Chalcogenide-Lewis Acid Mediated Reactions of Electron-Deficient Alkynes with Aldehydes

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Abstract: Reactions of but-3-yn-2-one (**2**) with aldehydes **1** in the presence of a Lewis acid and dimethyl sulfide (**3a**) predominantly gave (*E*)-α-(halomethylene)aldols **4**–**5** in high yields, while reactions of methyl propiolate (**6a**) mainly afforded (*Z*)-3-halogeno-2-(hydroxymethyl)acrylates **7**–**8** in low to moderate yields. A reaction of dimethyl acetylenedicarboxylate (**10**) with **1a** in the presence of $TiCl_4$ and 1,1,3,3-tetramethylthiourea (**3c**) produced maleate (*E*)-**11** (40%) and butenolide **12** (40%). When a reaction of **6a** with **1a** was carried out in the presence of $TiBr_4$ and **3a** (0.2 equiv) at $-20\,^{\circ}C$ for 60 h, 3-(methylthio)-2-(hydroxyalkyl)acrylate **9a** was obtained in an 8% yield. Experiments were conducted in order to elucidate the formation mechanism of **9a**, and it was made clear that **9a** was formed via the processes of the Michael addition of sulfide **3a** to alkynoate **6a** and an aldol reaction with **1a** and demethylation.

Keywords: aldol reaction · alkynes · C–C coupling · ketones · Michael addition

Introduction

We have developed the chalcogeno-Baylis–Hillman reaction catalyzed by a system using a Lewis acid and a chalcogenide.[1] The reaction mechanism does not involve the addition of the chalcogenide to an enone but involves processes in which a halogenide ion derived from the Lewis acid undergoes the Michael addition to an enone and the resulting enolate reacts with an aldehyde to give an α-halomethyl aldol.[2] The halomethyl aldol product can be converted into an α-methylene aldol (the Morita–Baylis–Hillman adduct) by preparative TLC on silica gel or by treatment with a base. This reaction proceeded quickly, and we thus overcame the drawback of the slow rate of the Morita–Baylis–Hillman reaction.[3] Therefore, this reaction can be used instead of the Morita–Baylis–Hillman reaction. It has been reported that reactions of thioesters or α-keto esters can proceed smoothly only under the reaction conditions we used.[4–7]

Since the Morita–Baylis–Hillman reaction involves the β-elimination or the retro-Michael reaction in the last step, the Morita–Baylis–Hillman reaction of active alkynes would not proceed. However, since the reaction we developed goes through the Michael and aldol reactions, we can anticipate the reaction of active alkynes as shown in Scheme 1: A complex formed from $TiCl_4$ and a chalcogenide reacts with an alkyne to form titanium chloroallenolate, which undergoes an aldol reaction with an aldehyde to afford an α-halomethylene aldol.

It has been reported that α-acetylenic ketones and esters underwent amine-promoted dimerization[8] and the Michael addition of triethylammonium salts.[9] Recently, Nair et al. examined the reaction of dimethyl acetylenedicarboxylate (DMAD) with aromatic aldehydes in the presence of pyridine and obtained 2-oxo-3-benzylidenesuccinates.[10] On the other hand, the phosphine-catalized reactions of DMAD with activated carbonyl compounds produced highly functionalized butenolides.[11]

α-Hydroxyalkyl- or α-aminoalkyl-acrylates are usually prepared from α-metallated acrylates and aldehydes[12–15] or imines.[13c] The Michael addition of an iodide ion and the subsequent aldol reaction of an aldehyde have been reported by some research groups.[16–18] The phosphine-catalyzed addition of imides, sulfonamide and carboxylates to alkynoates has been also reported.[19]

We now report the chalcogenide-$TiCl_4$-mediated reactions of alkynyl ketones and alkynoates.[20] Recently, Li et al. reported the $TiCl_4$-catalyzed reactions of alkynyl ketones with aldehydes, but the reactions of methyl propiolate or DMAD did not proceed under their conditions.[21]

Results and Discussion

We first conducted reactions of but-3-yn-2-one (**2**) with *p*-nitrobenzaldehyde (**1a**). The results are shown in Table 1.

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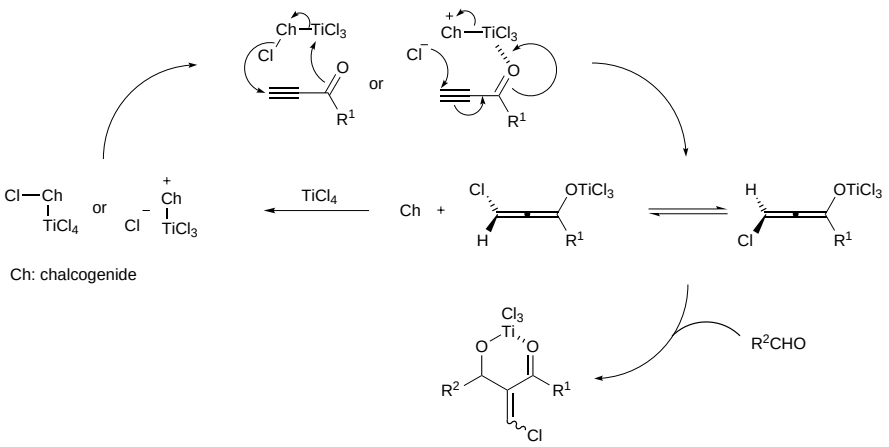
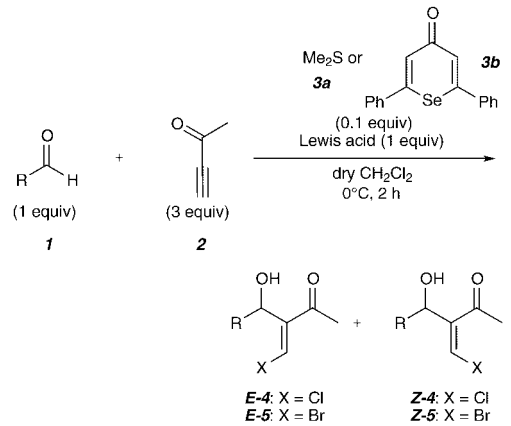


Scheme 1. Application of chalcogeno-Baylis–Hillman reaction to alkynes.

