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Metallic samarium and iodine promoted facile and efficient syntheses of trisubstituted alkenes from the acetates of Baylis–Hillman adducts

Jian Li,^a Hua Xu^b and Yongmin Zhang^{a,c,*}

^aDepartment of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310028, PR China ^bDepartment of Chemistry, State University of New York at Stony Brook, NY 11790, USA ^cState Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China

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Abstract—Promoted by samarium metal in the presence of a catalytic amount of iodine, the Baylis–Hillman adducts underwent reductive elimination to form (*E*)-methylcinnamic ester derivatives. When the iodine was used in 1:1 ratio with metallic samarium, stereospecific syntheses of allylic iodide derivatives, (2Z)-2-(iodomethyl)alk-2-enoates, were achieved. Thus, this gives a new approach to the selective construction of stereo-defined trisubstituted alkenes with the simple Sm/I₂ system. © 2005 Elsevier Ltd. All rights reserved.

The Baylis–Hillman reaction is well known as one of the powerful carbon-carbon bond-forming methods in organic synthesis.¹ The adducts of the reactions, 3-hydroxy-2-methylene-alkanoates (derived from acrylate esters), have been utilized as important precursors for stereoselective synthesis of different multifunctional molecules.² It is known to us that the trisubstituted alkene moiety with defined stereochemistry is present in naturally occurring bioactive molecules including terpenoids and insect pheromones.³ Consequently, a variety of methodologies for the syntheses of functionalized alkenes with stereo-defined double bonds have been well documented.⁴ Among these methods, direct reduction of Baylis-Hillman adducts opens a convenient and effective path to synthesize trisubstituted alkenes.⁵ Recently, we have also reported the SmI2-mediated reduction from Baylis-Hillman adducts towards this conversion.⁶ Although some reactions are satisfactory in terms of vield and stereoselectivity, however, most of the reagents used are sensitive to water or air, thereby the corresponding reactions have a requirement for complex experimental procedure such as inert atmosphere protection, which lower their attractiveness.

Recently, using metallic samarium as a reducing agent in organic transformation has attracted the attention of many organic chemists.⁷ This is due to the fact that metallic samarium is stable in air and has strong reducing power ($\text{Sm}^{3+}/\text{Sm} = -2.41 \text{ V}$) and it is a cheaper and more convenient metallic samarium which can be used directly as a reductant instead of SmI_2 .⁸ Accordingly, we envisioned the reduction of Baylis–Hillman adducts with metallic samarium. To the best of our knowledge, the reductive elimination of Baylis–Hillman adducts promoted by metallic samarium has not been reported so far.

Our first attempt was performed with the acetate of Baylis-Hillman adduct **1b** as substrate. To investigate suitable conditions for above transformation (Scheme 1), a series of experiments were tested (Table 1). As shown in Table 1, when **1b** was treated with 1 equiv Sm powder



Scheme 1.

Keywords: Samarium; Iodine; Baylis-Hillman adduct; Trisubstituted alkenes.

^{*} Corresponding author. E-mail: yminzhang@mail.hz.zj.cn

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Entry	Medium	Temperature	Time (h)	Yield ^b (%)
1	Sm/THF	rt	10	0
2	Sm/THF	Reflux	10	9
3	Sm/I2 (cat.)/THF	rt	5	15
4	Sm/I2 (cat.)/THF	Reflux	1	93
5	Sm/I2 (cat.)/CH3OH	Reflux	1	c
	Sm/1 M HCl	rt	1	30
6	Sm/NH ₄ Cl	rt	3	10

Table 1. Optimization of the reaction conditions^a

^a Treatment of **1b** with equivalent amount of Sm power.

^b Isolated yields based on substrate **1b**.

