

Three-Component Halo Aldol Condensation of Thioacrylates with Aldehydes Mediated by Titanium (IV) Halide[†]

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Abstract: α,β -Ethyl thioacrylate was difunctionalized by a tandem X-C/C=C bond formation reaction. The new system uses Ti (IV) halide as both the Lewis acidic promoter and the halogen source for the Michael-type addition onto the thioacrylate. The titanium enolate species resulting from Michael-type addition react with aldehydes followed by dehydration to afford trisubstituted olefin products. Complete geometric selectivity (>95%) and up to 72% yield have been obtained for 7 examples.

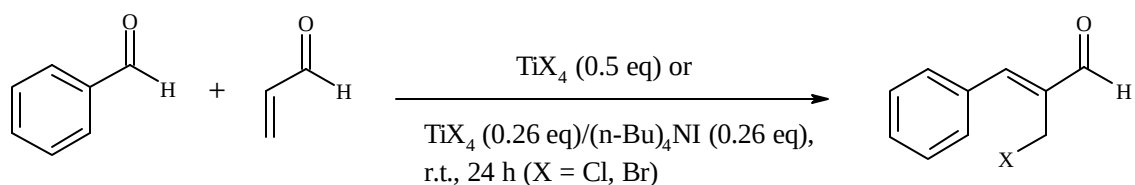
Keywords: Aldol reaction, halide, thioester.

Introduction

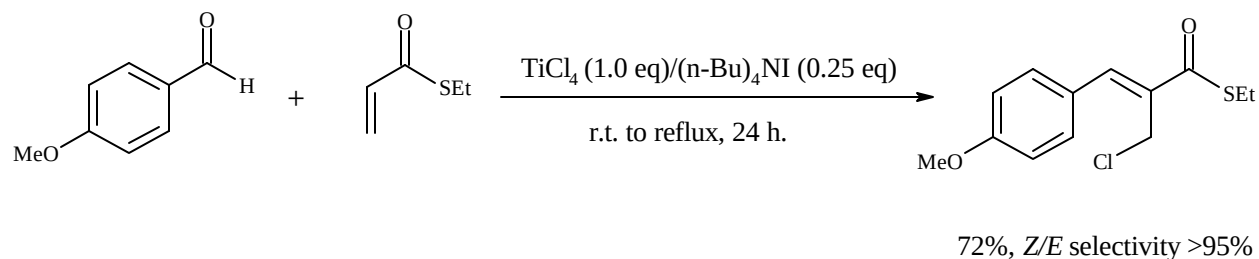
The Baylis-Hillman-type C(sp³)-C(sp²) single bond formation has become an active area in synthetic organic chemistry [1,3], but the direct carbon-carbon double formation under Baylis-Hillman-type conditions to give α -halomethyl vinyl carbonyl compounds have not been well documented. So far, the synthesis of α -halomethyl olefins has been achieved by treatment of Baylis-Hillman adducts with various halogenating

reagents such as NBS/Me₂S, hydrogen halides and CuBr₂/SiO₂ [4]. Recently, we developed a new method for the synthesis of α -halomethyl vinyl ketones via a one-pot tandem difunctionalization of α,β -unsaturated ketones [5,6]. The reaction was mediated in a highly stereoselective manner by a non-stoichiometric amount of titanium (IV) halides or a mixture of TiCl₄/(*n*-Bu)₄NI (and/or TiBr₄/(*n*-Bu)₄NI) (Scheme 1). To extend the scope of this reaction, we have utilized α,β -unsaturated alkyl acrylates and related substrates to replace the ketones for this new reaction but without success. We now found that α,β -unsaturated ethyl thioacrylate can be functionalized to afford α -halomethyl β -substituted vinyl thioesters under modified conditions. In this paper, we report this new method which is represented by Scheme 2.

