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Chalcogenide-$TiCl_4$-mediated reactions of *S*-ethyl thioacrylate with aldehydes

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Abstract

The reaction of *p*-nitrobenzaldehyde (**1a**) with *S*-ethyl thioacrylate (**2**) catalyzed by chalcogenide-$TiCl_4$ gave a mixture of Baylis–Hillman adduct **4a** and *syn*- and *anti*-2-(chloromethyl)-3-hydroxy-3-(*p*-nitrophenyl)propanethioates **5a** in the ratio of **4**:*syn*-**5**:*anti*-**5** = 5:65:30. The crude product obtained from the reaction of *p*-trifluoromethyl derivative **1b** with **2** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene to give **4** in 71% overall yield, while treatment of the crude product with Ti(O-*i*-Pr)$_4$ afforded isopropyl 2-(α-hydroxy-*p*-trifluoromethylbenzyl)acrylate **6** (49%), *S*-ethyl 2-(ethylthiomethyl)-3-hydroxy-3-(*p*-trifluoromethylphenyl)thiopropyonate **7** (2%) and *S*-ethyl 2-(chloromethyl)-3-(*p*-trifluoromethylphenyl)thioacrylate **8** (15%). Reactions of **2** with other various aldehydes followed by the treatment with DBU or Ti(O-*i*-Pr)$_4$ gave the thioacrylates **4** and isopropyl acrylates **6**, respectively, in fair to good yields. The formation mechanism for 2-(chloromethyl)propanethioate **5** is discussed.

Keywords: Acrylic acid thioester; Allylic alcohol; Baylis–Hillman reaction; Sulfide; Titanium tetrachloride

1. Introduction

In recent years much attention has been focused on the Baylis–Hillman reaction which constructs the carbon–carbon bond between an aldehyde and the vinylic position of active alkenes [1]. However, the reaction was usually quite slow, and a number of attempts have been made to increase the reaction rate through physical and chemical means. The Lewis acid-accelerated Baylis–Hillman reactions were reported by Aggarwal [2] and Kobayashi [3] groups. We developed the chalcogenide-$TiCl_4$ mediated reactions of active alkenes with aldehydes [4]. These reactions proceeded smoothly and were completed within 1 h; however, reactions of methyl acrylate were somewhat complicated and gave the adducts in low to moderate yields. The Baylis–Hillman adducts derived from acrylates were converted to synthetically useful compounds such as anti-aldol adducts [5], aziridines [6], epoxides [7], and triols [8] and widely used as the synthetic intermediates of natural products and biologically active compounds. Therefore, we directed our attention to acrylic thioesters, which would be more reactive than acrylic acid esters, and now describe the chalcogenide-$TiCl_4$ mediated reactions of the thioesters with aldehydes [9]. In addition, the Baylis–Hillman reaction of the thioester is also reported because the reaction has not been investigated.

2. Results and discussion

Reactions of 2 equiv. of *S*-ethyl thioacrylate (**2**) with *p*-nitrobenzaldehyde (**1a**) in the presence of 0.1 equiv. of a chalcogenide **3** and 1 equiv. of $TiCl_4$ in dichloromethane were examined at room temperature for 20 h (Scheme 1), and the results are shown in Table 1.

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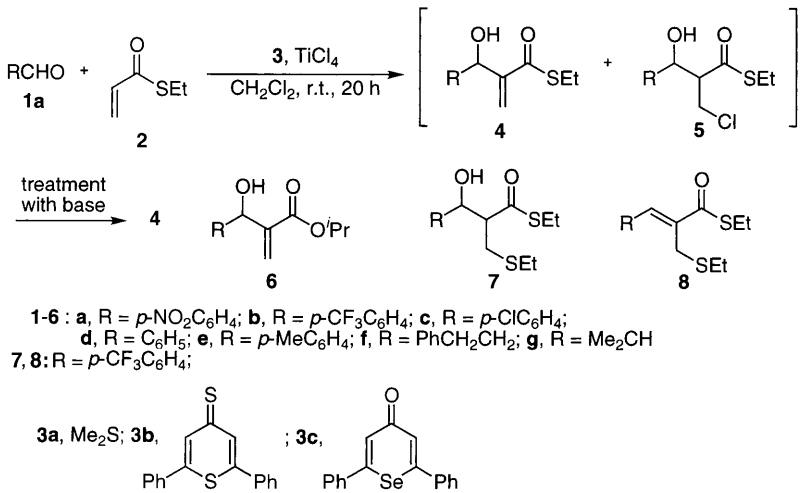
The reactions in entries 1–6 were given a mixture of the Baylis–Hillman product **4a** and the hydrogen chloride adduct **5a**, which could not be separated by preparative TLC on silica gel. Therefore, the crude product was treated with 1.5 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at room temperature for 1 h to give thioacrylate **4a** in 77% overall yield (entry 1). Compound **4a** was also obtained in 83% overall yield from the reaction of a crude mixture of **4a** and **5a** with 2 equiv. of diethylamine (entry 2). Treatment of a crude mixture of **4a** and **5a** with 2 equiv. of $Ti(O\text{-}i\text{-}Pr)_4$ caused transesterification besides dehydrochlorination to afford isopropyl 2-(α-hydroxy-*p*-nitrobenzyl)acrylate **6a** (72%) (entry 3). The compound **6a** showed signals due to the isopropyl group at δ 1.22, 1.23 and 5.04 and two vinyl proton signals at δ 5.81 and 6.37 in ^{1}H-NMR spectrum. Dichloromethane as a solvent decreased the yield of **4a** (entry 4). The $TiCl_4$-mediated reaction without chalcogenide catalyst gave acrylate **5** in 60% yield after treatment of the crude product with DBU (entry 5). Li et al. recently reported the $TiCl_4$-mediated reactions of aldehydes with active alkenes giving Baylis–Hillman adducts or the α-chloromethyl aldol-type compounds [11]. Reactions using chalcogenopyrones **3b** and **3c** followed by treatment with DBU gave better yields than that using **3a** (entries 6 and 7) [10]. On the other hand, the Baylis–Hillman reaction using 1,4-diazabicyclo[2.2.0]octane (DABCO) as a catalyst gave an adduct **4a** in 15% yield (Entry 7), but the reaction with tri-*n*-butylphosphine did not produce the adduct **4a** (Entry 8).

