

A novel C–C bond formation by Baylis–Hillman type reaction mediated by SmI₂: an effective approach to α -hydroxyalkylacrylamide synthesis

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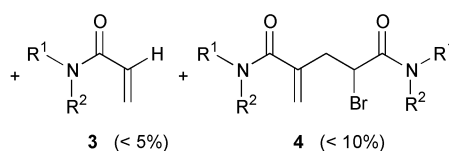
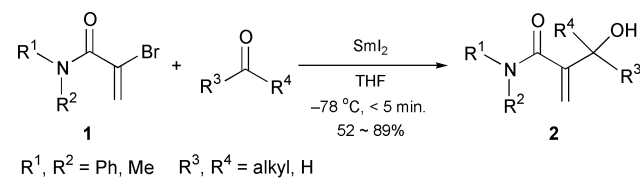
α -Bromoacrylamides (**1**) reacted with aldehydes or ketones, in the presence of SmI₂ at -78 °C in THF, within 5 min to produce Baylis–Hillman type reaction products (**2**) through an anionic process using vinylsamarium Grignard species in good yields (52–89%).

The construction of C–C bonds has been one of the most fundamental reactions in organic synthesis. The Baylis–Hillman reaction¹ produces multifunctional molecules that can be used for the synthesis of natural and unnatural products² through C–C bond formation between the α -position of activated alkene and carbon electrophiles having an electron-deficient sp² carbon atom under a basic catalyst, in particular a tertiary amine. But the reaction suffers from being inconveniently slow.¹ Furthermore, under normal circumstances acrylamides, crotonic derivatives, and ketones are inert substrates for the Baylis–Hillman reaction.^{1,3} Therefore a number of attempts^{2g,4,5} have been made to provide the corresponding adduct including the use of microwave irradiation and high pressure.⁶

Samarium diiodide has become a useful reagent for various organic reactions.⁷ Especially, SmI₂ can be used to generate organic radicals and to reduce alkyl radicals to alkylsamarium reagents that can be trapped by a variety of electrophiles to form a new C–C bond.^{7–9} However, there have been arguments that in general, vinyl- and aryl radicals do not usually undergo further reduction to vinyl- or arylsamarium reagents.⁹ We report here the first example of reactions *via* vinylsamarium species.

It has been found that α -bromoacrylamides (**1**) reacted with a variety of aldehydes or ketones in the presence of SmI₂ to give α -hydroxyalkylacrylamides (Baylis–Hillman adducts, **2**) within 5 min at -78 °C in THF in good yields (Scheme 1).

The reaction works best when 1 eq. of aldehyde and 3 eq. of SmI₂ are used in THF (run 2–5, Table 1). The crotonic derivative gave only the (*Z*)-isomer which was readily confirmed by ¹H NMR spectroscopy^{5a,b,d,f} and a variety of aldehydes and enolizable ketones also proceeded successfully in good yields. The results obtained are summarized in Table 1. Benzaldehyde and α,β -unsaturated carbonyl compounds are reduced to the corresponding alcohols without undergoing Baylis–Hillman type reaction: reduction of carbonyl groups must be faster than Baylis–Hillman type reaction.



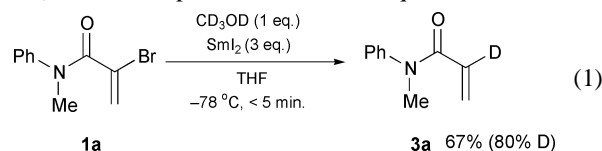
Scheme 1

Table 1 The reactions of acrylamides with various aldehydes and ketones^a

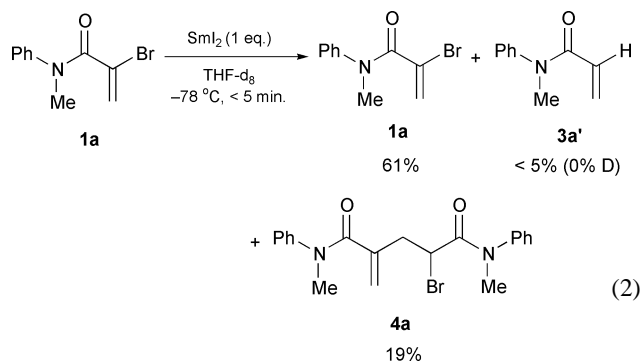
| Run | Acrylamide | R ³ | R ⁴ | Product | Yield ^b (%) | |
|-----|------------|------------------------------------|------------------------------------|-----------|------------------------|----|
| 1 | | Me | H | 2a | 81 | |
| 2 | | Et | H | 2b | 19 ^c | |
| 3 | | Et | H | 2b | 43 ^d | |
| 4 | | Et | H | 2b | 51 ^c | |
| 5 | | Et | H | 2b | 62 | |
| 6 | | PhCH ₂ CH ₂ | H | 2c | 70 | |
| 7 | | c-Hex | H | 2d | 88 | |
| 8 | | t-Bu | H | 2e | 63 | |
| 9 | | Me | Et | 2f | 89 | |
| 10 | | Me | CH ₂ CO ₂ Me | 2g | 52 | |
| 11 | | Me | CH ₂ Ph | 2b | 62 | |
| 12 | | -(CH ₂) ₄ - | | 2i | 63 | |
| 13 | | | Et | H | 2j | 76 |
| 14 | | | c-Hex | H | 2k | 77 |
| 15 | t-Bu | | H | 2l | 77 | |
| 16 | Me | | Et | 2m | 73 | |
| 17 | | Et | H | 2n | 81 | |
| 18 | | c-Hex | H | 2o | 53 | |

