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A Novel and Convenient Protocol for Synthesis of α-Haloacrylates

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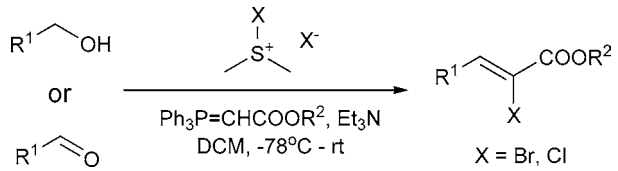
ABSTRACT



A novel and convenient protocol for synthesis of α-haloacrylates starting from phosphonium ylide and aldedyde or alcohol was described. Halodimethylsulfonium halide was used for the first time in halogenation of phosphonium ylide. Good yield as well as a high *Z*/*E* ratio were shown in representative cases, and an umpolung dimethyl sulfide–ylide species might be involved as an intermediate.

α-Haloacrylates are important functional intermediates and broadly used in the synthesis of polymers,[1] biologically active molecules,[2] as well as natural products,[3] especially when they were explored as good substrates in transition metal-catalyzed coupling reactions for synthesis of trisubstituted olefins.[4] Among the variety synthetic methods developed for synthesis of α-haloacrylates,[5,6] Wittig reaction starting from α-halophosphonium ylide and the corresponding aldehyde was still one of the most mild and straightforward synthetic protocols.[7] However, the methods for preparation of α-halophosphonium ylide were quite limited,[8] many of which suffered from the use of hazardous[9] or expensive halogenation reagents,[10] harsh reaction conditions,[11] and unavoidable side reactions.[12]

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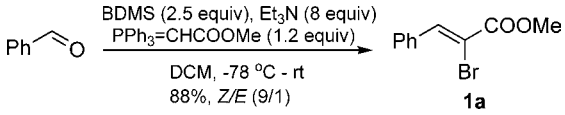
Recently, halodimethylsulfonium halide, particularly bromodimethylsulfonium bromide (BDMS),[13] has been found to be an effective halogenation reagent. For example, regioselective α-monobromination of α-keto esters and 1,3-diketones,[14] *p*-bromination of phenol and anilines,[15] and bromination of alkylic alcohol.[16] Moreover, chlorodimethylsulfonium chloride (CDMS) is not only a well-known Swern oxidation intermediate for the preparation of aldehyde or ketone from alcohol but also a highly selective chlorination reagent for allylic and benzylic alcohol.[17] However, since the substrates scope is relatively limited, utilizations of halodimethylsulfonium halide in halogenation are still needed to be further explored. Herein, we reported a convenient method for one-pot synthesis of α-haloacrylates from phosphonium ylide and alcohol or aldehyde, and the halodimethylsulfonium halide was utilized as newly halogenation reagent for in situ generation of α-halophosphonium ylide.

As part of our research program to develop new synthetic methodologies, we discovered that benzaldehyde could be easily converted into α-bromophenylacrylate in 88% yield with high *Z*/*E* ratio (9/1) by treatment with a premixed solution of phosphonium ylide, BDMS, and Et_3N in dichloromethane (Scheme 1). Moreover, it was found that excess

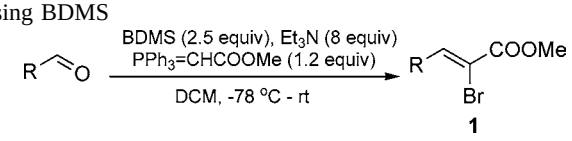
Scheme 1. One-Pot Synthesis of Methyl α-Bromophenylacrylate Using BDMS



amount of BDMS was crucial for the transformation, for example, when the amount of BDMS was decreased from 2.5 to 1.5 equiv, a mixture of α-bromophenylacrylate and phenylacrylate was generated.

Prompted by the above results, other aromatic aldehydes were also investigated under identical conditions. As shown in Table 1, α-bromoacrylates were generated from the corresponding aldehyde in good yield as well as high *Z*/*E* ratio. Aromatic substrates with electron-withdrawing groups gave much better yield and shorter reaction time (Table 1, entry 1).

