An efficient approach to (*E*)-β-methyl Baylis–Hillman adducts *via* indium-mediated allylation of aldehydes in aqueous media

Joo Hwan Cha,[a,b] Ae Nim Pae,[a] Kyung Il Il Choi,[a] Yong Seo Cho,*[a] Hun Yeong Koh[a] and Eun Lee*[b]

[a] *Biochemicals Research Center, Korea Institute of Science and Technology, Cheongryang P.O. Box 131, Seoul, 130-650, Korea. E-mail: ys4049@kist.re.kr; Fax:* +82-2-958-5189

[b] *School of Chemistry and Molecular Engineering, Seoul National University, Seoul, 151-742, Korea*

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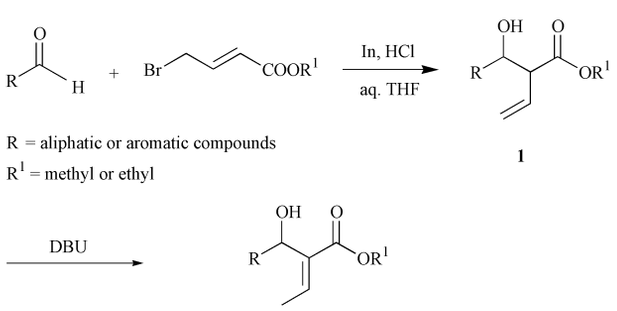
A new method has been developed for the synthesis of (*E*)-β-methyl Baylis–Hillman adducts with high *E*–*Z* (>93%) selectivity in modest to good yields. The process consists of two steps: an indium-mediated allylation reaction and a simple base-catalyzed isomerization step. Various aldehydes were allylated with allyl bromides using indium under very mild conditions in aqueous media. The allylation reactions of aromatic and aliphatic aldehydes were largely accelerated by the presence of HCl.

Introduction

The development of efficient approaches to multifunctionalized alkenes in a stereoselective fashion represents an important goal in organic chemistry which is still being actively explored.[1] In this respect, the Baylis–Hillman reaction has recently become an attractive objective in organic synthesis.[2–4] The various α-(hydroxyalkyl)acrylates derived from the Baylis–Hillman reaction can provide numerous chemically and biologically important precursors with a multifunctional array of groups.[5–6] Greene and coworkers have successfully applied the β-unsubstituted Baylis–Hillman adducts in the design and synthesis of analogs of the antitumor drug docetaxol.[7] The original Baylis–Hillman system has been limited in application to the synthesis of β-branched Baylis–Hillman adducts since the β-substituted acrylate olefin does not undergo the Baylis–Hillman reaction.[2a,8]

Herein, we wish to report an efficient approach to (*E*)-β-methyl Baylis–Hillman adducts (**1**) *via* indium-mediated allylation[9,10] of aldehydes in aqueous media followed by simple base catalyzed isomerization. This new method is represented in Scheme 1.

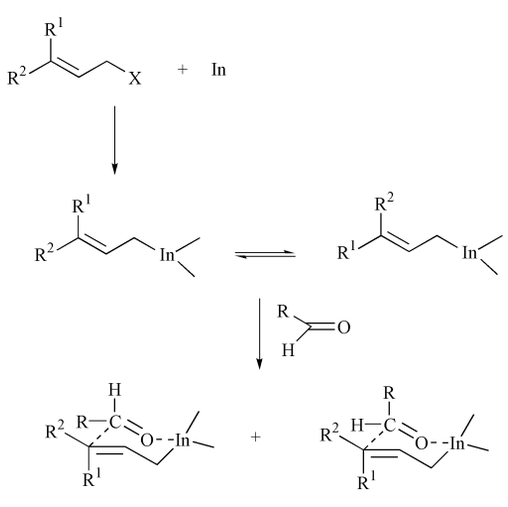


1 **2**

Scheme 1

Results and discussion

The indium-mediated Barbier type allylation reaction in the first step occurs smoothly at room temperature in aqueous media in the presence of HCl. As described in Table 1, various aldehydes reacted with methyl (or ethyl) 4-bromocrotonate in the presence of indium and HCl (1.5 equiv. based on indium) at room temperature in 25% aqueous THF solution to provide the corresponding compound **1** in 17–85 % yields. The major diastereomer was determined to have *anti* configuration by ^{1}H NMR analysis and comparison with known compounds.[10] The diastereoselectivity (*anti–syn*) might be governed by the steric size of the substituent of the aldehydes to give mainly the *anti*-isomer.[11] In the coupling with aldehyde, the reaction proceeds through a cyclic transition state with the carbonyl oxygen coordinated with the indium. The cyclic transition states (a and b) lead to the γ-adducts, but the diastereoselectivity is governed by the steric size of the aldehydic substituents, that is, quasi-equatorial (a) *versus* quasi-axial (b) positions (Scheme 2).

