 1 : 99 to 5 : 95 Et₂O / n-pentane gradient, Rf (1 : 99) = 0.15) afforded 4 (195 mg, 95% yield) as a colorless oil; ¹H-NMR δ 7.47-7.11 (m, 5H), 7.03 (dt, J = 15.4, 6.8 Hz, 1H), 6.10 (dt, J = 15.4, 1.6 Hz, 1H), 3.52 (d, J = 6.8 Hz, 2H), 2.94 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H); ¹³C-NMR δ 189.9, 143.1, 137.3, 129.4, 128.7, 128.6, 126.6, 38.3, 23.0, 14.7; MS (EI) m/z 206 (M⁺, 19), 146 (11), 145 (100), 127 (28), 117 (22), 116 (6), 115 (31), 91 (10); HRMS Calcd. for C₁₂H₁₄OS 206.0765, found 206.0756.

(=)-S-Ethyl 4-(trimethylsilyl)but-2-enethioate (5):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and allyltrimethylsilane (2.5 mmol, 397 μl) following the procedure described for 3 (reaction time: 2 h). Purification by flash column chromatography (SiO₂, 0.5 : 99.5 to 2 : 98 Et₂O / n-pentane gradient, Rf (2 : 98) = 0.4) afforded 5 (187 mg, 92% yield) as a colorless oil;
Straightforward synthesis of \( \alpha, \beta \)-unsaturated thioesters via olefin cross-metathesis with thioacrylate

\[ ^1H-NMR \; \delta \; 6.99 \; (dt, \; J = 15.3, \; 8.9 \; Hz, \; 1H), \; 5.97 \; (dt, \; J = 15.2, \; 1.3 \; Hz, \; 1H), \; 2.93 \; (q, \; J = 7.4 \; Hz, \; 2H), \; 1.72 \; (dd, \; J = 8.9, \; 1.3 \; Hz, \; 2H), \; 1.27 \; (t, \; J = 7.4 \; Hz, \; 3H), \; 0.06 \; (s, \; 9H); \; ^{13}C-NMR \; \delta \; 189.4, \; 144.2, \; 126.7, \; 24.9, \; 22.8, \; 14.8, \; -1.8, \; MS \; (EI) \; m/z \; 205 \; (8), \; 173 \; ([M-C_2H_5]^+, \; 48), \; 141 \; (60), \; 119 \; (21), \; 91 \; (5), \; 84 \; (5), \; 75 \; (7), \; 74 \; (9), \; 73 \; (100); \; HRMS \; Calcd. \; for \; C_7H_{13}OSiS = [M-C_2H_5]^+ \; 173.0456, \; found \; 173.0449. \]

**\((E)-6-(Ethylthio)-6-oxohex-4-enyl acetate (6):**

The title compound was prepared from \( S \)-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and 4-pentenyl acetate (2.5 mmol, 353 \( \mu \)l) following the procedure described for 3 (reaction time: 4 h). Purification by flash column chromatography (SiO\(_2\), 5 : 95 to 10 : 90 Et\(_2\)O / \( n \)-pentane gradient, \( R_f \) (10 : 90) = 0.25) afforded 6 (186 mg, 86% yield) as a colorless oil; \(^1H-NMR \; \delta \; 6.86 \; (dt, \; J = 15.5, \; 6.9 \; Hz, \; 1H), \; 6.11 \; (dt, \; J = 15.5, \; 1.6 \; Hz, \; 1H), \; 4.07 \; (t, \; J = 6.4 \; Hz, \; 2H), \; 2.93 \; (q, \; J = 7.4 \; Hz, \; 2H), \; 2.33-2.22 \; (m, \; 2H), \; 2.04 \; (s, \; 3H), \; 1.86-1.74 \; (m, \; 2H), \; 1.26 \; (t, \; J = 7.4 \; Hz, \; 3H); \; ^{13}C-NMR \; \delta \; 189.9, \; 170.9, \; 143.4, \; 129.2, \; 63.4, \; 28.6, \; 26.9, \; 23.0, \; 20.8, \; 14.7; \; MS \; (EI) \; m/z \; 216 \; (M^+, \; 2), \; 155 \; (19), \; 114 \; (6), \; 113 \; (100), \; 95 \; (31), \; 71 \; (6), \; 68 \; (6), \; 67 \; (45), \; 55 \; (6); \; HRMS \; Calcd. \; for \; C_{10}H_{16}O_3S \; 216.0820, \; found \; 216.0816.