Table 1. Reaction of but-3-yn-2-one (**2**) with aldehydes **1**.



Entry	R	Catalyst	Product	Yield [%]	*E*/*Z* ratio
1	*p*-$NO_2C_6H_4$ (**1a**)	**3a**/$TiCl_4$	**4a**	86	*E* only
2[a]	*p*-$NO_2C_6H_4$ (**1a**)	**3b**/$TiCl_4$	**4a**	89	*E* only
3	*p*-$NO_2C_6H_4$ (**1a**)	$TiCl_4$	**4a**	84	1:1
4	*p*-$NO_2C_6H_4$ (**1a**)	$TiBr_4$	**5a**	49	*E* only
5	*p*-$CF_3C_6H_4$ (**1b**)	**3a**/$TiCl_4$	**4b**	73	*E* only
6	*p*-FC_6H_4 (**1c**)	**3a**/$TiCl_4$	**4c**	89	*E* only
7	*p*-ClC_6H_4 (**1d**)	**3a**/$TiCl_4$	**4d**	73	*E* only
8	C_6H_5 (**1e**)	**3a**/$TiCl_4$	**4e**	84	20:1
9	*p*-$CH_3C_6H_4$ (**1f**)	**3a**/$TiCl_4$	**4f**	86	15:1
10	$PhCH_2CH_2$ (**1g**)	**3a**/$TiCl_4$	**4g**	84	20:1

[a] The condition was conducted at RT for 5 h.

The reaction of 3 equiv of **2** with 1 equiv of **1a** proceeded in the presence of 1 equiv of $TiCl_4$ and 0.1 equiv of dimethyl sulfide (**3a**) at 0 °C for 2 h to give (*E*)-α-chloromethylene aldol **4a** in an 86% yield (entry 1). On changing **3a** into 2,6-diphenylselenopyran-4-one (**3b**), the reaction was slow and continued at room temperature for 5 h (entry 2). The reaction using only $TiCl_4$ (without **3a**) gave a mixture of the *E* and *Z* isomers in a ratio of 1:1 (entry 3). Li's group obtained only the *E* isomer from the reaction using $TiCl_4$ at room temperature for 2 h.[21] The differences between Li's findings and ours will be discussed later. The reaction using $TiBr_4$ became complex and afforded (*E*)-**5a** in a 49% yield (entry 4). Reactions of aldehydes with an electron-withdrawing group **1b–d** gave only *E* isomers of **4b–d** in high yields, but reactions of benzaldehyde (**1e**) and *p*-tolualdehyde (**1f**) produced a diastereomixture of the *E* and *Z* isomers of **4e–f**. Hydrocinnamaldehyde (**1g**) reacted with **2** to give adduct **4g** in an 84% yield as a mixture of diastereoisomers (*E*/*Z* 20:1).

The diastereoisomers of the products were separated by preparative TLC on silica gel using CH_2Cl_2/EtOAc or recycling preparative HPLC on polystyrene gels using $CHCl_3$. Their stereostructure was determined by the NOE experiments between the vinyl proton and the methyl group for the *E* isomers and between the vinyl proton and the benzylic proton for the *Z* isomers. The major isomer of **4a** [(*E*)-**4a**] showed a 9% NOE enhancement between =CH and COMe, and the minor *Z* isomer [(*Z*)-**4a**] showed a 5% NOE enhancement between =CH and CHAr.

Next, we examined the reactions of acetylenic monoesters **6** with aldehydes **1**. The results are summarized in Table 2.

When reactions of 3 equiv of methyl propiolate (**6a**) with 1 equiv of *p*-nitrobenzaldehyde (**1a**) were conducted in the presence of 1 equiv of $TiCl_4$ and 0.1 equiv of **3a** at room temperature for 24 h, product **7a** was formed in a 53% yield as a mixture of diastereoisomers (*E*/*Z* 1:4) (entry 1). The prolonged reaction time increased the yields up to a 75% yield (entries 2 and 3). The use of 1 equiv of **3a** lowered the yield and diastereoselectivity (entry 4). When **3a** was not used but only titanium Lewis acid was used, the reaction did not proceed at all (entries 5 and 6). This finding indicates that a sulfide plays an important role in the tandem Michael–aldol reaction of acetylenic esters with aldehydes. A small amount of β-(methylthio)acrylate **9a** was obtained from the reactions using **3a** and $TiBr_4$ (entries 7–9). This implies that a sulfide can cause the Michael addition to an active alkene or alkyne; therefore, this subject will be discussed below. Reactions with other aldehydes **1b** and **1d** under the same conditions as those in entry 3 gave adducts **7b** (36%) and **7d** (47%), respectively (entries 10 and 11). A β-substituted alkynoate, methyl 2-butynoate (**6b**), reacted with **1a** to give adduct **7h** in a 25% yield (entry 12).