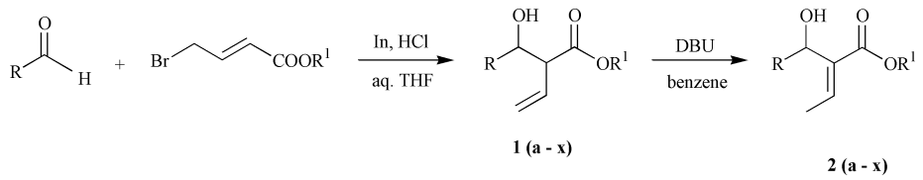


a, ***syn*** **b**, ***anti***

Scheme 2

The allylation reactions of aromatic and aliphatic aldehydes were largely accelerated by the presence of HCl. Most of the reactions were completed in a short period (~10 min) at room temperature. However, without HCl, the reaction needed a much prolonged reaction time (3–60 h). The allylated product **1**

Table 1 Indium-mediated allylation reaction of aldehyde[a] and base catalyzed isomerization[b]



1 (a - x) **2 (a - x)**

Entry	R	R^1	Yield (%) **1a**–**x**[c]	Diastereomeric ratio (*anti–syn*)[d]	Yield (%) **2a**–**x**[c]	*E–Z* ratio[e]
1	CH_3	Me (**a**)	64	67 : 33	88	93 : 7
		Et (**b**)	58	67 : 33	89	92 : 8
2	CH_3CH_2	Me (**c**)	40	75 : 25	82	98 : 2
		Et (**d**)	32	80 : 20	78	98 : 2
3	$(CH_3)_2CH$	Me (**e**)	46	90 : 10	91	98 : 2
		Et (**f**)	34	83 : 17	94	98 : 2
4	C_6H_5	Me (**g**)	68	86 : 14	88	96 : 4
		Et (**h**)	57	83 : 17	90	96 : 4
5	4-FC_6H_4	Me (**i**)	85	86 : 14	90	94 : 6
		Et (**j**)	68	86 : 14	92	96 : 4
6	4-ClC_6H_4	Me (**k**)	80	86 : 14	92	95 : 5
		Et (**l**)	66	89 : 11	96	96 : 4
7	4-$CH_3C_6H_4$	Me (**m**)	66	87 : 13	92	96 : 4
		Et (**n**)	52	83 : 17	88	97 : 3
8	4-$CH_3OC_6H_4$	Me (**o**)	53	86 : 14	93	97 : 3
		Et (**p**)	50	86 : 14	91	96 : 4
9	4-$CH_3SC_6H_4$	Me (**q**)	60	86 : 14	93	94 : 6
		Et (**r**)	52	86 : 14	89	96 : 4
10	3,4-$(CH_3O)_2C_6H_4$	Me (**s**)	49	75 : 25	82	94 : 6
		Et (**t**)	37	86 : 14	92	96 : 4
11	2-Naphthyl	Me (**u**)	61	90 : 10	86	93 : 7
		Et (**v**)	54	84 : 16	89	94 : 6
12	Furan-3-yl	Me (**w**)	27	75 : 25	92	94 : 6
		Et (**x**)	17	86 : 14	91	94 : 6

[a] Reaction conditions: aldehyde (1 mmol), allyl bromide (2 mmol), indium (2 mmol), HCl (2 mmol), 25% THF (6 mL), 23 °C, 10 min. [b] Reaction conditions: **1a**–**x** (1 mmol), DBU (1.1 mmol), benzene (2 mL), 23 °C, 50 min. [c] Isolated yield. [d] Diastereomeric ratios were determined by ^{1}H NMR. [e] *E–Z* ratio and geometry were determined by ^{1}H NMR and 1D difference NOE. In the case of **2a**, **2b** and **2g**, pure *E* and *Z* products were obtained by flash column chromatography.

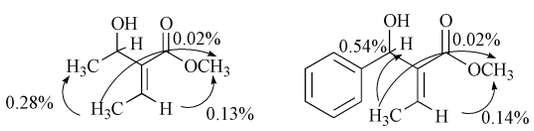


Fig. 1 ^{1}H NMR NOE analysis.

underwent base-catalyzed isomerization using DBU to give the corresponding (*E*)-β-methyl Baylis–Hillman adduct **2** in high yields, and with high *E–Z* (>93 %) selectivity. The resulting *E–Z* isomers could be readily separated by flash column chromatography.[12] The ^{1}H NMR spectrum of the *Z* isomer of **2a** exactly matches the values in the literature.[11a] The *E–Z* ratio and geometry of the *E* isomer were determined by ^{1}H NMR and NOE analysis as shown in Fig. 1.