**\((E)-Methyl 6-(ethylthio)-6-oxohex-4-enoate (7):**

The title compound was prepared from \( S \)-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and methyl 4-pentenoate (2.5 mmol, 285 mg) following the procedure described for 3 (reaction time: 4 h). Purification by flash column chromatography (SiO\(_2\), 5 : 95 to 10 : 90 Et\(_2\)O / \( n \)-pentane gradient, \( R_f \) (10 : 90) = 0.25) afforded 7 (184 mg, 91% yield) as a colorless oil; \(^1H-NMR \; \delta \; 6.85 \; (dt, \; J = 15.6, \; 6.5 \; Hz, \; 1H), \; 6.12 \; (dt, \; J = 15.6, \; 1.5 \; Hz, \; 1H), \; 3.68 \; (s, \; 3H), \; 2.93 \; (q, \; J = 7.4 \; Hz, \; 2H), \; 2.60-2.41 \; (m, \; 4H), \; 1.27 \; (t, \; J = 7.4 \; Hz, \; 3H); \; ^{13}C-NMR \; \delta \; 189.8, \; 172.5, \; 142.2, \; 129.3, \; 51.7, \; 32.1, \; 27.0, \; 23.0, \; 14.6; \; MS \; (EI) \; m/z \; 202 \; (M^+, \; 4), \; 142 \; (8), \; 141 \; (100), \; 113 \; (21), \; 109 \; (29), \; 81 \; (13), \; 71 \; (45), \; 59 \; (10), \; 53 \; (8); \; HRMS \; Calcd. \; for \; C_{9}H_{14}O_3S \; 202.0664, \; found \; 202.0673.
(E)-S-ethyl 3-phenylprop-2-enethioate (8):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and styrene (2.5 mmol, 287 μl) following the procedure described for 3 (reaction time: 18 h). Purification by flash column chromatography (SiO₂, 0.5 : 99.5 to 1 : 99 Et₂O / n-pentane gradient, Rᵣ (1 : 99) = 0.10) afforded 8 (139 mg, 72% yield) as a colorless oil; \(^{1}H\)-NMR δ 7.61 (d, \(J = 15.8\) Hz, 1H), 7.57-7.51 (m, 2H), 7.42-7.36 (m, 3H), 6.71 (d, \(J = 15.8\) Hz, 1H), 3.02 (q, \(J = 7.4\) Hz, 2H), 1.32 (t, \(J = 7.4\) Hz, 3H); \(^{13}C\)-NMR δ 189.9, 140.1, 134.1, 130.4, 128.9, 128.3, 125.0, 23.3, 14.8; MS (EI) \(m/z\) 192 (M⁺, 12), 132 (10), 131 (100), 103 (27), 77 (13); HRMS Calcd. for C₁₁H₁₂O₂S 192.0609, found 192.0599.