Very recently, we found that the α-chloromethyl aldol could be isolated by column chromatography and underwent dehydrochlorination during TLC on silica gel [12]. Therefore, the ^{1}H-NMR spectrum of the raw product without purification was measured to examine a product ratio. The ratio, **4**:*syn*-**5**:*anti*-**5** = 5:65:30, indicated that the chloromethyl derivatives, *syn*-**5** and *anti*-**5** were the main products and a small amount of **4** was formed during the reaction. These compounds were separated by the recycling preparative HPLC on polystyrene gels. The structures of the *syn*- and *anti*-isomers were determined by comparison of their ^{1}H-NMR spectra with those of the methyl ketone derivatives, the *syn*-isomer of which had been structure-determined by the X-ray crystallography [12]. The dif-



Scheme 1.

Table 1
Reactions of *S*-ethyl thioacrylate **2** with *p*-nitrobenzaldehyde **1a**

Entry [a]	Catalyst (equiv.)	Treatment with base (equiv.)	Product (% yield) [b]
1	**3a**(0.1)–$TiCl_4$(1)	DBU(1.5), toluene, r.t., 1 h	**4a** (77)
2	**3a**(0.1)–$TiCl_4$(1)	Et_2NH(2), toluene, r.t., 1 h	**4a** (83)
3	**3a**(0.1)–$TiCl_4$(1)	$Ti(O^iPr)_4$ (2), toluene, r.t., 1 h	**6a** (72)
4	**3a**(0.1)–$TiCl_4$(1)	$Ti(O^iPr)_4$ (2), CH_2Cl_2, r.t., 1 h	**6a** (55)
5	$TiCl_4$(1)	DBU(1.5), toluene, r.t., 1 h	**4a** (60)
6	**3b**(0.1)–$TiCl_4$(1)	DBU(1.5), toluene, r.t., 1 h	**4a** (90)
7	**3c**(0.1)–$TiCl_4$(1)	DBU(1.5), toluene, r.t., 1 h	**4a** (84)
8	DABCO(0.1)		**4a** (15)
9	Bu_3P(0.1)		**4a** (–)

[a] Two equiv. of **2** was used.
[b] Isolated yield based on **1a**.

Table 2
Product ratio of thioacrylate **4a** and β-chloropropanethioate **5a**

Entry	Reaction conditions		Time (h)	Ratio		
	Catalyst	Temperature		**4a**	*syn*-**5a**	*anti*-**5a**
1	**3a**	r.t.	20	5	65	30
2	**3a**	Reflux (CH_2Cl_2)	1.5	6	75	19
3	None	r.t.	20	6	70	24

Table 3
Conversion of β-chloropropanethioate **5a** into thioacrylate **4a**

Entry	Ratio before treatment [a]			Treatment	Ratio after treatment [a]		
	4a	*syn*-**5a**	*anti*-**5a**		**4a**	*syn*-**5a**	*anti*-**5**
1	19	59	22	Shaking with sat. $NaHCO_3$ aq.	19	59	22
2	25	50	25	Preparative TLC (AcOEt:hexane = 1:3)	53	38	9
3	20	56	24	Column chromatography (AcOEt:hexane = 1:3)	17	60	23
4		74	26	Recycle preparative HPLC ($CHCl_3$)		74	26

[a] The product ratio was determined from the intensities of the 3-H signals of the ^{1}H-NMR spectrum.

ferences in the ^{1}H-NMR signals between the isomers were as follows: (1) One of the methylene protones of the chloromethyl group of *syn*-**5** appeared at δ 3.96 (dd, $J = 9$ and 11 Hz) lower than that of *anti*-**5** at δ 3.81 (dd, $J = 6$ and 11 Hz). (2) The methine proton of *syn*-**5** α to the thioester group was observed as a doublet-of-doublet-of-doublet signal with coupling constants of $J = 4$, 6 and 9 Hz at δ 3.25 and that of *anti*-**5** as a doublet-of-triplet with coupling constants of $J = 5$ and 6 Hz at δ 3.27. A clear difference was not observed in the ratio of the products obtained from a reaction under reflux (Entry 2 in Table 2) or from that without chalcogenide catalyst (Entry 3). Interestingly, our results giving predominantly the syn-diastereomer *syn*-**5** were much different from the results of Li and his coworkers that only *anti*-isomers had been obtained from the $TiCl_4$-mediated reactions of some benzaldehydes with *N*-acryloyl benzoxalinone [11].

The product distribution was not changed by treatments with saturated aqueous $NaHCO_3$, column chromatography on silica gel or recycling preparative HPLC on polystyrene gels, but the TLC treatment caused dehydrochlorination to give acrylate **4a** as shown in Table 3. Degree of dehydrochlorination depends upon the developing temperature and time, i.e. development at the high temperature for a long period increased the thioacrylate **4a**. The α-chloromethylpropanethioate **5a** was more stable against preparative TLC on silica gel than the α-chloromethyl aldol, because the latter was dehydrochlorinated almost quantitatively by the TLC treatment under the same conditions [11].