Scheme 1



Scheme 2



Results and Discussion

The new one-pot and three-component reaction was performed simply by mixing the aldehyde, α,β -unsaturated thioester and TiCl₄/(*n*-Bu)₄NI in dichloromethane solution at room temperature followed by heating to reflux for 24 hours. The increased ratio of TiCl₄ to (*n*-Bu)₄NI (TiCl₄/(*n*-Bu)₄NI = 4/1) was proven to be necessary for the reaction, although relatively low yields were obtained for most cases at this stage as shown in Table 1, for which the relatively more complex and stable intermediates generated from the new thioester substrate are responsible. The initial reaction was carried out by reacting ethyl thioacrylate with benzaldehyde in the presence of TiCl₄ (0.5 eq), or TiCl₄ (0.26 eq)/(*n*-Bu)₄NI (0.26 eq) in dichloromethane at room temperature as previously described [5]. Unfortunately, only a tiny amount of the expected product was observed even after prolonged reaction times (>24 hours) with less than 50% consumption of starting material. The major side product was determined to be the undehydrated haloaldol adduct. Raising the reaction temperature resulted in little improvement, giving less than 30% yield. When the loading of TiCl₄ was increased to 1.0 equiv, the chemical yield was enhanced to 45%. Similar observations were realized for two other substrates, *p*-chloro and *p*-chlorobenzaldehyde (entries 3 and 4 of Table 1). Interestingly, the highest yield (72

%) was obtained when a strong electron-donating substituted aldehyde, *p*-methoxybenzaldehyde, was employed as the substrate (entry 2). For this substrate, a smaller amount of TiCl_4 (10 mol%) can also accomplish the reaction at room temperature without heating to give a similar yield. This observation can be explained by the fact that the electronically rich aldehyde helps to dissociate chlorine anion from TiCl_4 for the Michael-type addition.

Table 1. Results of $\text{TiCl}_4/(n\text{-Bu})_4\text{NI}$ -Mediated C=C Bond Formation

Entry	R-	product	m.p.(°C)	yield (%) ^a
1			oil	45
2 ^b			oil	72
3			oil	55
4			35-36	52
5	$\text{Me}(\text{CH}_2)_8\text{-}$		oil	56
6			oil	43
7			121-122	65

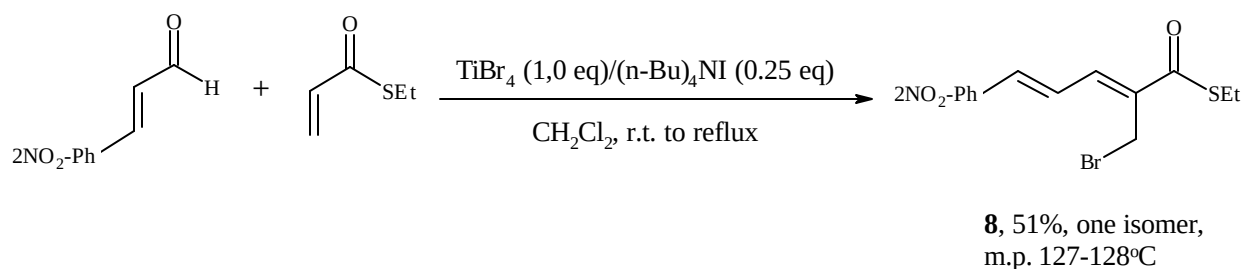
^a Purified yields. Only *Z/E* isomer was observed by crude $^1\text{H-NMR}$ determination. ^b The reaction can be finished at room temperature in the presence of 10 mol% of $(n\text{-Bu})_4\text{NI}$.

Even though aldol condensation products were produced predominantly for most cases, the nondehydrated aldol adducts were obtained in 82% yield when para-nitrobenzaldehyde was employed as the

carbonyl acceptor under the same conditions. The same situation was encountered when an acrylonitrile substrate was used as the Michael acceptor [7a]. As revealed in previous reports [5], the nondehydrated aldol adducts are also very useful for organic synthesis, particularly, when they are transformed to the Baylis-Hillman aldohols by treatment with tertiary amines [7].