(13) (E)-6-(ethylthio)-6-oxohex-4-enoic acid (9):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and 4-pentenoic acid (2.5 mmol, 258 μl) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO₂, 0.5 : 5 : 95 to 2 : 20 : 80 AcOH / EtOAc / n-pentane gradient, Rᵣ (1 : 10 : 90) = 0.2) afforded 9 (156 mg, 83% yield) as an off-white solid. Traces of AcOH could be removed by trituration from CHCl₃ with n-pentane; mp = 69.5-69.8 °C; \(^{1}H\)-NMR δ 10.20 (br s, 1H), 6.84 (dt, \(J = 15.4, 6.7\) Hz, 1H), 6.15 (dt, \(J = 15.5, 1.5\) Hz, 1H), 2.95 (q, \(J = 7.4\) Hz, 2H), 2.59-2.49 (m, 4H), 1.28 (t, \(J = 7.4\) Hz, 3H); \(^{13}C\)-NMR δ 190.0, 178.2, 141.9, 129.3, 32.0, 26.6, 23.0, 14.6; MS (EI) \(m/z\) 188 (M⁺, 12), 128 (7), 127 (100), 109 (14), 99 (52), 81 (14), 71 (7), 57 (39), 55 (9), 53 (22); HRMS Calcd. for C₈H₁₂O₃S 188.0507, found 188.0516.

(E)-S-Ethyl 7-hydroxyhept-2-enethioate (10):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and 5-hexen-1-ol (2.5 mmol, 300 μl) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO₂, 40 : 60 to 70 : 30 Et₂O / n-pentane gradient, Rᵣ (50 : 50) = 0.25) afforded 10 (175 mg, 93% yield) as a colorless oil; \(^{1}H\)-NMR
Straightforward synthesis of $\alpha,\beta$-unsaturated thioesters via olefin cross-metathesis with thioacrylate

$\delta$ 6.88 (dt, $J = 15.5, 6.9$ Hz, 1H), 6.11 (dt, $J = 15.5, 1.5$ Hz, 1H), 3.65 (t, $J = 5.2$ Hz, 2H), 2.93 (q, $J = 7.4$ Hz, 2H), 2.28-2.19 (m, 2H), 1.66-1.50 (m, 4H), 1.36 (br s, 1H), 1.27 (t, $J = 7.4$ Hz, 3H); $^{13}$C-NMR δ 190.2, 144.7, 128.6, 62.0, 31.8, 31.6, 24.0, 22.8, 14.6; MS (EI) $m/z$ 188 (M$^+$, 7), 127 (31), 99 (5), 82 (7), 81 (100), 79 (8), 68 (9), 57 (6), 55 (16), 53 (10); HRMS Calcd. for C$_9$H$_{16}$O$_2$S 188.0871, found 188.0876.

(E)-S-Ethyl 6-oxohex-2-enethioate (11):

![Chemical structure](image)

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and 1-pentenal (2.5 mmol, 247 μl) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO$_2$, 10 : 90 to 20 : 80 Et$_2$O / n-pentane gradient, $R_f$ (10 : 90) = 0.2) afforded 11 (129 mg, 75% yield) as a colorless oil; $^1$H-NMR δ 9.79 (t, $J = 1.1$ Hz, 1H), 6.84 (dt, $J = 15.4, 6.7$ Hz, 1H), 6.12 (dt, $J = 15.5, 1.5$ Hz, 1H), 2.93 (q, $J = 7.4$ Hz, 2H), 2.67-2.61 (m, 2H), 2.55-2.47 (m, 2H), 1.26 (t, $J = 7.4$ Hz, 3H); $^{13}$C-NMR δ 200.0, 189.5, 142.0, 129.2, 41.5, 24.1, 22.9, 14.5; MS (EI) $m/z$ 172 (M$^+$, 29), 112 (8), 111 (100), 83 (49), 55 (46), 53 (7); HRMS Calcd. for C$_8$H$_{12}$O$_2$S 172.0558, found 172.0557.