In summary, a new method has been developed for the synthesis of (*E*)-β-methyl Baylis–Hillman adducts with high *E–Z* selectivity in modest to good yields. The indium-mediated allylation reaction followed by a simple base-catalyzed isomerization step provided a new synthetic route to β-branched Baylis–Hillman adducts. The reaction can be easily performed at room temperature without inert atmosphere protection.

Experimental

All starting materials were obtained commercially from Aldrich or prepared by known methods. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$, unless otherwise stated, on a Bruker Avance DPX-300 NMR spectrometer with tetramethylsilane as internal standard. High resolution mass spectra were determined with a JEOL JMS-AX505 WA HP 5890 series II using Chemical Ionization (CI^+) mode. GC/MSD were obtained on a Hewlett Packard 5890.

Allylation reactions of aliphatic or aromatic aldehydes. General procedure

To a solution of 4-chlorobenzaldehyde (200 mg, 1.42 mmol) in 25% aq. THF (12 mL) were added methyl 4-bromocrotonate (382 mg, 2.13 mmol) and indium powder (254 mg, 2.13 mmol). Then, 6 M HCl (355 μL, 2.13 mmol) was added slowly to the reaction mixture at 23 °C. After stirring for 10 minutes, the reaction mixture was extracted with ethyl acetate (5 mL × 3) and the organic solution was washed with water (5 mL × 2) and brine. The solution was dried over anhydrous $MgSO_4$, filtered, evaporated and purified by flash chromatography (EtOAc–hexane, 1/3, v/v) to give a product (**1k**) as an oil. **1k**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.11 (m, 4H), 5.88–5.76 (m, 1H), 5.15 (d, 1H, J = 10.2 Hz), 5.03 (d, 1H, J = 17.1 Hz), 4.90 (d, 1H, J = 5.8 Hz), 3.51 (s, 3H), 3.18 (m, 1H), 2.98 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) 173.2, 139.7, 133.9, 131.7, 128.7, 128.1, 121.3, 73.6, 58.3, 52.5; HRMS [CI, M^+], Anal. calcd. for $C_{12}H_{13}ClO_3$ 240.0553, found 240.0553.

Preparation of Baylis–Hillman adducts. General procedure

The methyl 2-[(4-chlorophenyl)hydroxymethyl]but-2-enoate (53 mg, 0.22 mmol) and DBU (33 μL, 0.22 mmol) were dissolved in 2 mL of benzene at rt. After stirring for 50 minutes, the reaction mixture was poured into a mixture of ethyl acetate and water (2 mL/2 mL, v/v) and the solution extracted with ethyl acetate (2 mL × 3). The organic solution was washed with water (5 mL × 2) and brine. The solution was dried over anhydrous $MgSO_4$, filtered, evaporated and dried *in vacuo* to give a product (**2k**) as an oil. **2k**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.17 (m, 4H), 7.01 (q, 1H, J = 7.3 Hz), 5.60 (s, 1H), 3.61 (s, 3H), 1.89 (d, 3H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 167.8, 141.7, 140.8, 133.5, 133.3, 128.8, 127.1, 69.1, 52.3, 14.7;

HRMS [CI, M^+], Anal. calcd. for $C_{12}H_{13}ClO_3$ 240.0553, found 240.0549

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12 ^{1}H and ^{13}C NMR data for **2a** (*E*) and **2a** (*Z*): **2a** (*E*) ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (q, 1H, J = 7.2 Hz), 4.74 (q, 1H, J = 6.5 Hz), 3.76 (s, 3H), 3.62 (d, 1H, J = 10.9 Hz), 1.84 (d, 3H, J = 7.2 Hz), 1.40 (d, 3H, J = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 167.9, 138.3, 135.2, 64.9, 51.9, 23.3, 14.0. **2a** (*Z*) ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (q, 1H, J = 7.2 Hz), 4.49 (q, 1H, J = 6.5 Hz), 3.80 (s, 3H), 2.59 (d, 1H, J = 6.7 Hz), 1.99 (d, 3H, J = 7.2 Hz), 1.35 (d, 3H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 168.4, 136.9, 136.2, 69.8, 51.7, 22.91, 15.9.