Next, we applied the above reaction to various aldehydes (Table 4).

Reaction of *p*-trifluoromethylbenzaldehyde (**1b**) with thioester **2** in the presence of dimethyl sulfide (**3a**)-$TiCl_4$ followed by treatment with DBU (Method A) afforded thioacrylate **4b** in 71% yield (entry 1). When the crude product of the reaction of **1b** with **2** was treated with $Ti(O\text{-}i\text{-}Pr)_4$ in toluene (Method B), transesterification and substitution reaction besides dehydrochlorination occurred to afford isopropyl 2-(α-hydroxy-*p*-trifluoromethylbenzyl)acrylate **6b** (49%), *S*-ethyl 2-(ethylthiomethyl)-3-hydroxy-3-(*p*-trifluoromethylphenyl)propanethioate **7** (2%) and *S*-ethyl 2-(ethylthiomethyl)-

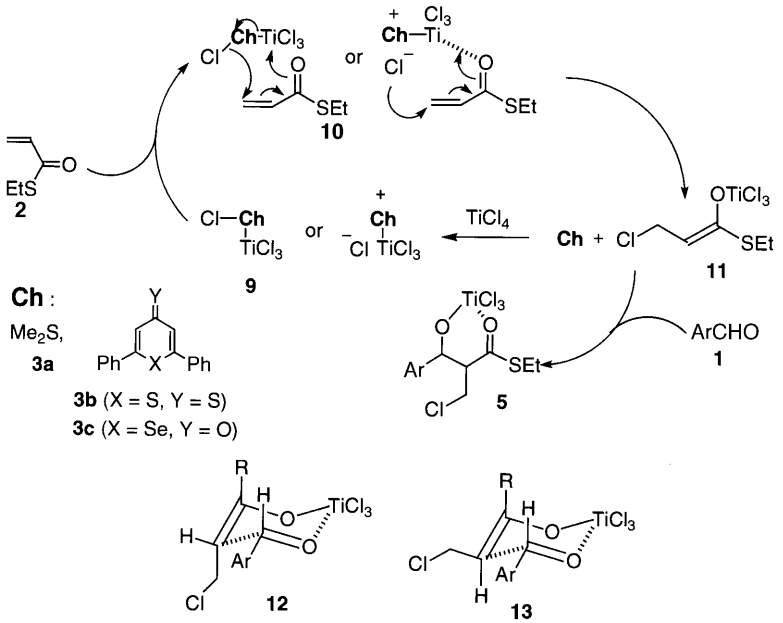
Table 4
Reactions of *S*-ethyl thioacrylate **2** with aldehydes **1**

Entry [a]	RCHO	Treatment with base [b]	Product (% yield) [c]
1	**1b**	Method A	**4b** (71)
2	**1b**	Method B	**6b** (49)
3	**1b**	Method C	**6b** (60)
4	**1c**	Method A	**4c** (70)
5	**1c**	Method B	**6c** (23)
6	**1c**	Method C	**6c** (47)
7	**1d**	Method A	**4d** (50)
8	**1d**	Method C	**6d** (46)
9	**1e**	Method A	**4e** (62)
10	**1e**	Method C	**6e** (51)
11	**1f**	Method A	**4f** (64)
12	**1f**	Method C	**6f** (60)
13	**1g**	Method A	**4g** (50)

[a] *S*-Ethyl thioacrylate (2 equiv.), **3a** (0.1 equiv.) and $TiCl_4$ (1 equiv.) were used.

[b] See Section 3.

[c] Isolated yield based on an aldehyde. Products other than *S*-ethyl thioacrylate **4** and isopropyl acrylate **6** were not isolated except for entry 2.



Scheme 2.

3-(*p*-trifluoromethylphenyl)thioacrylate **8** (15%) (Entry 2). The ^{1}H-NMR spectrum of compound **7** showed signals due to two *S*-ethyl groups at δ 1.16 and 1.17 (each t, $J = 7$ Hz, CH_3), and 2.47 and 2.86 (each q, $J = 7$ Hz, CH_2). The acrylate **8** was a mixture of *E*- and *Z*-isomers. The ^{1}H-NMR and IR spectra exhibited no absorption of a hydroxy group, but instead the ^{1}H-NMR spectrum showed a pair of signals owing to olefinic protons at δ 6.69 and 7.64 for the *E*- and *Z*-isomers, respectively, and two pairs of an *S*-ethyl signals. The undesired products **7** and **8** were formed by substitution of the chloro group for the ethanethiolate ion liberated by transesterification as mentioned above. Therefore, we treated the crude product with Ti(O-*i*-Pr)$_4$ in the presence of iodomethane to capture the ethanethiolate ions (Method C). Yields of isopropyl acrylates **6** were consequently increased (entries 3 and 6). Reactions of other aromatic aldehydes **1c–e** and aliphatic aldehydes **1f–g** provided α-(hydroxymethyl)acrylic acid thioesters **6c–g** and esters **4c–g** in moderate yields (entries 4–13).

A plausible mechanism for the formation of 2-(chloromethyl)thioacrylates **5** is discussed in Scheme 2.