(E)-S-Ethyl 7-bromohept-2-enethioate (12):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and 6-bromohex-1-ene (2.5 mmol, 337 μl) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO$_2$, 0.5 : 99.5 to 2 : 98 Et$_2$O / n-pentane gradient, $R_f$ (1 : 99) = 0.10) afforded 12 (180 mg, 72% yield) as a colorless oil; $^1$H-NMR δ 6.86 (dt, $J = 15.5, 6.9$ Hz, 1H), 6.12 (dt, $J = 15.5, 1.5$ Hz, 1H), 3.41 (t, $J = 6.6$ Hz, 2H), 2.94 (q, $J = 7.4$ Hz, 2H), 2.28-2.18 (m, 2H), 1.95-1.83 (m, 2H), 1.71-1.58 (m, 2H), 1.28 (t, $J = 7.4$ Hz, 3H); $^{13}$C-NMR δ 189.9, 143.9, 129.0, 33.1, 31.9, 31.1, 26.4, 23.0, 14.7; MS (EI) $m/z$ 252 (M$^+$, 11), 250 (M$^+$, 11), 192 (7), 190 (8), 189 (100), 177 (9), 175 (9), 81 (13), 55 (58); HRMS Calcd. for C$_9$H$_{15}$OSBr 250.0027, found 250.0034.
(E)-S-Ethyl 4-hydroxypent-2-enethioate (13):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and 3-buten-2-ol (2.5 mmol, 217 μl) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO₂, 10 : 90 to 50 : 50 Et₂O / n-pentane gradient, Rf (30 : 70) = 0.25) afforded 13 (106 mg, 66% yield) as a yellowish oil; ¹H-NMR δ 6.79 (dd, J = 15.5, 4.5 Hz, 1H), 6.22 (dd, J = 15.5, 1.7 Hz, 1H), 4.39 (qdd, J = 6.6, 4.6, 1.6 Hz, 1H), 3.27 (br s, 1H), 2.87 (q, J = 7.4 Hz, 2H), 1.25 (d, J = 6.7 Hz, 3H), 1.20 (t, J = 7.4 Hz, 3H); ¹³C-NMR δ 190.6, 146.8, 126.0, 66.6, 23.1, 22.3, 14.4; MS (EI) m/z 160 (M⁺, 5), 115 (7), 100 (5), 99 (100), 71 (20), 55 (9); HRMS Calcd. for C₇H₁₂O₂S 160.0558, found 160.0550.

(E)-S-Ethyl 4-hydroxy-4-methylpent-2-enethioate (14):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and 2-methyl-3-buten-2-ol (2.5 mmol, 261 μl) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO₂, 20 : 80 to 40 : 60 Et₂O / n-pentane gradient, Rf (30 : 70) = 0.3) afforded 14 (124 mg, 71% yield) as a yellowish oil; ¹H-NMR δ 6.86 (d, J = 15.5 Hz, 1H), 6.26 (d, J = 15.5 Hz, 1H), 2.90 (q, J = 7.4 Hz, 2H), 2.35 (br s, 1H), 1.33 (s, 6H), 1.23 (t, J = 7.4 Hz, 3H); ¹³C-NMR δ 190.6, 150.2, 124.7, 70.6, 29.1, 23.1, 14.6; MS (EI) m/z 174 (M⁺, 5), 115 (7), 100 (5), 99 (100), 71 (20), 55 (9); HRMS Calcd. for C₈H₁₄O₂S 174.0715, found 174.0721.

(E)-S-Ethyl 4-(4-methylphenylsulfonamido)but-2-enethioate (15):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and N-allyl-4-methylbenzenesulfonamide (2.5 mmol, 528 mg) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO₂, 20 : 80 to 60 : 40 Et₂O / n-pentane gradient, Rf (30 : 70) = 0.3) afforded 15 (176 mg, 71% yield) as a white
Straightforward synthesis of α,β-unsaturated thioesters via olefin cross-metathesis with thioacrylate