The reaction of DMAD (**10**) with **1a** afforded adduct **11** (30%) and methyl 4-chloro-2-(4-nitrophenyl)-5-oxo-2,5-dihydrofuran-3-carboxylate (**12**) (10%) (Table 3, entry 1). When 1,1,3,3-tetramethyl-thiourea (**3c**) was used instead of **3a**, the yields of both **11** and **12** were increased to a 40% yield (entry 2). The geometry of **11** was determined to be *E* from the ^{1}H NMR spectrum showing a singlet at $\delta = 6.06$ due to the benzylic proton, which is very close to that of (*E*)-**7a** ($\delta = 6.05$). Incidentally, the benzylic proton of (*Z*)-**7a** appeared at $\delta = 5.61$. Furthermore, it is known that (*Z*)-2-(hydroxymethyl)but-2-enedioic esters readily cyclize to furanone deriva-

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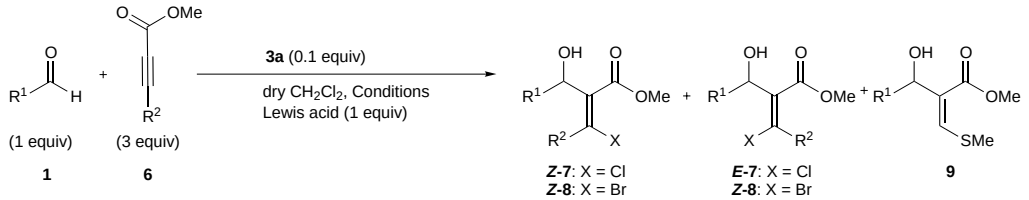
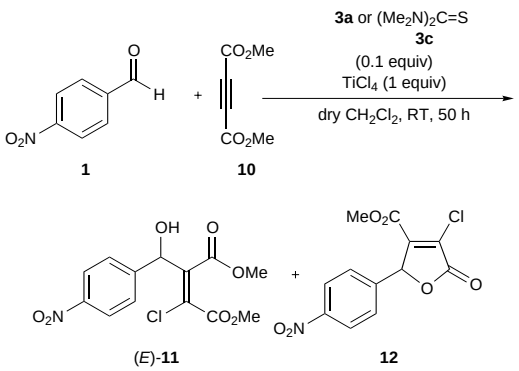
Table 2. Reaction of alkyne carboxylic ester **6** with aldehydes **2**.



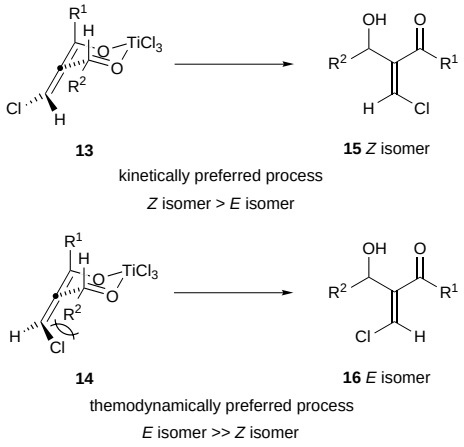
Entry	R^1	R^2	Conditions	Catalyst	Products	Yield [%]	*E*/*Z* ratio
1	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	RT, 24 h	**3a**/$TiCl_4$	**7a**	53	1:4
2	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	RT, 41 h	**3a**/$TiCl_4$	**7a**	70	1:6
3	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	RT, 50 h	**3a**/$TiCl_4$	**7a**	75	1:7
4[a]	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	RT, 50 h	**3a**/$TiCl_4$	**7a**	34	1:3
5	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	RT, 50 h	$TiCl_4$		no reaction	
6	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	RT, 50 h	$TiBr_4$		no reaction	
7	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	RT, 50 h	**3a**/$TiBr_4$	**8a**	37	1:2
					9a	trace	
8[b]	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	– 20 °C, 60 h	**3a**/$TiBr_4$	**8a**	9	1:1.3
					9a	8	
9[b]	*p*-$NO_2C_6H_4$ (**1a**)	H (**6a**)	– 40 °C, 60 h	**3a**/$TiBr_4$	**8a**	trace	
					9a	5	
10	*p*-$CF_3C_6H_4$ (**1b**)	H (**6a**)	RT, 50 h	**3a**/$TiCl_4$	**7b**	36	1:6
11	*p*-ClC_6H_4 (**1d**)	H (**6a**)	RT, 50 h	**3a**/$TiCl_4$	**7d**	47	1:7
12	*p*-$NO_2C_6H_4$ (**1a**)	CH_3 (**6b**)	RT, 50 h	**3a**/$TiCl_4$	**7h**	25	1:1

[a] **3a** (1 equiv) was used. [b] **3a** (0.2 equiv) was used.

Table 3. Reaction of dimethyl acetylene dicarboxylate (**10**) with *p*-nitrobenzaldehyde (**2**).



Entry	Chalcogenide	Products (Yield [%])
1	**3a**	(*E*)-**11** (30), **12** (10)
2	**3c**	(*E*)-**11** (40), **12** (40)



Scheme 2. Mechanism for formation of α-(chloromethylene)aldols **15** and **16**.

tives,[11, 22] some of which exert specific and strong pharmacological and agrochemical activities.[23]

The mechanism for the formation of *E* and *Z* isomers of α-halomethylene aldols is shown in Scheme 2.

An allenolate is formed by the addition of a chloride ion to an ynone as shown in Scheme 1 and reacts with an aldehyde via the cyclic transition state **13** or **14**.[16] The transition state **13** has no steric repulsion between the hydrogen of the allenolate and the R^2 substituent of the aldehyde, while the transition state **14** has a steric hindrance between the chlorine atom and the R^2 group. Therefore, **13** is more stable than **14**, and *Z* isomer **15** is formed from **13** via the kinetically preferred process. On the other hand, *E* isomer **16** is more stable than **15** and is produced from **14** via the thermodynamically preferred process. Our findings that reactions of but-3-yn-2-one predominantly formed (*E*)-α-halomethylene aldol and reactions of alkynoates preferentially produced (*Z*)-acrylates are in good agreement with Taniguchi's findings.[16] The ratio of the *Z* isomers increased in the reactions of alkynyl ketone **2** with aldehydes possessing a formyl group-stabilizing substituent **1e–g** (entries 8–10 in Table 1) or of alkynyl esters **6a–b** (Table 2), probably because these reactions were slower than those of **2** with aldehydes bearing an electron-withdrawing group **1a–d** and were governed by the kinetically controlled process.