As in the previous systems studied [5,6], dichloromethane was proven to be the most effective solvent for this reaction. Besides titanium tetrachloride, its bromide counterpart (TiBr_4) can also be utilized as the Lewis acid promoter and the halogen source (Scheme 3). The latter process gives a slightly lower yield (51%) with complete geometric selectivity. For both TiCl_4 and TiBr_4 -based systems, no iodinated products were observed even in the presence of tetrabutylammonium iodide. The major role of the iodine anion of tetrabutylammonium iodide would then be to push Br^- or Cl^- off their corresponding titanium halides. This observation tells that α,β -unsaturated ethyl thioacrylate is not a good enough Michael-type acceptor to accept iodine anion under the present conditions. This is in contrast to the previous processes [5,6c], where the iodinated products were either formed predominantly or in small amounts.

Scheme 3



The mechanism of this process could be similar to those of previous X-C/C-C and X-C/C=C bond formation reactions [3-5, 7a]. In the initial step, one of the chlorine anions released from TiCl_4 is added onto the α,β -unsaturated thioester to give titanium enolates. The enolate formation is accelerated by the coordination of the carbonyl oxygen onto the titanium halide ($\text{C=O} \cdots \text{Ti}$ interaction)[8] to further free the chlorine anion from TiCl_4 . This coordination can also polarize the α,β -conjugate C=C double bond to favor the conjugate addition. The resulting titanium species can serve as Lewis acids to activate aldehydes for the subsequent carbonyl additions.

Conclusions

A new three-component reaction system has been developed for the synthesis of α -halomethyl α,β -unsaturated thioesters via tandem formations of X-C and C=C bonds. Both TiCl_4 and TiBr_4 can be used as the halogen sources and promoters for α,β -unsaturated thioester substrates. An increased ratio of $\text{TiCl}_4/(n\text{-Bu})_4\text{NI}$ (4:1) has been proven to be necessary for the reaction. Complete geometric selectivity has been obtained for all cases which were examined.

Acknowledgments

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Experimental

General

Dichloromethane and propionitrile was dried and freshly distilled from calcium hydride under a nitrogen atmosphere. Other commercial chemicals were used without further purification and their stoichiometries were calculated based on the purities reported by the manufacturers. Flash chromatography was performed on E. Merck silica gel 60 (230-400 mesh). Thin layer chromatography was performed on Merck Kieselgel 60 GF₂₅₄ plates (0.2 mm thickness). ¹H-NMR (300 MHz) and ¹³C-NMR spectra (75 MHz) spectra were recorded on a Varian 300 MHz NMR spectrometer using CDCl₃ as solvent. The spectral data are reported in the following format: chemical shift (all relative to Me₄Si as an internal reference standard unless otherwise indicated), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, b = broad).

Typical Experimental Procedure

Benzaldehyde (0.107 g, 1.00 mmol), tetrabutylammonium iodide (0.094 g, 0.25 mmol) and CH₂Cl₂ (3.0 mL) were loaded into a clean, dry round bottomed flask. The flask was attached to a reflux condenser and the contents protected by nitrogen gas. A solution of ethyl thioacrylate (0.15 g, 1.30 mmol) in 2 mL of CH₂Cl₂ and 1 M titanium chloride (1.0 mL) in the same solvent were then added dropwise via a syringe. The reaction mixture was stirred for 1 h at room temperature and then heated to reflux. The reaction was monitored by GC or TLC until the aldehyde was completely consumed. The reaction was then quenched by saturated aqueous NaHSO₃. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 5.0 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated. Purification was carried out by column chromatography (ethyl acetate/hexane = 1:20, v/v) to give the product **1** (0.108 g, 45 % yield) as a colorless oil.

Spectral data

- 1:** ¹H-NMR: δ 7.80 (s, 1H), 7.57-7.55 (m, 2H), 7.46-7.43 (m, 3H), 4.49 (s, 2H), 3.04 (q, J = 7.42 Hz, 2H), 1.34 (t, J = 7.42 Hz, 3H); ¹³C-NMR: δ 192.0, 141.3, 136.1, 133.8, 129.8, 129.7, 128.9, 38.4, 23.8, 14.5.
- 2:** ¹H-NMR: δ 7.77 (s, 1H), 7.59-7.56 (m, 2H), 7.00-6.97 (m, 2H), 4.53 (s, 2H), 3.86 (s, 3H), 3.03 (q, J = 7.42 Hz, 2H), 1.33 (t, J = 7.42 Hz, 3H); ¹³C-NMR: δ 192.0, 141.6, 138.7, 133.9, 132.0, 128.3, 114.4, 55.4, 38.9, 23.7, 14.6.