solid; mp = 68.5-69.4 °C; \(^1\)H-NMR δ 7.73 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 6.63 (dt, J = 15.5, 5.1 Hz, 1H), 6.14 (dt, J = 15.5, 1.7 Hz, 1H), 5.20 (t, J = 6.3 Hz, 1H), 3.77-3.69 (m, 2H), 2.89 (q, J = 7.4 Hz, 2H), 2.41 (s, 3H), 1.23 (t, J = 7.4 Hz, 3H); \(^1^\)C-NMR δ 189.4, 143.7, 137.9, 136.5, 129.8, 129.2, 127.0, 43.6, 23.2, 21.4, 14.5; MS (EI) m/z 299 (M⁺, 0.7), 239 (6), 238 (40), 156 (7), 155 (89), 144 (23), 92 (9), 91 (100), 82 (10), 65 (13), 55 (7); HRMS Calcd. for C\(_{13}\)H\(_{17}\)NS\(_2\)O\(_3\) 299.0650, found 299.0666.

\((E)-4-(Ethylthio)-4-oxobut-2-enyl acetate (16):\)

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and \textit{cis}-1,4-diacetoxo 2-butene (1.5 mmol, 239 μl) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO\(_2\), 5 : 95 to 10 : 90 Et\(_2\)O / n-pentane gradient, R\(_f\) (10 : 90) = 0.30) afforded 16 (123 mg, 65% yield) as a colorless oil; \(^1\)H-NMR δ 6.82 (dt, J = 15.6, 4.6 Hz, 1H), 6.27 (dt, J = 15.6, 1.9 Hz, 1H), 4.72 (dd, J = 4.6, 1.9 Hz, 2H), 2.95 (q, J = 7.4 Hz, 2H), 2.11 (s, 3H), 1.26 (t, J = 7.4 Hz, 3H); \(^1^\)C-NMR δ 189.3, 170.1, 136.6, 128.7, 62.3, 23.2, 20.6, 14.6; MS (EI) m/z 234 (6), 188 (M⁺, 10), 159 (23), 132 (10), 131 (15), 127 (34), 111 (17), 85 (100), 71 (10), 57 (5); HRMS Calcd. for C\(_8\)H\(_{12}\)O\(_3\)S 188.0507, found 188.0514.

\((E)-S\)-ethyl 4-bromobut-2-enethioate (17):

The title compound was prepared from S-ethyl thioacrylate 2 (1.0 mmol, 116 mg) and \textit{trans}-1,4-dibromo 2-butene (1.5 mmol, 321 mg) following the procedure described for 3 (second portion of 2 mol% catalyst added after 16 h; total reaction time: 24 h). Purification by flash column chromatography (SiO\(_2\), 0.5 : 99.5 to 2 : 98 Et\(_2\)O / n-pentane gradient, R\(_f\) (2 : 98) = 0.25) afforded 17 (134 mg, 64% yield) as a yellowish oil; \(^1\)H-NMR δ 6.91 (dt, J = 15.2, 7.3 Hz, 1H), 6.27 (dt, J = 15.2, 1.2 Hz, 1H), 4.00 (dd, J = 7.3, 1.2 Hz, 2H), 2.97 (q, J = 7.4 Hz, 2H), 1.29 (t, J = 7.4 Hz, 3H); \(^1^\)C-NMR δ 189.0, 137.1, 130.8, 29.1, 23.2, 14.5; MS (EI) m/z 250 (7), 210 (M⁺, 6), 208 (M⁺, 7), 189 (22), 149 (55), 147 (100), 129 (12), 121 (5), 119 (6), 113 (9), 103 (9), 91 (7), 85 (6), 83 (8), 69 (6), 68 (22), 57 (7), 55 (5); HRMS Calcd. for C\(_6\)H\(_9\)OSBr 207.9557, found 207.9563.
References:


7 For a review on thioester chemistry developed in the last ten years, see: Fujiwara, S.-I.; Kambe, N. Top. Curr. Chem. 2005, 251, 87-140.


11 The classical synthetic methods are described in the Supporting Information of ref 9b.
Straightforward synthesis of α,β-unsaturated thioesters via olefin cross-metathesis with thioacrylate

12 See chapter 4, Experimental Part.