^c A complex mixture was obtained.

in a solution of THF at room temperature, no reaction occurred even after 10 h. Only trace amount of the reductive product **2b** was formed during the same period of time when the same reaction was conducted under reflux (Table 1, entry 2). However, when a catalytic amount of iodine was added, both rate and yield of this reaction were increased. Given the Sm/I₂ (cat.)/THF system, the reductive reaction was finished within 1 h to give the product 2b in 93% yield under reflux (Table 1, entry 4) or in 15% yield at room temperature (Table 1, entry 3). The results illustrate that, iodine readily catalyze this reaction meanwhile the temperature has a significant impact on the reaction yield. Subsequently, we have attempted other usual systems such as Sm/CH₃OH, Sm/HCl and Sm/NH₄Cl, all gave unsatisfactory results. Thus, we gave up our efforts on seeking other reductive system and select the efficient Sm/I₂ (cat.)/THF system as our standard reaction condition. During our studies, we also tried to increase the amount of samarium, but the experimental results showed that excessive samarium does not help. Increasing the amount of iodine, however, leads to another new transformation, which will be described in the following discussion (Scheme 2).

To see if the elimination reaction has a generality, a variety of the acetates of Baylis-Hillman adducts were treated with samarium in the presence of a catalytic amount of iodine in THF under reflux and the results were listed in Table 2. As seen in Table 2, the reductive elimination process proceeded smoothly to afford methylcinnamic esters 2 within a few hours in moderate to excellent yields with total (E)-stereoselectivity. The ¹H NMR spectra analyses indicated the absence of any (Z)-isomer, which was in accordance with our previous work.⁶ When substrates with *ortho-* and *para-*electron-withdrawing groups substituted in aromatic ring were used, products 2 were often obtained in good yields along with short reaction time (Table 2, entries 2 and 3), whereas substrates containing electron-donating groups in the aromatic ring usually gave moderate yields with pro-



Table 2. Reductive elimination reaction of the acetates of Baylis–Hillman $\operatorname{adducts}^{\operatorname{a}}$

Entry	Ar	Product	Time (h)	Yield ^{b,c} (%)
1	C ₆ H ₅	2a	3	82
2	$2-Cl-C_6H_4$	2b	1	93
3	$4-Cl-C_6H_4$	2c	1.5	95
4	$4-CH_3-C_6H_4$	2d	4	67
5		2e	3	72
6	$2-CH_3O-C_6H_4$	2f	4.5	65
7	$4-CH_3O-C_6H_4$	2g	4	78
8	$3-Br-C_6H_4$	2h	2	80

^a All reactions were carried out with 2 mmol Sm power and 0.2 mmol I_2 in THF under reflux.

^b Isolated yields based on substrates 1.

^c All products were characterized by ¹H NMR, MS and IR.

longed reaction time. During our investigation, a light blue colour was occasionally observed when the reaction was carried out under the selected conditions, which indicated the existence of Sm(II) species. Thus, we assumed that the present reductive elimination reaction might experience a similar process to our previous work.⁶ More detailed study about the reaction will be further investigated (Scheme 3).

During the above contents we have mentioned that the excessive amount of samarium did not help the formation of the reductive product 2. Nevertheless, when the amount of iodine was increased continually, to our surprise, a different reaction occurred. In a typical procedure, when 2 mmol 1 was treated with 2 mmol Sm power and 2 mmol I₂ in THF under reflux, a new product 3 was obtained in 95% yield. Compound 3 was later confirmed as allylic iodide derivative, (2Z)-2-(iodo-methyl)alk-2-enoates, by their spectral (¹H NMR and MS) data. The ¹H NMR spectra also indicated no formation of the (2E)-isomer. It is well known that (2Z)-2-(halomethyl)alk-2-enoates are widely employed in the syntheses of various naturally occurring bioactive compounds and their analogues, such as α -methylene- γ -butyrolactone, α -alkylidene- β -lactam and flavanoid.⁹ Consequently, the syntheses of (2Z)-2-(bromomethyl)alk-2-enoates and (2Z)-2-(chloromethyl)alk-2-enoates species were extensively studied and a variety of synthetic methods have been developed.^{5b,10} The preparation of corresponding allylic iodide analogues, howrarely investigated comparatively. ever, were Moreover, the traditional synthetic method also suffered from obvious drawbacks such as the use of strong acid.¹¹ Thus, this method gave a simple and efficient method to prepare (2Z)-2-(iodomethyl)alk-2-enoates 3.





