

# A Novel and Convenient Protocol for Synthesis of $\alpha$ -Haloacrylates

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## ABSTRACT



A novel and convenient protocol for synthesis of  $\alpha$ -haloacrylates starting from phosphonium ylide and aldehyde 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.

$\alpha$ -Haloacrylates are important functional intermediates and broadly used in the synthesis of polymers,<sup>1</sup> biologically active molecules,<sup>2</sup> as well as natural products,<sup>3</sup> especially when they were explored as good substrates in transition metal-catalyzed coupling reactions for synthesis of trisubstituted olefins.<sup>4</sup> Among the variety synthetic methods developed for synthesis of  $\alpha$ -haloacrylates,<sup>5,6</sup> Wittig reaction starting from  $\alpha$ -halo-phosphonium ylide and the corresponding aldehyde was still one of the most mild and straightforward synthetic protocols.<sup>7</sup> However, the methods for preparation of  $\alpha$ -halophosphonium ylide were quite limited,<sup>8</sup> many of which suffered from the

use of hazardous<sup>9</sup> or expensive halogenation reagents,<sup>10</sup> harsh reaction conditions,<sup>11</sup> and unavoidable side reactions.<sup>12</sup>

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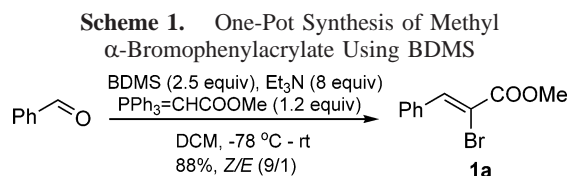
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Recently, halodimethylsulfonium halide, particularly bromodimethylsulfonium bromide (BDMS),<sup>13</sup> has been found to be an effective halogenation reagent. For example, regioselective  $\alpha$ -monobromination of  $\alpha$ -keto esters and 1,3-diketones,<sup>14</sup> *p*-bromination of phenol and anilines,<sup>15</sup> and bromination of allylic alcohol.<sup>16</sup> 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.<sup>17</sup> 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  $\alpha$ -haloacrylates from phosphonium ylide and alcohol or aldehyde, and the halodimethylsulfonium halide was utilized as newly halogenation reagent for in situ generation of  $\alpha$ -halophosphonium ylide.

As part of our research program to develop new synthetic methodologies, we discovered that benzaldehyde could be easily converted into  $\alpha$ -bromophenylacrylate in 88% yield with high *Z/E* ratio (9/1) by treatment with a premixed solution of phosphonium ylide, BDMS, and Et<sub>3</sub>N in dichloromethane (Scheme 1). Moreover, it was found that excess



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  $\alpha$ -bromophenylacrylate and phenylacrylate was generated.

Prompted by the above results, other aromatic aldehydes were also investigated under identical conditions. As shown in Table 1,  $\alpha$ -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).

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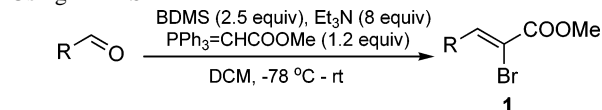
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**Table 1.** One-Pot Synthesis of Methyl  $\alpha$ -Bromoacrylates Using BDMS

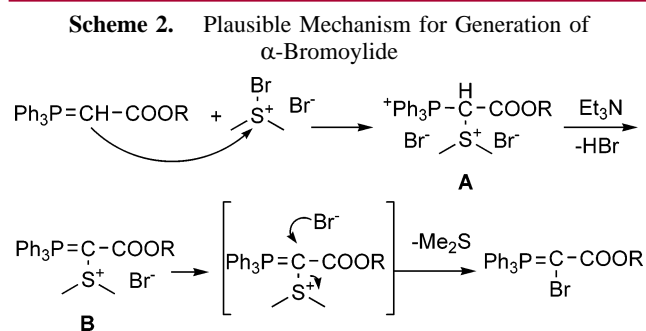


entry	R	product	yield <sup>a</sup> (%)	<i>Z/E</i> <sup>b</sup>
1 <sup>c</sup>	4-NO <sub>2</sub> -Ph	<b>1b</b>	97	13:1
2	2-Cl-4-Cl-Ph	<b>1c</b>	98	12:1
3	4-F-Ph	<b>1d</b>	91	9:1
4	4-OMe-Ph	<b>1e</b>	86	6:1
5	3,4-OCH <sub>2</sub> O-Ph	<b>1f</b>	90	9:1
6	2-naphthyl	<b>1g</b>	99	14:1
7	2-pyridyl	<b>1h</b>	81	5:1
8	2-thiophenyl	<b>1i</b>	87	5:1
9	2-furyl	<b>1j</b>	94	8:1

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> 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<sub>3</sub>N at  $-78^{\circ}\text{C}$  in dichloromethane. The mixture was stirred at room temperature for 24 h. It was found that no  $\alpha$ -bromophenylacrylate was detected by NMR analysis of the crude product, which ruled out the Wittig olefination–bromination pathway<sup>18</sup> and, in turn, strongly suggested that a rapid generated  $\alpha$ -bromoylide intermediate might be involved in the process.

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



$\alpha$ -carbon of phosphonium ylide by cationic sulfur of BDMS afforded the ylide–BDMS adduct **A**. With the assistance of base, dehydrobromination took place to deliver labile dimethyl sulfide–ylide species **B**. The latter then served as umpolung ylide<sup>8</sup> and subsequently reacted with bromide anion nucleophile to achieve the final  $\alpha$ -bromophosphonium ylide.