- 3: $^1\text{H-NMR}$: δ 7.73 (s, 1H), 7.52-7.41 (m, 4H), 4.45 (s, 2H), 3.04 (q, $J=7.41\text{Hz}$, 2H), 1.33 (t, $J=7.41\text{Hz}$, 3H); $^{13}\text{C-NMR}$: δ 191.7, 139.7, 136.5, 135.9, 132.1, 130.9, 129.1, 38.1, 23.8, 14.5.
- 4: $^1\text{H-NMR}$: δ 7.71 (s, 1H), 7.61-7.58 (m, 2H), 7.45-7.42 (m, 2H), 4.45 (s, 2H), 3.05 (q, $J=7.42\text{ Hz}$, 2H), 1.34 (t, $J=7.42\text{ Hz}$, 3H); $^{13}\text{C-NMR}$: δ 191.9, 139.9, 136.7, 132.7, 132.2, 131.2, 131.1, 124.4, 38.2, 23.9, 14.5.
- 5: $^1\text{H-NMR}$: δ 6.94 (t, $J=7.56\text{Hz}$, 1H), 4.33 (s, 2H), 2.97 (q, $J=7.42\text{Hz}$, 2H), 2.35 (q, $J=7.46\text{Hz}$, 2H), 1.55-1.50 (m, 2H), 1.37-1.21 (m, 5H), 0.88 (m, 3H); $^{13}\text{C-NMR}$: δ 191.5, 146.7, 137.0, 36.5, 31.8, 29.4, 29.3 (2), 29.2, 28.9, 28.4, 23.4, 22.6, 14.6, 14.1.
- 6: $^1\text{H-NMR}$: δ 7.56-7.46 (m, 3H), 7.40-7.35 (m, 3H), 7.20-7.04 (m, 2H), 4.54 (s, 2H), 3.02 (q, $J=7.43\text{Hz}$, 2H), 1.31 (t, $J=7.43\text{Hz}$, 3H); $^{13}\text{C-NMR}$: δ 190.9, 143.6, 141.2, 135.7, 134.4, 129.8, 128.9, 127.7, 122.3, 36.8, 23.6, 14.7.
- 7: $^1\text{H-NMR}$: δ 8.03 (dd, $J=1.28, 8.16\text{Hz}$, 1H), 7.76 (dd, $J=1.37, 7.86\text{ Hz}$, 1H), 7.67 (m, 1H), 7.59-7.47 (m, 3H), 7.11 (dd, $J=11.3, 15.2\text{Hz}$, 1H), 4.53 (s, 2H), 3.03 (q, $J=7.41\text{Hz}$, 2H), 1.33 (t, $J=7.41\text{Hz}$, 3H); $^{13}\text{C-NMR}$: δ 191.1, 148.1, 139.8, 137.4, 136.6, 133.4, 131.5, 129.7, 128.7, 126.9, 125.0, 36.5, 23.7, 14.6.
- 8: $^1\text{H-NMR}$: δ 8.03 (dd, $J=1.28, 8.6\text{Hz}$, 1H), 7.77 (dd, $J=1.28, 7.9\text{Hz}$, 1H), 7.67 (m, 1H), 7.61-7.45 (m, 3H), 7.10 (dd, $J=11.3, 15.2\text{Hz}$, 1H), 4.43 (s, 2H), 3.04 (q, $J=7.41\text{Hz}$, 2H), 1.33 (t, $J=7.41\text{Hz}$, 3H); $^{13}\text{C-NMR}$: δ 190.9, 148.1, 139.2, 137.1, 137.0, 133.5, 131.6, 129.7, 128.7, 127.1, 125.1, 23.8, 23.1, 14.6.

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