Next, we discuss the formation of α-(methylthiomethylene)aldol **9a** obtained from the reaction of **6a** with *p*-nitrobenzylaldehyde (**1a**) (entries 7–9 in Table 2). Possible formation mechanisms for **9a** are shown in Scheme 3.

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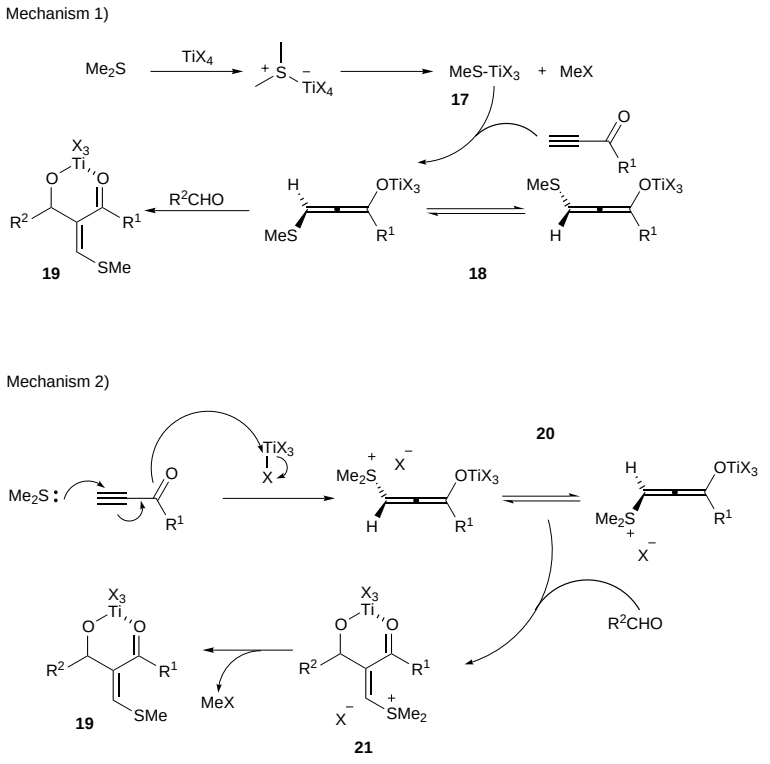


Scheme 3. Possible mechanism for formation of α-(methylthiomethylene)aldol **19**.

It is known that a Lewis acid TiX_4 and a sulfide form a complex.[24] If the complex formed from TiX_4 and dimethyl sulfide (**3a**) releases MeX to generate a new Lewis acid, MeS-TiX_3 **17** in mechanism 1), **17** reacts with an alkynoate to afford γ-(methylthio)allenolate **18**. The reaction of the allenolate **18** with an aldehyde gives an aldol product **19**. On the other hand, mechanism 2) involves the Michael addition of dimethyl sulfide (**3a**) to an alkynoate by activation with TiX_4. The resulting γ-(dimethylsulfonio)allenolate **20** reacts with an aldehyde to form α-(dimethylsulfoniomethylene)aldol **21**, which changes into an aldol product **19** accompanied by demethylation.

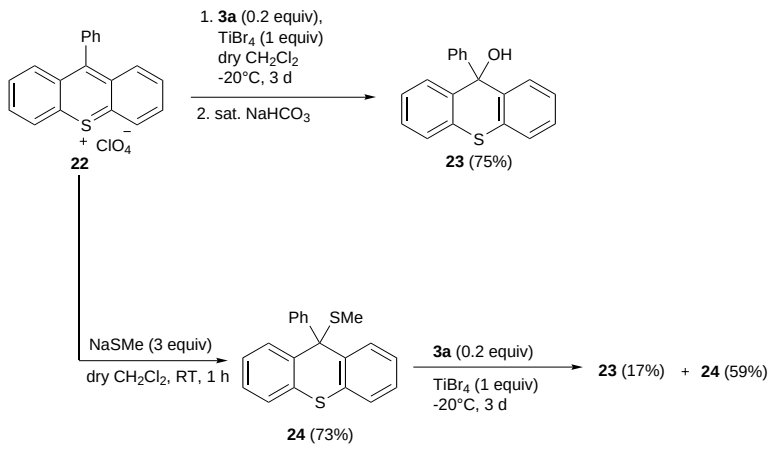
If the reaction proceeds via mechanism 1), the Lewis acid **17** generated in situ works as an equivalent of MeS^-. We selected 9-phenylthioxanthylium salt (**22**) as an acceptor of MeS^- and conducted the reactions shown in Scheme 4.

A reaction of **22** (1 equiv) with **3a** (0.2 equiv) and $TiBr_4$ (1 equiv) was conducted in dichloromethane at $-20\,^{\circ}C$ for 3 d. The product was not 9-(methylthio)-9-phenylthioxanthene (**24**) but 9-phenyl-thioxanthenol (**23**) in a 75% yield. Product **23** would be formed by the hydrolysis of **22**, but it is possible that the desired product **24** would be first produced and transformed into **22** in an acidic reaction medium because **24** has an acid-sensitive triphenylmethyl moiety. Then the resulting **22** would be hydrolyzed to give **23** when the reaction is worked up. In order to confirm this hypothesis, we prepared an authentic sample of **24** in a 73% yield by the reaction of **22** with sodium methanethiolate and then treated it with $TiBr_4$ under the same conditions as those of the reaction of **22**, **3a** and $TiBr_4$. Compound **24** was converted into **23** in a 17% yield, but the unreacted **24** was recovered in a 59% yield. From these findings, it was revealed that the Lewis acid **17** was not generated in situ and aldol **19** was not formed via mechanism 1).

