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Straightforward Synthesis of α,β-Unsaturated Thioesters via Ruthenium-Catalyzed Olefin Cross-Metathesis with Thioacrylate

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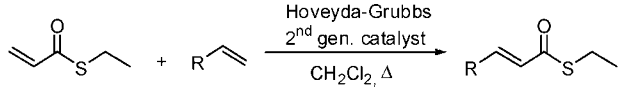

The cross-metathesis reaction of *S*-ethyl thioacrylate with a variety of olefins is effectively catalyzed by using a ruthenium benzylidene olefin metathesis catalyst. This reaction provides a convenient and versatile route to substituted α,β-unsaturated thioesters, key building blocks in organic synthesis.

Thioesters are highly relevant 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 that of 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 many other well-known transformations including α-alkylations,[4] selective reductions,[4,5] and Pd-catalyzed coupling reactions[6] among others.[7] α,β-Unsaturated thioesters show important differences in their reactivity as Michael acceptors compared to oxoesters.[3d,8] They have been found to be excellent substrates for 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 α,β-unsaturated thioesters through classic methods,[11] such as DCC/DMAP-coupling of acids with thiols and transesterification with trimethylsilyl thioethers, due to 1,4-addition of thiolate to the product. As routine application of α,β-unsaturated thioesters relies on methods that give ready access to these compounds, we were interested in whether it was possible to synthesize these compounds via cross-metathesis with a thioacrylate.

Ruthenium-catalyzed olefin metathesis has emerged as one of the most versatile of synthetic methods over the past decade.[12] 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.[13] The increased functional group tolerance as a result of the development of new catalysts (Figure 1), their commercial availability, and the Grubbs model to predict the selectivity[14] have enhanced greatly the utility of cross-metathesis reactions.

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. Although the use of other sulfur-containing alkenes has been described previously, to the best of our knowledge the use of thioacrylate compounds has so far not been reported.[15]

Thioacrylates are not commercially available and the current preparative methods are either unsafe or expensive.[16] However,

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(11) The classical synthetic methods are described in the Supporting Information of ref 9b.

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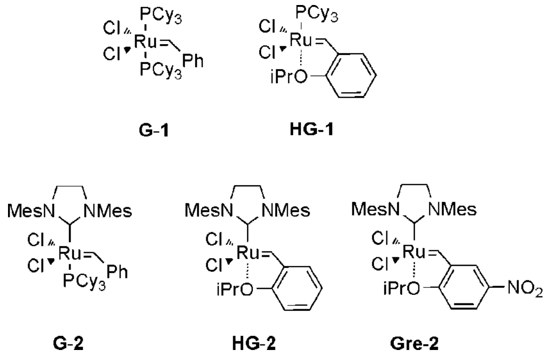
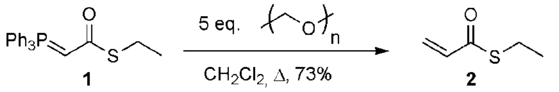


FIGURE 1. Ruthenium-based metathesis catalysts: Grubbs 1st generation (**G-1**), Hoveyda−Grubbs 1st generation (**HG-1**), Grubbs 2nd generation (**G-2**), Hoveyda−Grubbs 2nd generation (**HG-2**), and Grela's catalyst (**Gre-2**).

SCHEME 1. Preparation of *S*-Ethyl Thioacrylate through a Wittig Reaction

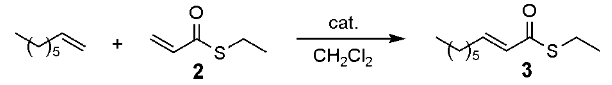


it was found that compound **2** (Scheme 1) could be prepared from Wittig reagent **1**, which is readily available from bromoacetic acid, through DCC/DMAP-coupling followed by reaction with PPh_3.[17] We could obtain **2** in 73% yield after refluxing **1** in CH_2Cl_2 with 5 equiv of paraformaldehyde.[18] 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 large scale.

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 1). The results are summarized in Table 1, entries 1−5. As expected according to the Grubbs model,[14] both the Grubbs and the Hoveyda−Grubbs first generation catalysts (**G-1** and **HG-1**) were found to be unsuitable for the reaction, since only dimerization of the 1-octene was observed.

When using 2 mol % of the Grubbs second generation catalyst (**G-2**), full conversion of the thioacrylate was observed after 20 h at rt and product **3** could be isolated in 76% yield. However, the Hoveyda−Grubbs second generation catalyst (**HG-2**)[19] gave a cleaner reaction and under the same conditions **3** was obtained in 93% with this catalyst. The **Gre-2** catalyst, reported by Grela,[20] was tested also, due to its known potential in metathesis reactions with electron-deficient olefins. This did not result in full conversion, however, and **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 1. Cross-Metathesis Reactions with *S*-Ethyl Thioacrylate and 1-Octene[a]



entry	cat.	*T*	time	yield (%)
1	**G-1** (2 mol %)	rt	20 h	nd[b]
2	**HG-1** (2 mol %)	rt	20 h	nd[b]
3	**G-2** (2 mol %)	rt	20 h	76
4	**HG-2**(2 mol %)	rt	20 h	93
5	**Gre-2** (2 mol %)	rt	20 h	72
6	**HG-2**(2 mol %)	reflux	60 min	94
7	**HG-2**(1 mol %)	reflux	120 min	94
8	**HG-2** (0.5 mol %)	reflux	24 h	42

[a] Reaction conditions: **2** (1.0 mmol), 1-octene (2.5 equiv), catalyst (0.5−2.0 mol %), CH_2Cl_2 (c = 0.4 M). [b] Only formation of tetradec-7-ene observed.