Table 1. One-Pot Synthesis of Methyl α-Bromoacrylates Using BDMS



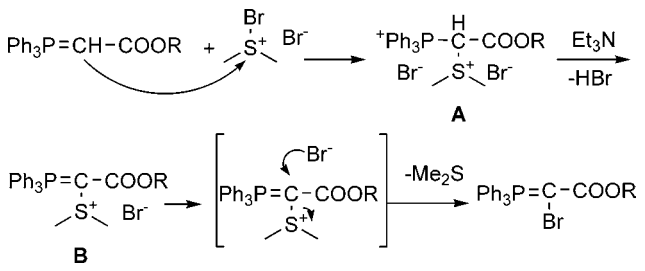
entry	R	product	yield[a] (%)	*Z*/*E*[b]
1[c]	4-NO_2Ph	**1b**	97	13:1
2	2-Cl-4-Cl-Ph	**1c**	98	12:1
3	4-F-Ph	**1d**	91	9:1
4	4-OMe-Ph	**1e**	86	6:1
5	3,4-OCH_2O-Ph	**1f**	90	9:1
6	2-naphthyl	**1g**	99	14:1
7	2-pyridyl	**1h**	81	5:1
8	2-thiophenyl	**1i**	87	5:1
9	2-furyl	**1j**	94	8:1

[a] Isolated yield. [b] Determined by ^1H NMR. [c] Reaction was accomplished within 4 h

To investigate the reaction mechanism, methyl cinnamate was treated directly with 2.5 equiv of BDMS and 8 equiv of Et_3N at −78 °C in dichloromethane. The mixture was stirred at room temperature for 24 h. It was found that no α-bromophenylacrylate was detected by NMR analysis of the crude product, which ruled out the Wittig olefination−bromation pathway[18] and, in turn, strongly suggested that a rapid generated α-bromoylide intermediate might be involved in the process.

A plausible mechanism for generation of α-bromoylide was shown in Scheme 2. At first, electrophilic attack on the

Scheme 2. Plausible Mechanism for Generation of α-Bromoylide



α-carbon of phosphonium ylide by cationic sulfur of BDMS afforded the ylide−BDMS adduct **A**. With the assistnace of base, dehydrobromination took place to deliver labile dimethyl sulfide−ylide species **B**. The latter then served as umpolung ylide[8] and subsequently reacted with bromide anion nucleophile to achieve the final α-bromophosphonium ylide.

In contrast with BDMS, synthetic application of chlorodimethylsulfonium chloride (CDMS) as halogenation

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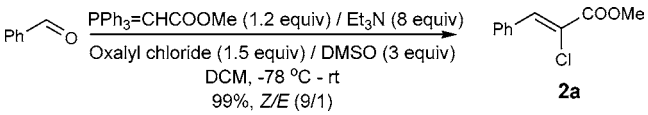
reagent was largely ignored, although selective chlorination of allylic and benzylic alcohol was early discovered by Corey.[17] α-Chlorination of ketone by CDMS is also mentioned in the literature as a side reaction under typical Swern oxidation conditions.[19] Based on BDMS results, we then turned our attention to investigate whether CDMS could be utilized as a chlorination reagent for the transformation of phosphonium ylide to chloroylide.

Likewise, benzaldehyde was employed as a model compound, and CDMS was in situ generated by addition of oxalyl chloride to a solution of DMSO in DCM at −78 °C. To our delight, in a similar manner, the desired α-chlorophenylacrylate was obtained in 99% yield with a high *Z*/*E* ratio (9/1), and only 1.5 equiv of CDMS was needed for the transformation (Scheme 3). Notably, it is worth mentioning

Scheme 3. One-pot Synthesis of Methyl α-Chlorophenylacrylate under Swern Conditions

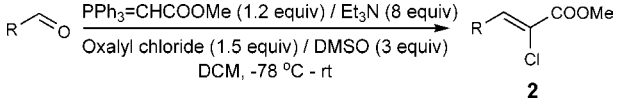


2a

that the conversion could be achieved by simple sequential addition of phosphonium ylide, Et_3N, and benzaldehyde to the solution of freshly prepared CDMS at −78 °C without the need to prepare chloroylide in advance, and no competitive phenylacrylate was detected.

Similarly, other aromatic aldehydes with either electron-donating or -withdrawing groups underwent the desired conversion (Table 2). Furthermore, aliphatic aldehyde could

Table 2. One-Pot Synthesis of Methyl α-Chloroacrylates under Swern Conditions



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entry	R	product	yield[a] (%)	*Z*/*E*[b]
1	4-NO_2Ph	**2b**	97	100:0
2	2-Cl-4-Cl-Ph	**2c**	91	18:1
3	4-Cl-Ph	**2d**	90	8:1
4	3,4-OCH_2O-Ph	**2e**	91	7:1
5	2-naphthyl	**2f**	96	9:1
6	2-furyl	**2g**	99	100:0
7	$PhCH_2CH_2$	**2h**	99	11:1

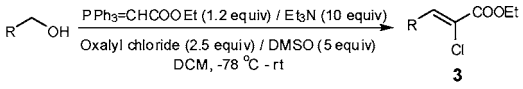
[a] Isolated yield. [b] Determined by ^{1}H NMR.

give excellent results as well (Table 2, entry 7). Unfortunately, it was found that ketone failed to provide tetrasubstituted α-chloroacrylate under the same conditions.