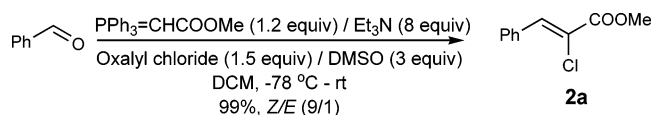
In contrast with BDMS, synthetic application of chlorodimethylsulfonium chloride (CDMS) as halogenation

(18) Chow mentioned that BDMS could brominate  $\alpha,\beta$ -unsaturated ketone, but for conjugated ester substrate, only sluggish addition happened. See: Chow, Y. L.; Bakker, B. H. *Can. J. Chem.* **1982**, 60, 2268.

reagent was largely ignored, although selective chlorination of allylic and benzylic alcohol was early discovered by Corey.<sup>17</sup>  $\alpha$ -Chlorination of ketone by CDMS is also mentioned in the literature as a side reaction under typical Swern oxidation conditions.<sup>19</sup> 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  $-78^\circ\text{C}$ . To our delight, in a similar manner, the desired  $\alpha$ -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

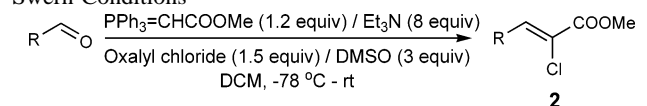
**Scheme 3.** One-pot Synthesis of Methyl  $\alpha$ -Chlorophenylacrylate under Swern Conditions



that the conversion could be achieved by simple sequential addition of phosphonium ylide,  $\text{Et}_3\text{N}$ , and benzaldehyde to the solution of freshly prepared CDMS at  $-78^\circ\text{C}$  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  $\alpha$ -Chloroacrylates under Swern Conditions



entry	R	product	yield <sup>a</sup> (%)	<i>Z/E</i> <sup>b</sup>
1	4-NO <sub>2</sub> Ph	<b>2b</b>	97	100:0
2	2-Cl-4-Cl-Ph	<b>2c</b>	91	18:1
3	4-Cl-Ph	<b>2d</b>	90	8:1
4	3,4-OCH <sub>2</sub> O-Ph	<b>2e</b>	91	7:1
5	2-naphthyl	<b>2f</b>	96	9:1
6	2-furyl	<b>2g</b>	99	100:0
7	PhCH <sub>2</sub> CH <sub>2</sub>	<b>2h</b>	99	11:1

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by <sup>1</sup>H NMR.

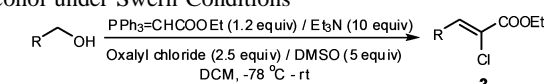
give excellent results as well (Table 2, entry 7). Unfortun-

nately, it was found that ketone failed to provide tetrasubstituted  $\alpha$ -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  $\alpha$ -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  $\alpha$ -chloro phosphonium ylide and as oxidation reagent for conversion of alcohol to aldehyde.

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

**Table 3.** One-Pot Synthesis of  $\alpha$ -Chloroacrylates from Primary Alcohol under Swern Conditions



entry	substrate	product	yield (%) <sup>a</sup>	<i>Z/E</i> <sup>b</sup>
1	PhCH <sub>2</sub> OH	<b>3a</b>	91	8:1
2	4-OMe-PhCH <sub>2</sub> OH	<b>3b</b>	88	7:1
3	4-F-PhCH <sub>2</sub> OH	<b>3c</b>	91	7:1
4	4-Cl-PhCH <sub>2</sub> OH	<b>3d</b>	93	6:1
5 <sup>d</sup>	4-NO <sub>2</sub> -PhCH <sub>2</sub> OH	<b>3e</b>	96	8:1
6	2-furylCH <sub>2</sub> OH	<b>3f</b>	80	8:1
7		<b>3g</b>	77	7:1
8		<b>3h</b>	77	8:1
9		<b>3i</b>	85	4:1
10		<b>3j</b>	90	8:1 <sup>c</sup>

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by GC. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Reaction was accomplished within 4 h

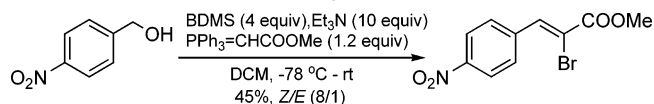
A variety of benzylic alcohols provided the desired  $\alpha$ -chloroacrylates in excellent yield with good *Z/E* ratio; for substrates bearing electron-withdrawing group, such as 4-nitrobenzylic alcohol, the reaction time was significantly shortened to 4 h (Table 3, entry 5). Functional aliphatic alcohol 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  $\alpha$ -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  $\alpha$ -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.<sup>20</sup>

In conclusion, a novel and efficient method for synthesis of  $\alpha$ -haloacrylates was described. The synthetic protocol

(20) Only a few examples using BDMS 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.

involved in situ halogenation of phosphonium ylide by halodimethylsulfonium halide, which opened a simple way for rapid access to  $\alpha$ -haloacrylates from aldehyde and phosphonium ylide with Z-selectivity. In addition, primary alcohol could be directly transformed to corresponding  $\alpha$ -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.

**Acknowledgment.** This work was supported by the Shanghai Municipal Committee of Science & Technology and the National Natural Science Foundation of China.

**Supporting Information Available:** General experimental procedures for synthesis of  $\alpha$ -chloroacrylate and  $\alpha$ -bromoacrylate. Characterization data and <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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