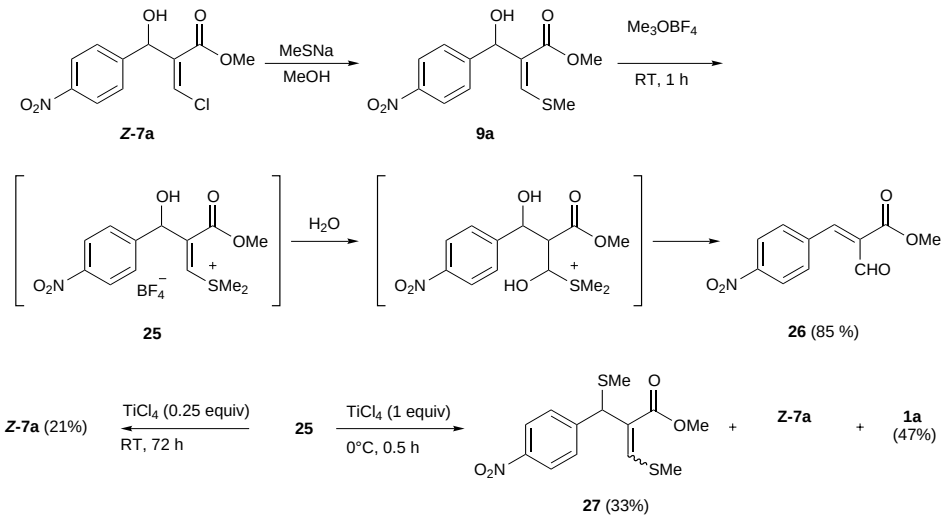
Since the intramolecular Michael addition reaction of a sulfide group to an enone moiety in an acidic medium is known,[25, 26] it might be difficult but possible to cause the Michael addition of dimethyl sulfide to an electron-deficient alkyne. Sulfonium salts bearing an alkyl group undergo dealkylation with halide ions.[27] Based on these reports, sulfide **19** should be formed via mechanism 2).

In order to examine the reactivity of sulfide **9a** and sulfonium salt **25**, we prepared them and conducted their reactions shown in Scheme 5.

Sulfide **9a** was derived with the retained configuration by the reaction of (*Z*)-β-chloroacrylate (*Z*)-**7a** with sodium methanethiolate via the addition and elimination processes.[28] The methylation of sulfide **9a** with the Meerwein reagent gave α-formylcinnamate **26** in an 85% yield, which would be formed via the following processes: addition of water to the α-carbon of sulfonium salt **25**, elimination of dimethyl sulfide (**3a**), ketonization and elimination of water. Attempts to



Scheme 4. Attempt to trap methanethiolate ion.



Scheme 5. Reaction of vinylsulfonium salt **25**.

isolate sulfonium salt **25** were unsuccessful because of its lability. When sulfonium salt **25** was prepared in situ and then treated with 0.25 equiv of $TiCl_4$, (*Z*)-β-chloroacrylate (*Z*)-**7a** was obtained in a 21 % yield. When 1 equiv of $TiCl_4$ was used, methyl 3-methylthio-2-[1-methylthio-1-(*p*-nitrophenyl)methyl]acrylate **27**(33 %) as a mixture of *E* and *Z* isomers, (*Z*)-**7a** (6 %) and **1a** (47 %) were obtained. The bis(methylthio) derivative **27** would be formed from the substitution reaction of the hydroxy group of **9a** for a methanethiolate ion that is generated by the retro-aldol reaction of **9a** under acidic reaction conditions. The chloride (*Z*)-**7a** would be formed via the addition of a chloride ion and the successive elimination of dimethyl sulfide (**3a**) with the retention of the configuration,[29] although a pathway via the reaction of aldehyde **1a** with methyl propiolate (**6a**) resulting from the retro-aldol reaction of **9a** could not be completely excluded. The aldehyde **1a** would be given from the retro-aldol reaction of **26** which occurred during purification of the raw product because the ^{1}H NMR spectrum of the raw product had exhibited signals due to **26**. The reaction of sulfonium salt **25** with trimethylsulfoxonium iodide did not give a β-iodoacrylate but gave a complex mixture.

In conclusion, we developed chalcogenide-$TiCl_4$-mediated reactions of α-acetylenic ketones and esters with aldehydes giving (*E*)-α-(halomethylene)aldols and (*Z*)-3-halogeno-2-(hydroxylmethyl)acrylates. Since the products have transformable functional groups, we could utilize them as useful intermediates for the synthesis of biologically active compounds.

Experimental Section

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 FT/IR-230 spectrophotometer. ^{1}H NMR spectra were recorded on 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 with $CDCl_3$ as an internal standard ($\delta = 77.0$). 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 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. CH_2Cl_2 was washed with water, dried over $CaCl_2$, and freshly distilled from P_4O_{10}. 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).

General: For data of compounds **4a**, **c**–**g**, **5a** and **7a**, **b**, **d**, **h**, see Supporting Information.

A typical reaction of but-3-yn-2-one (2) with an aldehyde: *p*-Trifluoromethylbenzaldehyde (**1b**, 87 mg, 0.5 mmol) and dimethyl sulfide (**3a**) (3 mg, 0.05 mmol) were added to a solution of but-3-yn-2-one (**2**) (102 mg, 1.5 mmol) in dry dichloromethane (1.5 mL). $TiCl_4$ (55 µL, 0.5 mmol) was added dropwise at 0 °C. The mixture was stirred for 2 h and then quenched by adding saturated aqueous $NaHCO_3$ solution (1.5 mL). The inorganic precipitate was removed by filtration through Celite, and the filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with hexane/ethyl acetate (2:1) to give (*E*)-4-chloro-3-[1-hydroxy-1-(4-trifluoromethylphenyl)-methyl]but-3-en-2-one [(*E*)-**4b**] in a 73 % yield.