With the best catalyst, **HG-2**, the reaction temperature and catalyst loading were varied (Table 1, entries 6−8). The reaction can be accelerated substantially by elevating the reaction temperature: heating the mixture 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 a 42% yield of **3**.

These optimized conditions for the cross-metathesis reaction can be applied to a wide range of substrates to provide various α,β-unsaturated thioesters (Table 2).[21] The reactions were performed in CH_2Cl_2 heated to reflux with 2 mol % **HG-2**. Most cross-metathesis partners with a terminal olefin and which were not branched on the allylic position led to fast reactions, which provided the products in excellent yields (Table 2, entries 1−4). Thioesters with a phenyl ring or trimethylsilyl group at the γ-position (products **4** and **5**) or a more remote oxoester group (products **6** and **7**) were thus obtained.

Reaction with styrene, featuring a conjugated double bond, required an extended reaction time (Table 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 (Table 2, entries 6−9); the same held for secondary and tertiary unprotected allylic alcohols and allyl tosylamide (Table 2, 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 with only 1.5 equiv of the cross-metathesis partner and again two portions of the catalyst were needed (Table 2, entries 13 and 14). Crotonic acid thioesters with an acetoxy or bromo substituent at the γ-position (products **16** and **17**, respectively) were obtained in good yield after 24 h.

In conclusion, 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

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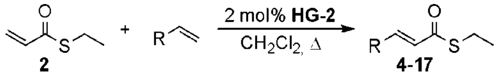
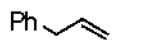
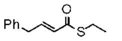
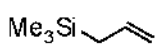
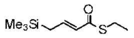
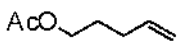
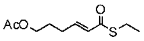
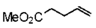
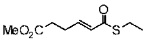
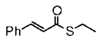
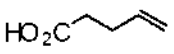
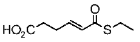
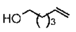
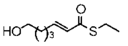
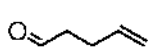
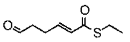
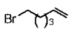
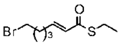
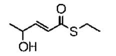
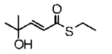
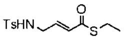
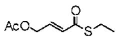
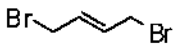
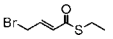
(21) Cross-metathesis with 3,3-dimethyl-1-butene was attempted but product formation was not observed. The reaction was performed under the regular conditions (as specified in Table 2), although with 3,3-dimethyl-1-butene as cosolvent.

TABLE 2. Cross-Metathesis Reactions with *S*-Ethyl Thioacrylate and a Range of Olefins[a]



entry	CM-partner	product		time	yield
1			**4**	1 h	95%
2			**5**	2 h	92%
3			**6**	4 h	86%
4			**7**	4 h	91%
5			**8**	18 h	72%
6[b]			**9**	24 h	83%
7[b]			**10**	24 h	93%
8[b]			**11**	24 h	75%
9[b]			**12**	24 h	75%
10[b]			**13**	24 h	66%
11[b]			**14**	24 h	71%
12[b]			**15**	24 h	59%
13[b,c]			**16**	24 h	65%
14[b,c]			**17**	24 h	64%

[a] Reaction conditions: **2** (1.0 mmol), CM-partner (2.5 equiv), Hoveyda−Grubbs 2nd generation catalyst (2.0 mol %), CH_2Cl_2 (c = 0.4 M), reflux; [b] Hoveyda−Grubbs 2nd generation catalyst (4.0 mol %) added in 2 portions. [c] CM-partner (1.5 equiv).

generation catalyst is demonstrated. The high functional group tolerance of the reaction allows the preparation of a broad range of versatile functionalized α,β-unsaturated thioesters.

Experimental Section

***S*-Ethyl Thioacrylate (2).** A flame-dried Schlenk flask under N_2 atmosphere was charged with Wittig reagent **1** (29.8 g, 82 mmol), paraformaldehyde (12.3 g, 410 mmol), and CH_2Cl_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 pentane (100 mL) and filtered over silica. The filtercake was washed (10:90 Et_2O/pentane, 250 mL) and the filtrates combined. Hydroquinone (ca. 30 mg) was added to the solution to prevent polymerization 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 °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 °C. ^{1}H NMR δ 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); ^{13}C NMR (400 MHz, CDCl3) δ 190.0, 134.9, 125.7, 22.9, 14.4; MS (EI) m/z 116 (M^+, 37), 91 (6), 89 (6), 86 (17), 84 (25), 62 (10), 61 (16), 55 (100); HRMS calcd for C_5H_8OS 116.0296, found 116.0299.

Typical Procedure for the Cross-Metathesis Reaction with Thioacrylate: Synthesis of (*E*)-*S*-Ethyl Non-2-enethiolate (3). A flame-dried Schlenk flask under N_2 atmosphere was charged with *S*-ethyl thioacrylate **2** (1.0 mmol, 116 mg), 1-octene (2.5 mmol, 395 μL), and CH_2Cl_2 (2.5 mL). Hoveyda−Grubbs second 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 (SiO_2, 0.5: 99.5 to 5: 95 Et_2O/pentane gradient, R_f (2:98) 0.45), which afforded **3** (188 mg, 94% yield) as a colorless oil; ^{1}H NMR δ 6.89 (dt, J = 15.5 and 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), 1.35−1.24 (m, 9H), 0.88 (t, J = 6.9 Hz, 1H); ^{13}C 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 $C_{11}H_{20}OS$ 200.1235, found 200.1236.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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