A chalcogenide reacts with $TiCl_4$ to form trichlorotitanium-chalcogenonium chloride **9**. The highly electron-deficient titanium coordinates with thioester **2** and the chloride ion nucleophilically attacks the positively charged β-carbon of the thioester **2**. The resulting complex **10** changes into titanium enolate **11** and the chalcogenide is regenerated. The titanium enolate **11** thus formed reacts with an aldehyde **1** to give an adduct **5**. Very recently, Li and his coworkers reported that the reaction proceeded by the assistance of $TiCl_4$ only [11]. This suggested us that a chalcogenide was not necessary for the reaction of enone **5** with aldehyde **1**. However, their result giving only the products with *anti*-configuration is much different from ours giving the *syn*-products predominantly. Reaction of methyl propiolate with an aldehyde did not proceed without dimethyl sulfide [13]. The diastereoselection would be induced in the reaction of titanium enolate **10** with an aldehyde. Chelated cyclic transition states are more convenient to explain the diastereoselectivity of the reactions of thioesters **2** with aldehydes **1** because of high Lewis acidity of the trichlorotitanium enolates [14,15]. The reactions proceed mainly via the transition state **12** and diastereoselectively give the *syn*-products. The *anti*-isomers are formed via the transition state **13** derived from *E*-enolates.

In conclusion, we developed the synthetic method for 2-(chloromethyl)-3-hydroxypropanethioates and 2-(hydroxymethyl)thioacrylates utilizing the chalcogenide-$TiCl_4$ reactions of *S*-ethyl thioacrylate with aldehydes.

3. Experimental

Melting points were obtained with a Yanagimoto micro-melting-point apparatus and are uncorrected. IR spectra of solids (KBr) and liquids (NaCl) were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL GX-270 (270 MHz) or a JEOL EX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. ^{13}C-NMR spectra were obtained on a JEOL EX-400 spectrometer. Mass spectra were recorded on a JEOL

JMS-SX102A spectrometer with a direct-insertion probe at 70 eV. Elemental analyses of new compounds were performed by a Yanaco CHN Corder MT-5. All chromatographic isolations were accomplished with BW-350 (Fuji Silysia) for column chromatography or with Kieselgel 60 PF_{254} containing gypsum (Merck) for preparative TLC. Dichloromethane was dried and freshly distilled over phosphorus pentoxide. The recycling preparative HPLC was performed by LC-918 liquid chromatography (Japan Analytical Industry Co., Ltd.) equipped with JAIGEL-1H and -2H columns (polystyrene gels).

3.1. The chalcogeno-Baylis–Hillman reactions of S-ethyl thioacrylate with aldehydes and subsequent treatment of the product with a base

3.1.1. General procedure

$TiCl_4$ (55 μl; 1 mmol) was added to a solution of an aldehyde **1** (0.5 mmol), *S*-ethyl thioacrylate (**2**) [16] (116 mg; 1 mmol) and dimethyl sulfide (**3a**) (3 mg; 0.05 mmol) in dry dichloromethane (5 ml) at room temperature (r.t.). The mixture was stirred at r.t. for 20 h, and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was treated as follows: Method A: DBU (114 mg; 0.75 mmol) was added to a solution of the residue in dry toluene (5 ml) at r.t., and the mixture was stirred at that temperature for 1 h. Toluene (5 ml) was added to it and washed with 1 N HCl (5 ml) and saturated aqueous $NaHCO_3$ (5 ml) successively. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC eluting with EtOAc–hexane (1:3, v/v). 2,6-Diphenyl thiopyran-4-thione (**3b**) [17] and selenopyran-4-one (**3c**) [17] were used as a chalcogenide catalyst instead of dimethyl sulfide (**3a**) in entries 6 and 7 in Table 1, respectively [10].

S-Ethyl 2-[1-hydroxy-1-(4-nitrophenyl)methyl]propenethioate (**4a**): pale yellow powders, m.p. 53.0–53.5°C. Anal. Calc. for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found C, 53.79; H, 4.91; N, 5.17. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3 H, t, $J=7$ Hz, CH_3), 2.89 (2 H, q, $J=7$ Hz, CH_2), 3.31 (1 H, br s, OH), 5.67 (1 H, s, benzylic H), 5.89 and 6.34 (each 1 H, s, olefinic H), 7.55 and 8.19 (each 2 H, d, $J=9$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.6 (q), 23.7 (t), 73.0 (d), 123.9 (d), 125.0 (t), 127.6 (d), 147.8 (s), 148.6 (s), 150.0 (s), 194.2 (s). MS (EI) m/z (rel. int.%): 267 (M^+, 19%), 160 (base). IR (KBr) νmax/cm^{-1}: 3446 (OH), 1653 (C=O), 1521 and 1348 (NO_2).

S-Ethyl 2-[1-hydroxy-1-(4-trifluoromethylphenyl)-methyl]propenethioate (**4b**): colorless oil. Anal. Calc. for $C_{13}H_{13}F_3O_2S$: C, 53.79; H, 4.51. Found: C, 53.98; H, 4.58. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3 H, t, $J=7$ Hz, CH_3), 2.90 (2 H, q, $J=7$ Hz, CH_2), 3.08 (1 H, br s, OH), 5.64 (1 H, s, benzylic H), 5.85 and 6.32 (each 1 H, s, olefinic H), 7.49 and 7.61 (each 2 H, d, $J=8$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.4 (q), 23.3 (t), 73.0 (d), 124.1 (s, $^1J_{CF}$ 272), 124.5 (t), 125.4 (d, $^3J_{CF}$ 4), 126.9 (d), 136.0 (s, $^2J_{CF}$ 32), 144.9 (s), 149.0 (s), 194.1 (s). MS (EI) m/z (rel. int.%): 290 (M^+, 23%), 229 (base). IR (NaCl film) νmax/cm^{-1}: 3440 (OH), 1659 (C=O), 1125 (CF_3).