(*E*)-4-Chloro-3-[1-hydroxy-1-(4-trifluoromethylphenyl)methyl]but-3-en-2-one [(*E*)-4b]: white powder (from AcOEt/hexane); m.p. 61–64 °C (m.p. 68–70 °C[21]); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.33$ (s, 3H; Me), 4.43 (d, $J = 11$ Hz, 1H; OH), 5.98 (d, $J = 11$ Hz, 1H; benzylic H), 7.48–7.52 (m, 3H; ArH, olefinic H), 7.58–7.60 (m, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 27.0$ (q), 70.3 (d), 125.39 (d), 125.43 (d), 129.5 (s), 129.8 (s), 136.5 (d), 142.7 (s), 145.5 (s), 198.1 (s); IR (KBr) $\tilde{\nu} = 3510$ (OH), 1669 cm^{-1} (C=O); MS (EI): *m*/*z* (%): 278 (4) [M^+], 127 (100); elemental analysis calcd (%) for $C_{12}H_{10}ClF_3O_2$: C 51.72, H 3.62; found: C 51.74, H 3.62.

Reaction of methyl propiolate (6a) with aldehyde 1a: *p*-Nitrobenzaldehyde (**1a**) (76 mg, 0.5 mmol) and dimethyl sulfide (**3a**) (6 mg, 0.1 mmol) were added to a solution of methyl propiolate (**6a**) (126 mg, 1.5 mmol) in dry dichloromethane (1.5 mL). $TiBr_4$ (184 mg, 0.5 mmol) was added to the mixture at −20 °C. The whole mixture was stirred for 60 h at the same temperature and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (1.5 mL). The inorganic precipitate was removed by filtration through Celite. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with hexane/ethyl acetate (2:1) to give **8a** and **9a**.

Methyl (*E*)-3-bromo-2-[1-hydroxy-1-(4-nitrophenyl)methyl]acrylate [(*E*)-8a]: yellow powder (from AcOEt/hexane); m.p. 70–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.75$ (s, 3H; OMe), 4.25 (d, $J = 11$ Hz, 1H; OH), 6.03 (d, $J = 11$ Hz, 1H; benzylic H), 7.86 (s, 1H; olefinic H), 7.60 and 8.21 (each d, $J = 9$ Hz, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.7$ (q), 71.6 (d), 123.7 (d), 126.0 (d), 126.1 (d), 136.9 (s), 147.4 (s), 148.5 (s), 164.4 (s); IR (KBr) $\tilde{\nu} = 3486$ (OH), 1708 (C=O), 1523 (NO_2), 1349 cm^{-1} (NO_2); MS (EI): *m*/*z* (%): 203 (100); [M^+], *m*/*z* 315 or 317, was not observed; elemental analysis calcd (%) for $C_{11}H_{10}BrNO_5$: C 41.76, H 3.19, N 4.43; found: C 42.01, H 3.35, N 4.33.

Methyl (*Z*)-3-bromo-2-[1-hydroxy-1-(4-nitrophenyl)methyl]acrylate [(*Z*)-8a]: yellow powder (from AcOEt/hexane); m.p. 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.38$ (d, $J = 6.0$ Hz, 1H; OH), 3.75 (s, 3H; OMe), 5.62 (d, $J = 6.0$ Hz, 1H; benzylic H), 7.05 (s, 1H; olefinic H), 7.55, 8.21 (d, $J = 8.8$ Hz, each 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.3$ (q), 74.4 (d), 116.7 (d), 123.8 (d), 127.3 (d), 138.6 (s), 147.4 (s), 147.7 (s), 165.6 (s); IR (KBr) $\tilde{\nu} = 3480$ (OH), 1707 (C=O), 1522 (NO_2), 1346 cm^{-1} (NO_2); MS (EI):

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m/z (%): 203 (100); [M^+], *m/z* 315 or 317, was not observed; elemental analysis calcd (%) for $C_{11}H_{10}BrNO_5$: C 41.76, H 3.19, N 4.43; found: C 42.00, H 3.29, N 4.34.

Methyl (*Z*)-2-[1-hydroxy-1-(4-nitrophenyl)methyl]3-methyl-sulfanyl acrylate [(*Z*)-9a]: yellow powder (from AcOEt/hexane); m.p. 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H; SMe), 3.08 (d, $J = 5.5$ Hz, 1H; OH), 3.75 (s, 3H; OMe), 5.62 (d, $J = 5.5$ Hz, 1H; benzylic H), 7.20 (s, 1H; olefinic H), 7.56, 8.20 (d, $J = 8.8$ Hz, each 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.6$ (q), 51.7 (q), 73.3 (d), 123.6 (d), 125.2 (s), 127.1 (d), 147.3 (s), 149.5 (s), 151.0 (d), 166.1 (s); IR (KBr) $\tilde{\nu} = 3503$ (OH), 1671 (C=O), 1517 (NO_2), 1344 cm^{-1} (NO_2); MS (EI): *m/z* (%): 283 (22) [M^+], 236 (100); elemental analysis calcd (%) for $C_{12}H_{13}NO_5S$: C 50.88, H 4.63, N 4.94; found: C 50.72, H 4.61, N 4.92.