Table 3. Stereospecific syntheses of (2Z)-2-(iodomethyl)alk-2-enoates^a

Entry	Ar	R	Product	Yield ^{b,c} (%)
1	C ₆ H ₅	Me	3a	90
2	$2-Cl-C_6H_4$	Me	3b	95
3	$4-Cl-C_6H_4$	Me	3c	93
4	$4-CH_3-C_6H_4$	Me	3d	91
5		Me	3e	88
6	2-CH ₃ O-C ₆ H ₄	Me	3f	87
7	$4-CH_3O-C_6H_4$	Me	3g	93
8		Me	3h	97
9	C_6H_5	Et	3i	91
10	$2-Cl-C_6H_4$	Et	3j	87
11	$4-CH_3-C_6H_4$	Et	3k	95

 $^{\rm a}$ All reactions were carried out with 2 mmol Sm power and 2 mmol I_2 in THF under reflux and finished within 25 min.

^b Isolated yields based on substrates 1.

^c All produced were characterized by ¹H NMR, IR and MS.

Subsequently, a series of substrates were tested in the above conditions and the results were listed in Table 3. As we can see, the iodination reaction is a quick process and all reactions were finished within 25 min. In fact, the product 3 was so rapidly formed that nearly no reductive product 2 was obtained under this reaction condition. Moreover, this reaction was also stereospecific and the product 3 was almost afforded in quantitative yield with total (Z)-stereoselectivity. Mechanistically, we proposed that the above iodination reaction proceeded via the Sm(III) specie generated from samarium and iodine. According to literature,¹² FeCl₃ and InCl₃ can effectively catalyze the formation of the corresponding allylic chlorides derivatives from Baylis-Hillman adducts, therefore we assume the conversion to product **3** is promoted by the Sm(III) species analogously.

In conclusion, the samarium-promoted transformation from Baylis–Hillman adducts offers a convenient and efficient method for the syntheses of trisubstituted alkenes (*E*)-methylcinnamic ester **2** and (2*Z*)-2-(iodomethyl)alk-2-enoates **3**, respectively,¹³ by controlling the amount of iodine used. The advantages of this method are readily available starting materials,¹⁴ simple operational procedures as well as high potential for large-scale preparations. As a result, it can be expected that the present methodology will find its application in research.

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13. A typical procedure is as follows: Preparation of compound 2: to a mixture of Sm powder (2 mmol) and iodine (0.2 mmol) in THF (20 mL), the acetate of Baylis–Hillman adduct 1 (2 mmol) was added at 65 °C with magnetic stirring. The resulting solution was carried out under reflux until the substrate disappeared. Then, the reaction was quenched with dilute hydrochloric acid (0.1 M, 5 mL) and extracted with diethyl ether (3 × 30 mL). The organic phase was successively washed with water (20 mL), saturated brine (15 mL) and dried over anhydrous Na_2SO_4 . The solvents were removed under reduced pressure to give the crude product, which were purified by preparative TLC using ethyl acetate– cyclohexane (1:5) as eluent.

Preparation of compound **3**: to a mixture of Sm powder (2 mmol) and iodine (2 mmol) in THF (20 mL), the acetate of Baylis–Hillman adduct **1** (2 mmol) was added at 65 °C with magnetic stirring. The resulting solution proceeded under reflux and finished within 25 min. Then, the reaction was quenched with dilute hydrochloric acid (0.1 M, 5 mL)

and extracted with diethyl ether $(3 \times 30 \text{ mL})$. The organic phase was successively washed with saturated Na₂S₂O₃ (15 mL), saturated brine (15 mL) and dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure to give the crude product, which were purified by preparative TLC using ethyl acetate–cyclohexane (1:5) as eluent.

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