S-Ethyl 2-[1-hydroxy-1-(4-chlorophenyl)methyl]propenethioate (**4c**): colorless oil. Anal. Calc. for $C_{12}H_{13}ClO_2S$: C, 56.14; H, 5.10. Found: C, 55.94; H, 5.15. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3 H, t, $J=7$ Hz, CH_3), 2.89 (2 H, q, $J=7$ Hz, CH_2), 2.98 (1 H, d, $J=5.5$ Hz, OH), 5.57 (1 H, d, $J=5.5$ Hz, benzylic H), 5.83 and 6.28 (each 1 H, s, olefinic H), 7.28–7.33 (4 H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.4 (q), 23.3 (t), 72.8 (d), 124.0 (t), 128.0 (d), 128.6 (d), 133.7 (s), 139.4 (s), 149.3 (s), 194.0 (s). MS (EI) m/z (rel. int.%): 256 (M^+, 20%), 195 (base); IR (NaCl film) νmax/cm^{-1}: 3433 (OH), 1659 (C=O).

S-Ethyl 2-[1-hydroxy-1-phenylmethyl]propenethioate (**4d**): colorless oil. Anal. Calc. for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35. Found: C, 64.35; H, 6.23. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3 H, t, $J=7$ Hz, CH_3), 2.88 (2 H, q, $J=7$ Hz, CH_2), 2.97 (1 H, d, $J=5$ Hz, OH), 5.60 (1 H, d, $J=5$ Hz, benzylic H), 5.83 and 6.28 (each 1 H, s, olefinic H), 7.26–7.35 (5 H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.4 (q), 23.3 (t), 73.4 (d), 123.8 (t), 126.6 (d), 127.9 (d), 128.5 (d), 140.9 (s), 149.7 (s), 194.0 (s). MS (EI) m/z (rel. int.%): 222 (M^+, 45%), 117 (base); IR (NaCl film) νmax/cm^{-1}: 3360 (OH), 1660 (C=O).

S-Ethyl 2-[1-hydroxy-1-(4-tolyl)methyl]propenethioate (**4e**): pale yellow oil. Anal. Calc. for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 65.84; H, 6.87. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3 H, t, $J=7$ Hz, CH_3), 2.33 (3 H, s, $CH_3C_6H_4$), 2.866 and 2.870 (each 1 H, q, $J=7$ Hz, CH_2), 5.56 (1 H, s, benzylic H), 5.84 and 6.26 (each 1 H, s, olefinic H), 7.14 and 7.23 (each 2 H, d, $J=8$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.4 (q), 21.1 (q), 23.2 (t), 73.1 (d), 123.5 (t), 126.5 (d), 129.1 (d), 137.6 (s), 137.9 (s), 149.8 (s), 193.8 (s). MS (EI) m/z (rel. int.%): 236 (M^+, 25%), 175 (base); IR (NaCl film) νmax/cm^{-1}: 3442 (OH), 1662 (C=O).

S-Ethyl 2-[1-hydroxy-3-phenylpropyl]propenethioate (**4f**): pale yellow oil. Anal. Calc. for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 66.91; H, 7.26. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3 H, t, $J=7$ Hz, CH_3), 1.90–1.99 (2 H, m, CH_2CHOH), 2.63 (1 H, d, $J=7$ Hz, OH), 2.66–2.72 and 2.76–2.83 (each 1 H, m, benzylic H), 2.92 (2 H, q, $J=7$ Hz, CH_2CH_3), 4.47 (1 H, dt, $J=7$ and 6 Hz, CHOH), 5.82 and 6.16 (each 1 H, s, olefinic H), 7.16–7.29 (5 H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.5 (q), 23.2 (t), 31.9 (t), 37.6 (t), 71.2 (d), 122.6 (t),

125.8 (d), 128.35 (d), 128.41 (d), 141.5 (s), 150.3 (s), 194.4 (s). MS (FAB) m/z (rel. int.%): 251 ($M^+ + 1$, 80%), 171 (base). IR (NaCl film) νmax/cm^{-1}: 3440 (OH), 1659 (C=O).

S-Ethyl 2-(1-hydroxy-2-methylpropyl)propenethioate (**4g**): colorless oil. Anal. Calc. for $C_9H_{16}O_2S$: C, 57.41; H, 8.57. Found: C, 57.15; H, 8.33. ^{1}H-NMR ($CDCl_3$) δ: 0.89 and 0.94 (each 3 H, d, $J = 7$ Hz, CH_3CH), 1.28 (3 H, t, $J = 7$ Hz, CH_3CH_2), 1.88 (1 H, septet, $J = 7$, $CH(CH_3)_2$), 2.40 (1 H, d, $J = 7$ Hz, OH), 2.92 (2 H, d, $J = 7$ Hz, CH_2CH_3), 4.14 (1 H, t, $J = 7$ Hz, CHOH), 5.77 and 6.18 (each 1 H, s, olefinic H). ^{13}C-NMR ($CDCl_3$) δ: 14.5 (q), 17.4 (q), 19.4 (q), 23.3 (t), 32.7 (d), 77.9 (d), 123.4 (d), 149.5 (s), 194.6 (s). MS (EI) m/z (rel. int.%): 154 ($M^+ + 1$, 3%), 154 (base). IR (NaCl film) νmax/cm^{-1}: 3420 (OH), 1645 (C=O).