Methyl (*E*)-2-[1-hydroxy-1-(4-nitrophenyl)methyl]3-methyl-sulfanyl acrylate [(*E*)-9a]: yellow powder (from AcOEt/hexane); m.p. 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.53$ (s, 3H; SMe), 3.71 (s, 3H; OMe), 4.25 (br s, 1H; OH), 5.71 (brs, 1H; benzylic H), 7.77 (s, 1H; olefinic H), 7.60 and 8.18 (d, $J = 8.5$ Hz, each 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.0$ (q), 51.9 (q), 70.4 (d), 123.4 (d), 126.2 (s), 126.2 (d), 147.0 (s), 148.8 (d), 149.7 (s), 165.0 (s); IR (KBr) $\tilde{\nu} = 3486$ (OH), 1673 (C=O), 1515 (NO_2), 1350 cm^{-1} (NO_2); MS (EI): *m/z* (%): 283 (22) [M^+], 236 (100); elemental analysis calcd (%) for $C_{12}H_{13}NO_5S$: C 50.88, H 4.63, N 4.94; found: C 50.75, H 4.69, N 4.93.

Reaction of dimethyl acetylenedicarboxylate (10) with *p*-nitrobenzaldehyde (1a): *p*-Nitrobenzaldehyde (**1a**) (76 mg, 0.5 mmol) and 1,1,3,3-tetramethyl-2-thiourea (**3c**) (6 mg, 0.05 mmol) were added to a solution of **10** (213 mg, 1.5 mmol) in dry dichloromethane (1.5 mL). $TiCl_4$ (55 μL, 0.5 mmol) was added dropwise at room temperature. The mixture was stirred for 50 h and then quenched by adding saturated aqueous $NaHCO_3$ solution (2 mL). The inorganic precipitate was removed by filtration through Celite, and the filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to give a mixture of (*E*)-2-chloro-3-[1-hydroxy-1-(4-nitrophenyl)methyl]but-2-enedioic dimethyl ester [(*E*)-**11**] and 4-chloro-2-(4-nitro-phenyl)-5-oxo-2,5-dihydrofuran-3-carboxylic methyl ester (**12**). The mixture was separated by recycling preparative HPLC eluting with chloroform.

(*E*)-2-Chloro-3-[1-hydroxy-1-(4-nitrophenyl)methyl]but-2-enedioic dimethyl ester [(*E*)-11]:colorless needles (from hexane/chloroform); m.p. 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.48$ (d, $J = 7$ Hz, 1H; OH), 3.76, 3.87 (each 3H, s; CO_2Me), 6.06 (d, $J = 7$ Hz, 1H; benzylic H), 7.66, 8.23 (each d, $J = 8$ Hz, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 53.2$ (q), 53.8 (q), 71.3 (d), 123.8 (d), 127.1 (d), 129.4 (s), 140.0 (s), 146.3 (s), 147.8 (s), 162.1 (s), 164.9 (s); IR (KBr): $\tilde{\nu} = 3481$ (OH), 1716 (C=O), 1523 (NO_2), 1342 cm^{-1} (NO_2); MS (EI): *m/z* (%): 329 (1) [M^+], 147 (100); elemental analysis calcd (%) for $C_{13}H_{12}ClNO_7$: C 47.36, H 3.67, N 4.25; found: C 47.15, H 3.65, 4.31.

4-Chloro-2-(4-nitrophenyl)-5-oxo-2,5-dihydrofuran-3-carboxylic methyl ester (12): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.83$ (s, 3H; CO_2Me), 6.24 (s, 1H; benzylic H), 7.52, 8.27(each d, $J = 9$ Hz, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 53.2$ (q), 80.8 (d), 124.1 (d), 128.4 (d), 130.7 (s), 139.6 (s), 145.3 (s), 148.8 (s), 159.8 (s), 166.0 (s); IR (KBr): $\tilde{\nu} =$ 3349 (OH), 1791 (C=O), 1732 (C=O), 1523 (NO_2), 1351 cm^{-1} (NO_2); MS (EI): *m/z* (%): 297 (22)[M^+], 268 (100); HRMS (EI): calcd for $C_{13}H_8ClNO_6$: 297.0040; found: 297.0034 [M^+].

Reaction of 9-phenylthioxanthylium perchlorate (22) with $TiBr_4$ and dimethyl sulfide (3a): $TiBr_4$ (184 mg, 0.5 mmol) was added to a stirred solution of 9-phenylthioxanthylium perchlorate[30] (**22**) (186 mg, 0.5 mmol) and dimethyl sulfide (**3a**) (6 mg, 0.1 mmol) in dry dichloromethane (1.5 mL) at −20 °C. The mixture was stirred at the same temperature for 3 days and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (1.5 mL). The inorganic precipitate was removed by filtration through Celite, and the filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with CH_2Cl_2/AcOEt (100:1) to give 9-phenylthioxanthen-9-ol (**23**) in a 75% yield. Product **23** was identical with an authentic sample prepared from thioxanthone and phenylmagnesium bromide.[30]

Synthesis of 9-methylthio-9-phenylthioxanthene (24): A 15% aqueous sodium methanethiolate solution (700 mg, 1.5 mmol) was added to a solution of **22** (186 mg, 0.5 mmol) in dichloromethane (1.5 mL) at room temperature. The mixture was stirred at the same temperature for 1 h and then poured into water and extracted with dichloromethane. The extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with CH_2Cl_2/AcOEt (100:1) to give **24** in a 73% yield.

9-Methylthio-9-phenylthioxanthene (24): colorless prisms (from AcOEt/hexane); m.p. 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.75$ (s, 3H; SMe), 7.07–7.09 (m, 4H; ArH), 7.18–7.20 (m, 2H; ArH), 7.33–7.38 (m, 5H; ArH), 7.46–7.47 (m, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.3$ (q), 62.1 (s), 125.6 (d), 126.0 (d), 127.0 (d), 127.2 (d), 128.0 (d), 130.3 (d), 131.0 (d), 132.2 (s), 136.7 (s), 137.1 (s), 142.5 (s); MS (EI) *m/z* (%): 320 (1) [M^+], 273 (100); elemental analysis calcd (%) for $C_{20}H_{16}S_2$: C 74.96, H 5.03; found: C 75.03, H 5.05.