Keeping in mind the fact that CDMS is a typical Swern oxidation intermediate, in principle, it is possible to accomplish one-pot synthesis of α-chloroacrylate from alcohol. Under such circumstances, the in situ generated CDMS intermediate must serve as a bifunctional reagent, both as chlorination reagent for transformation of phosphonium ylide to α-chloro phosphonium ylide and as oxidation reagent for conversion of alcohol to aldehyde.

As we expected, primary alcohol could be smoothly transformed to α-chloroacrylate when the amount of CDMS was increased to 2.5 equiv under similar conditions (Table 3).

Table 3. One-Pot Synthesis of α-Chloroacrylates from Primary Alcohol under Swern Conditions



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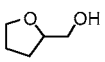
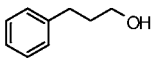
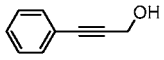
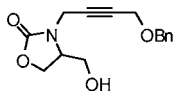
entry	substrate	product	yield (%)[a]	*Z*:*E*[b]
1	$PhCH_2OH$	**3a**	91	8:1
2	4-OMe-$PhCH_2OH$	**3b**	88	7:1
3	4-F-$PhCH_2OH$	**3c**	91	7:1
4	4-Cl-$PhCH_2OH$	**3d**	93	6:1
5[d]	4-NO_2-$PhCH_2OH$	**3e**	96	8:1
6	2-furylCH_2OH	**3f**	80	8:1
7		**3g**	77	7:1
8		**3h**	77	8:1
9		**3i**	85	4:1
10		**3j**	90	8:1[c]

[a] Isolated yield. [b] Determined by GC. [c] Determined by ^{1}H NMR. [d] Reaction was accomplished within 4 h

A variety of benzylic alcohols provided the desired α-chloroacrylates in excellent yield with good *Z*/*E* ratio; for substrates bearing electron-withdrawing group, such as 4-nitrobenzylic alcohol, the reaction time was significantly shortened to 4 h (Table 3, entry 5). Functional aliphatic alcohol could also give satisfactory results (Table 3, entries 7−10). Although the synthetic protocol has some limitations, for example, secondary alcohol could not give the corresponding tetrasubstituted α-chloroacrylate, it provided a useful alternative over conventional methods for the same transformation, since our method can save at least two more

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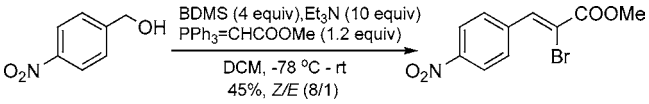
steps without the need to prepare aldehyde and chloroylide, respectively.

Unlike CDMS, only 45% yield was obtained when BDMS was used to perform the one-pot synthesis of α-bromoacrylate starting from alcohol (Scheme 4), the results probably

Scheme 4. Synthetic Attempt Using BDMS as Bifunctional Reagent



due to the weaker oxidative property of BDMS.[20]

In conclusion, a novel and efficient method for synthesis of α-haloacrylates was described. The synthetic protocol involved in situ halogenation of phosphonium ylide by halodimethylsulfonium halide, which opened a simple way for rapid access to α-haloacrylates from aldehyde and phosphonium ylide with *Z*-selectivity. In addition, primary alcohol could be directly transformed to corresponding α-chloroacrylate in one pot by treatment with CDMS and phosphonium ylide, in which CDMS served both as chlorination and oxidation reagent. An umpolung dimethyl sulfide−ylide species might be involved in the process, further studies on the mechanism of this reaction are currently underway.

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Supporting Information Available: General experimental procedures for synthesis of α-chloroacrylate and α-bromoacrylate. Characterization data and ^{1}H NMR and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Only a few examples using BMDS as oxidative reagent. See: (a) Palomo, C.; Ontoria, J. M.; Odriozola, J. M.; Alzpurua, J. M.; Ganboa, I. *Chem. Commun.* **1990**, 248. (b) Cossio, F. P.; Lopez, C.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1988**, *29*, 4339. (c) Olah, G. A.; Vankar, Y. D.; Arvanaghi, M. *Tetrahedron Lett.* **1979**, *20*, 3653.