3.1.2. Method B

Ti(O-*i*-Pr)$_4$ (0.3 ml, 1 mmol) was added to a solution of the residue in dry toluene (5 ml) at r.t., and the mixture was stirred for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitate was removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. Isopropyl acrylates **6** were purified by preparative TLC on silica gel eluting with EtOAc–hexane (1:3, v/v). The products were precisely examined only in the case of *p*-nitro derivative **1a** (entry 3 in Table 1). Isopropyl 2-(α-hydroxy-*p*-nitrobenzyl)acrylate (**6a**), *S*-ethyl 2-(ethylthiomethyl)-3-hydroxy-3-(*p*-nitrophenyl)propanethioate (**7**) and *S*-ethyl 2 - (ethylthiomethyl) - 3 - (*p* - nitrophenyl)thioacrylate (**8**) were isolated in 72, 2, and 15%, respectively.

S-Ethyl 2-(ethylthio)methyl-3-hydroxy-3-(4-trifluoromethylphenyl)propanethioate (**7**): pale red oil. ^{1}H-NMR ($CDCl_3$) δ: 1.16 and 1.17 (each 3 H, t, $J = 7$ Hz, CH_3), 2.47 (2 H, q, $J = 7$ Hz, $CH_2SCH_2CH_3$), 2.73 (1 H, dd, $J = 4$ and 13 Hz, CH_2Cl), 2.86 (2 H, q, $J = 7$ Hz, $COSCH_2CH_3$), 3.15 (1 H, s, OH), 2.96 (1 H, dd, $J = 9$ and 13 Hz, CH_2Cl), 3.08 (1 H, ddd, $J = 4$, 5 and 9 Hz, 2-H), 5.09 (1 H, d, $J = 5$ Hz, benzylic H), 7.48 and 7.61 (each 2 H, d, $J = 8$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.29 (q), 14.33 (q), 23.7 (t), 26.5 (t), 28.7 (t), 60.9 (d), 73.8 (d), 124.0 (s, $^1J_{CF}$ 272), 125.3 (d, $^3J_{CF}$ 4), 126.6 (d), 130.1 (s, $^2J_{CF}$ 33), 144.5 (s), 201.4 (s). MS (EI) m/z (rel. int.%): 352 (M^+, 25%), 55 (base). HRMS. Calc. for $C_{15}H_{19}F_3O_2S_2$: 352.0778. Found: 352.0786. IR (NaCl film) νmax/cm^{-1}: 3440 (OH), 1659 (C=O), 1125 (CF_3).

S-Ethyl 2 - (ethylthio)methyl - 3 - (4 - trifluoromethylphenyl)propenethioate (**8**): a mixture of *E*-and *Z*-isomers in the ratio of *E:Z* = 1:2; colorless oil; Anal. Calc. for $C_{15}H_{17}F_3OS_2$: C, 53.87; H, 5.12. Found: C, 53.89; H, 5.07. ^{1}H-NMR ($CDCl_3$) δ : *E*-isomer: 1.23 (3 H, t, $J = 7$ Hz, $COSCH_2CH_3$), 1.29 (3 H, t, $J = 7$ Hz, $CH_2SCH_2CH_3$), 2.59 (2 H, q, $J = 7$ Hz, $CH_2SCH_2CH_3$), 2.93 (2 H, q, $J = 7$ Hz, $COSCH_2CH_3$), 3.53 (2 H, s, $CH_2SCH_2CH_3$), 6.69 (1 H, s, olefinic H), 7.40 and 7.55 (each 2 H, d, $J = 8$ Hz, ArH). *Z*-Isomer: 1.23 (3 H, t, $J = 7$ Hz, $COSCH_2CH_3$), 1.34 (3 H, t, $J = 7$ Hz, $CH_2SCH_2CH_3$), 2.60 (2 H, q, $J = 7$ Hz, $CH_2SCH_2CH_3$), 3.04 (2 H, q, $J = 7$ Hz, $COSCH_2CH_3$), 3.64 (2 H, s, $CH_2SCH_2CH_3$), 7.64 (1 H, s, olefinic H), 7.64 and 7.68 (each 2 H, d, $J = 8$ Hz, ArH); ^{13}C-NMR ($CDCl_3$) δ : 14.2 (q), 14.3 (q), 14.5 (q), 23.8 (t), 23.9 (t), 25.5 (t), 27.3 (t), 28.2 (t), 36.2 (t), 123.9 (s, $^1J_{CF}$ 272), 124.0 (s, $^1J_{CF}$ 272), 125.1 (d, $^3J_{CF}$ 4), 125.6 (d, $^3J_{CF}$ 4), 129.1 (d), 129.8 (d), 130.1 (s, $^2J_{CF}$ 33), 130.5 (d), 130.7 (s, $^2J_{CF}$ 33), 136.2 (d), 138.2 (s), 138.5 (s), 140.0 (s), 140.2 (s), 193.4 (s), 195.9 (s); MS (EI) m/z (rel. int.%): 334 (M^+, 60%), 273 (base). IR (NaCl film) νmax/cm^{-1}: 1660 (C=O), 1126 (CF_3).

3.1.3. Method C

Iodomethane (71 mg; 0.5 mmol) and Ti(O-*i*-Pr)$_4$ (0.3 ml; 1 mmol) were added to a solution of the residue in dry toluene (5 ml) at r.t. The mixture was stirred for 1 h and worked up in a similar way to Method B. Products other than isopropyl acrylates **6b–f** were not isolated in Entry 4 in Table 1 and Entries in Table 4 where Methods B and C were used. Results are shown in Tables 1 and 2.