Synthesis of methyl 2-[1-hydroxy-1-(4-nitrophenyl)methyl]3-methylsulfanyl acrylate (9a): A 15% aqueous solution of sodium methanethiolate (1.40 g, 3.0 mmol) was added to a solution of (*Z*)-**7a** (543 mg, 2.0 mmol) in MeOH (2.0 mL) at room temperature. The mixture was stirred at the same temperature for 10 min and then poured into water and extracted with dichloromethane. The extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel using hexane/AcOEt (5:1) to give **9a** in a 78% yield. The product was identical with a sample obtained from the reaction of methyl propiolate with **1a** in Table 2.

Methylation of sulfide 9a: Me_3OBF_4 (177 mg, 1.2 mmol) was added to a solution of **9a** (283 mg, 1.0 mmol) in dry dichloromethane (2.0 mL) at 0 °C. The mixture was stirred at room temperature for 1 h, and then the solvent was evaporated under reduced pressure. The residue was washed with Et_2O to give methyl (*E*)-2-formyl-3-(4-nitrophenyl)propenoate (**26**) in an 85% yield.

Methyl (*E*)-formyl-3-(4-nitrophenyl)propenoate (26): pale yellow needles (from AcOEt/hexane); m.p. 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.88 (s, 3H; SMe), 7.58 (s, 1H; olefinic H), 7.68, 8.28 (d, $J = 8.8$ Hz, each 2H; ArH), 9.72 (s, 1H; CHO); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.9$ (q), 124.0 (d), 130.6 (d), 136.2 (s), 138.6 (s), 146.2 (d), 148.9 (s), 165.1 (s), 188.7 (d); IR (KBr): $\tilde{\nu} = 1738$ (C=O), 1675 (C=O), 1516 (NO_2), 1350 cm^{-1} (NO_2); MS (EI): *m/z* (%): 235 (10) [M^+], 203 (100); HRMS (EI) calcd for $C_{11}H_9NO_5$: 235.0481; found: 235.0486 [M^+].

Reaction of sulfonium salt 25 with $TiCl_4$: a) Me_3OBF_4 (18 mg, 0.12 mmol) was added to a solution of **9a** (28 mg, 0.1 mmol) in dry dichloromethane (0.5 mL) at 0 °C. The mixture was stirred at room temperature for 1 h followed by the addition of $TiCl_4$ (3 μL, 0.03 mmol) and stirred for 3 days. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution, and the inorganic precipitate was removed by filtration through Celite. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with ethyl acetate/hexane (3:10) to give methyl (*Z*)-3-chloro-2-[1-hydroxy-1-(4-nitrophenyl)methyl]acrylate (**7a**) in a 21% yield. The product was identical with an authentic *Z* isomer obtained from the reaction of **6a** with **1a**.

b) Me_3OBF_4 (35 mg, 0.24 mmol) was added to a solution of **9a** (57 mg, 0.2 mmol) in dichloromethane (1.0 mL) at 0 °C. The mixture was stirred at room temperature for 1 h followed by the addition of $TiCl_4$ (22 μL, 0.2 mmol) and stirred for 30 minutes. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution, and the inorganic precipitate was removed by filtration through Celite. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with ethyl acetate/hexane (3:10) to give acrylate **27** as a mixture of the *E* and *Z* isomers (*E*/*Z* 2:5) and (*Z*)-**7a** in 38% and 6% yields, respectively.

Methyl (*E*)-3-methylthio-2-[1-methylthio-1-(4-nitrophenyl)methyl]acrylate [(*E*)-27]: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.04$ (s, 3H; SMe), 2.46 (s, 3H; SMe), 3.71 (s, 3H; OMe), 5.05 (s, 1H; benzylic H), 7.48 (d, $J = 8.8$ Hz, 2H; ArH), 7.51 (s, 1H; olefinic H), 8.16 (d, $J = 8.8$ Hz, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.2$ (q), 19.8 (q), 51.3 (d), 51.8 (q), 122.1(s), 123.8 (d), 128.9 (d), 147.0 (s), 148.0 (s), 151.5 (d), 166.0 (s); IR (NaCl) $\tilde{\nu} = 1705$ (C=O), 1520 (NO_2), 1347 cm^{-1} (NO_2); MS (EI): *m/z* (%): 313 (10) [M^+], 266 (100); HRMS (EI) calcd for $C_{13}H_{15}O_4NS_2$: 313.0442; found: 313.0434 [M^+].

Methyl (*Z*)-3-methylthio-2-[1-methylthio-1-(4-nitrophenyl)methyl]acrylate [(*Z*)-27]: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3H;

SMe), 2.47 (s, 3H; SMe), 3.70 (s, 3H; OMe), 5.18 (s, 1H; benzylic H), 7.68 (d, $J = 8.5$ Hz, 2H; ArH), 7.77 (s, 1H; olefinic H), 8.16 (d, $J = 8.5$ Hz, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.4$ (q), 18.8 (q), 49.4 (d), 52.0 (q), 123.4 (d), 125.3 (s), 129.0 (d), 146.6 (s), 146.9 (s), 148.3 (d), 164.6 (s); IR (NaCl) $\tilde{\nu} = 1704$ (C=O), 1520 (NO_2), 1346 cm^{-1} (NO_2); MS (EI) m/z (%): 313 (15) [M^+], 266 (100); HRMS (EI) calcd for $C_{13}H_{15}O_4NS_2$ 313.0442; found: 313.0446 [M^+].

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