^a All reactions were performed with SmI₂ (3 eq.) and aldehyde or ketone (1 eq.) in THF at -78 °C, unless otherwise noted. ^b Isolated Yields. ^c Performed with SmI₂ (1 eq.). ^d Performed with SmI₂ (2 eq.). ^e Performed with SmI₂ (2.5 eq.).

Here a question is raised as to whether the reaction proceeds *via* anionic or radical species. Treatment of **1a** with SmI₂ (3 eq.)–CD₃OD (1 eq.) in THF afforded **3a** (67%, 80% deuterated product) as the main product as shown in eqn. 1. The amount of



deuterium incorporation was determined by ¹H NMR and mass spectroscopy. On the other hand, when **1a** was treated with SmI₂ (1 eq.) and THF-d₈ as a solvent, no deuterated acrylamide was detected, whereas α -bromoacrylamides acted as an electrophile to form **4a** (eqn. 2).^{7a,10} If the vinyl radical species (**A**) exists for long time it should abstract one D from THF-d₈. If the reaction undergoes samarium Grignard type reaction, it should require more than 2 eq. of SmI₂ to consume the starting acrylamide.



Judging from the three observations, an anion species (**B**) appears to be involved in the reaction (Fig. 1). The reaction might proceed *via* an allenolate intermediate (**C**).^{5,11} Ethyl α -bromoacrylate or 2-bromocyclohex-2-en-1-one did not give the desired products. A phenyl group in the amide seems to enable the formation of the vinylsamarium intermediate (**B**). The α -carbon of the acrylamide bearing phenyl group is more electron-deficient than other moieties bearing alkyl or hydrogen. Therefore, the vinyl radical can undergo further reduction to vinylsamarium reagent **B** by a further mole of SmI_2 . These results imply that the reduction of the vinyl radical should be faster than hydrogen abstraction from THF. To our knowledge, *this is the first example of the generation of the vinyl samarium intermediate by means of the reduction of bromovinyl compounds!* It is noteworthy that the reaction with enolizable ketones also affords the Baylis–Hillman products.

In summary, it has been demonstrated that the reaction of α -bromoacrylamides with aldehydes or ketones in the presence of SmI_2 can provide Baylis–Hillman adducts through an anionic process, solving several problems of Baylis–Hillman reaction. Baylis–Hillman reactions require long reaction times and a

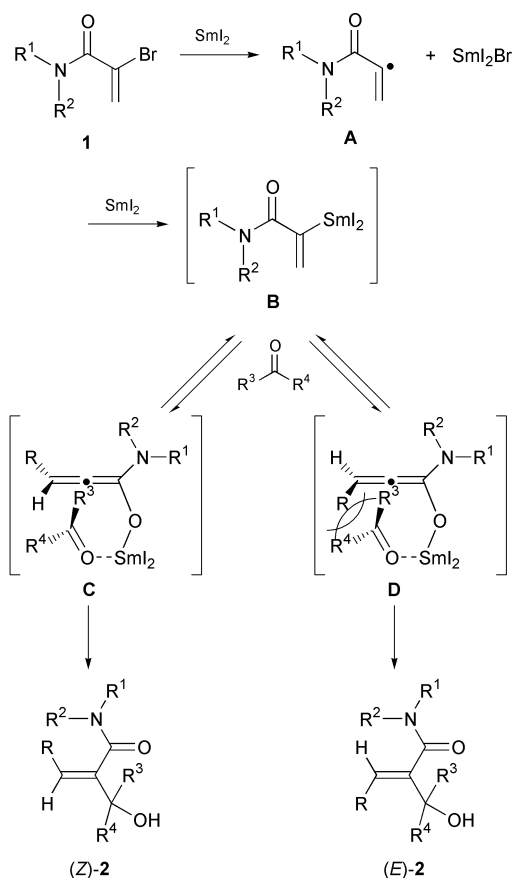


Fig. 1 Possible mechanism.

tertiary amine as a catalyst and its scope is limited to aldehydes as acrylamides, crotonic derivatives and ketones are not reactive. However, a Baylis–Hillman type reaction mediated by SmI_2 is available for both aldehydes and ketones under mild reaction conditions and with short reaction times.

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- Organosamarium intermediates appear to be initiated but unstable in solution.⁷ In the absence of electrophiles such as aldehydes or ketones, the organosamarium species reacted with the substrate itself to form **4a** together with the dehalogenated byproduct **3a'**.
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