Isopropyl 2-[1-hydroxy-1-(4-nitrophenyl)methyl]propenoate (**6a**): pale yellow powders, m.p. 62.0–62.5°C. Anal. Calc. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found C, 58.71; H, 5.76; N, 5.25. ^{1}H-NMR ($CDCl_3$) δ: 1.22 and 1.23 (each 3 H, d, $J = 6$ Hz, CH_3), 3.40 (1 H, br s, OH), 5.04 (1 H, septet, $J = 6$ Hz, CH), 5.61 (1 H, s, benzylic H), 5.81 and 6.37 (each 1 H, s, olefinic H), 7.57 and 8.20 (each 2 H, d, $J = 9$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.6 (q), 69.1 (d), 72.9 (d), 123.6 (d), 126.8 (t), 127.3 (d), 141.5 (s), 147.4 (s), 148.8 (s), 165.5 (s). MS (EI) m/z (rel. int.%): 265 (M^+, 2%), 206 (base). IR (KBr) νmax/cm^{-1}: 3447 (OH), 1699 (C=O), 1521 and 1347 (NO_2).

Isopropyl 2-[1-hydroxy-1-(4-trifluoromethylphenyl)-methyl]propenoate (**6b**): pale yellow oil. Anal. Calc. for $C_{13}H_{15}F_3O_3$: C, 58.33; H, 5.24. Found: C, 58.05; H, 5.32. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (6 H, d, $J = 6$ Hz, $CH_3 \times 2$), 3.33 (1 H, br s, OH), 5.04 (1 H, septet, $J = 6$ Hz, CH), 5.58 (1 H, s, benzylic H), 5.79 and 6.35 (each 1 H, s, olefinic H), 7.50 and 7.60 (each 2 H, d, $J = 8$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.6 (q), 68.9 (d), 73.0 (d), 124.1 (s, $^1J_{CF}$ 272), 125.3 (d, $^3J_{CF}$ 4), 126.4 (d), 126.8 (t), 129.9 (s, $^2J_{CF}$ 33), 141.8 (s), 145.4 (s), 165.7 (s). MS (EI) m/z (rel. int.%): 288 (M^+, 3%), 173 (base). IR (NaCl film) νmax/cm^{-1}: 3462 (OH), 1711 (C=O), 1126 (CF_3).

Isopropyl 2-[1-hydroxy-1-(4-chlorophenyl)methyl]-propenoate (**6c**): pale yellow oil. Anal. Calc. for $C_{13}H_{15}ClO_3$: C, 61.30; H, 5.94. Found: C, 61.03; H, 5.99. ^{1}H-NMR ($CDCl_3$) δ: 1.19 and 1.22

(each 3 H, d, $J = 6$ Hz, CH_3), 3.28 (1 H, d, $J = 5.5$ Hz, OH), 5.02 (1 H, septet, $J = 6$ Hz, CH), 5.49 (1 H, d, $J = 5.5$ Hz, benzylic H), 5.78 and 6.31 (each 1 H, s, olefinic H), 7.30 (4 H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.61 (q), 21.64 (q), 68.7 (d), 72.7 (d), 125.8 (t), 128.0 (d), 128.4 (d), 133.4 (s), 140.0 (s), 142.2 (s), 165.7 (s). MS (EI) m/z (rel. int.%): 254 (M^+, 13%), 139 (base); IR (NaCl film) νmax/cm^{-1}: 3446 (OH), 1708 (C=O).

Isopropyl 2-[1-hydroxy-1-phenylmethyl]propenoate (**6d**): colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.18 and 1.21 (each 3 H, d, $J = 6$ Hz, CH_3), 3.14 (1 H, d, $J = 5.5$ Hz, OH), 5.02 (1 H, septet, $J = 6$ Hz, CH), 5.54 (1 H, d, $J = 5.5$ Hz, benzylic H), 5.79 and 6.31 (each 1 H, s, olefinic H), 7.26–7.38 (5 H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.6 (q), 21.7 (q), 68.6 (d), 73.4 (d), 125.7 (t), 126.6 (d), 127.7 (d), 128.4 (d), 141.4 (s), 142.5 (s), 165.9 (s). MS (EI) m/z (rel. int.%): 220 (M^+, 13%), 105 (base). HRMS. Calc. for $C_{14}H_{18}O_3$: 220.0997. Found: 220.1103. IR (NaCl film) νmax/cm^{-1}: 3448 (OH), 1715 (C=O).

Isopropyl 2-[1-hydroxy-1-(4-tolyl)methyl]propenoate (**6e**): pale yellow oil. Anal. Calc. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.31; H, 7.91. ^{1}H-NMR ($CDCl_3$) δ: 1.19 and 1.22 (each 3 H, d, $J = 6$ Hz, CH_3), 2.33 (3 H, s, $CH_3C_6H_4$), 3.02 (1 H, br s, OH), 5.02 (1 H, septet, $J = 6$ Hz, CH), 5.51 (1 H, s, benzylic H), 5.79 and 6.30 (each 1 H, s, olefinic H), 7.14 and 7.25 (each 2 H, d, $J = 8$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.1 (q), 21.6 (q), 21.7 (q), 68.5 (d), 73.2 (d), 125.4 (t), 126.5 (d), 129.0 (d), 137.4 (s), 138.5 (s), 142.6 (s), 165.9 (s). MS (EI) m/z (rel. int.%): 234 (M^+, 15%), 119 (base). IR (NaCl film) νmax/cm^{-1}: 3325 (OH), 1715 (C=O).

Isopropyl 2-[1-hydroxy-3-phenylpropyl]propenoate (**6f**): colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.277 and 1.283 (each 3 H, d, $J = 6$ Hz, CH_3), 1.97 (2 H, dt, $J = 6.3$ and 8 Hz, CH_2CHOH), 2.70 and 2.82 (each 1 H, dt, $J = 8$ and 14 Hz, benzylic H), 2.73 (1 H, d, $J = 6.5$ Hz, OH), 4.40 (1 H, dt, $J = 6.5$ and 6.3 Hz, CHOH), 5.10 (1 H, septet, $J = 6$ Hz, CH), 5.76 and 6.21 (each 1 H, s, olefinic H), 7.17–7.30 (5 H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (q), 32.1 (t), 37.7 (t), 68.5 (d), 71.2 (d), 124.7 (t), 125.9 (d), 128.4 (d), 128.5 (d), 141.7 (s), 142.8 (s), 166.1 (s). MS (FAB) m/z (rel. int.%): 249 ($M^+ + 1$, 27%), 154 (base). HRMS(FAB). Calc. for $C_{15}H_{20}O_3$ + H: 249.1491. Found: 249.1500. IR (NaCl film) νmax/cm^{-1}: 3447 (OH), 1710 (C=O).

3.2. Isolation of syn- and anti-isomers of ethyl 2-chloromethyl-3-hydroxy-3-(p-nitrophenyl)thioacrylate

$TiCl_4$ (55 μl, 1 mmol) was added to a solution of *p*-nitrobenzaldehyde (**1a**) (75 mg; 0.5 mmol), *S*-ethyl thioacrylate (**2**) (116 mg; 1 mmol) and dimethyl sulfide (**3a**) (3 mg; 0.05 mmol) in dry dichloromethane (5 ml) at r.t. The mixture was stirred at r.t. for 20 h, and then the reaction was worked up in a similar way to the method described in Section 3.1. The raw product was purified by column chromatography on silica gel eluting with EtOAc:hexane (1:3, v/v) to give a mixture of diastereomers. The diastereomers were separated by recycling preparative HPLC eluting with chloroform.

S-Ethyl (2*R**, 3*R**)-2-chloromethyl-3-hydroxy-3-(4-nitrophenyl)propanethioate (*syn*-**5a**): white prisms (ether-hexane), m.p. 32.0–32.5°C. Anal. Calc. for $C_{12}H_{14}NO_4S$: C, 47.45; H, 4.65; N, 4.61. Found: C, 47.53; H, 4.61; N, 4.57. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3 H, t, $J = 7$ Hz, CH_3), 2.86 (2 H, q, $J = 7$ Hz, CH_2), 3.15 (1 H, s, OH), 3.69 (1 H, ddd, $J = 4$, 6 and 9 Hz, 2-H), 3.69 (1 H, dd, $J = 4$ and 11 Hz, CH_2Cl), 3.96(1 H, dd, $J = 9$ and 11 Hz, CH_2Cl), 5.14 (1 H, d, $J = 4$ Hz, benzylic H), 7.54 and 8.20 (each 2 H, d, $J = 8$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.2 (q), 23.8 (t), 40.8 (t), 62.3 (d), 72.3 (d), 123.6 (d), 127.2 (d), 147.8 (s), 199.2 (s). MS (EI) m/z (rel. int.%): 303 (M^+, 5%), 152 (base). IR (KBr) νmax/cm^{-1}: 3500 (OH), 1667 (C=O), 1519 and 1347 (NO_2), 700(C–Cl).

S-Ethyl (2*R**, 3*S**)-2-chloromethyl-3-hydroxy-3-(4-nitrophenyl)propanethioate (*anti*-**5b**): white powders, m.p. 41.0–41.5°C. Anal. Calc. for $C_{12}H_{14}NO_4S$: C, 47.45; H, 4.65; N, 4.6. Found: C, 47.68; H, 4.63; N, 4.61. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3 H, t, $J = 7$ Hz, CH_3), 2.86 (2 H, q, $J = 7$ Hz, CH_2), 3.27 (1 H, dt, $J = 5$ and 6 Hz, 2-H), 3.42 (1 H, d, $J = 7$ Hz, OH), 3.69 and 3.81 (each 1 H, dd, $J = 6$ and 11 Hz, CH_2Cl), 5.24 (1 H, dd, $J = 5$ and 7 Hz, benzylic H), 7.53 and 8.23 (each 2 H, d, $J = 9$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 14.3 (q), 23.9 (t), 42.2 (t), 61.3 (d), 72.0 (d), 123.7 (d), 126.8 (d), 147.7 (s), 148.0 (s), 199.2 (s). MS (EI) m/z (rel. int.%): 303 (M^+, 3%), 152 (base). IR (KBr) νmax/cm^{-1}: 3495 (OH), 1670 (C=O), 1521 and 1348 (NO_2), 700 (C–Cl).

3.3. The Baylis–Hillman reactions of S-ethyl propanethioate with p-nitrobenzaldehyde

A mixture of aldehyde **1a** (75 mg, 0.5 mmol), thioacrylate **2a** (116 mg, 1 mmol) and DABCO (6 mg, 0.05 mmol) or *n*-tributylphosphine (11 μl, 0.05 mmol) in dry dichloromethane (3 ml) was stirred at r.t. for 20 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative TLC on silica gel eluting with EtOAc:hexane (1:3, v/v). The product and the yield were listed in Table 1.

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