Pergamon

Tetrahedron Letters 43 (2002) 5677–5680

TETRAHEDRON LETTERS

# Synthesis of β-iodo-α-(hydroxyalkyl)acrylates: a convenient and stereoselective reaction

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Received 15 February 2002; accepted 3 June 2002

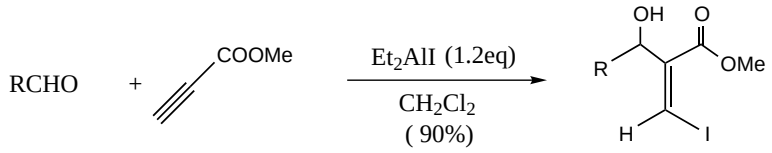
**Abstract**—An efficient one-pot, three-component coupling reaction for the synthesis of β-iodo-α-(hydroxyalkyl)acrylates has been developed. As the iodine source as well as the Lewis acid mediator, diethyl aluminium iodide undergoes a Michael-type addition with methyl propynoate to form an active β-iodo allenolate intermediate, which in turn attacks various aldehydes or ketones to afford β-iodo Baylis–Hillman adducts in excellent yields with high *Z*-selectivity. 

The Baylis–Hillman type coupling is one of the most important carbon–carbon bond-forming processes in organic synthesis.[1–3] Highly functionalized Baylis–Hillman adducts can then be subjected to subsequent transformations for the synthesis of natural products and synthetic derivatives.[4] However since β-substituted acrylate olefins cannot currently undergo the Baylis–Hillman reaction,[1a,5,6] alternative methods for synthesizing β-substituted acrylate olefins are required.

The synthesis of β-iodo Baylis–Hillman ketones was initially carried out by Kishi et al.[7] via a $TiCl_4$-promoted conjugative addition of tetrabutylammonium iodide ($(n\text{-Bu})_4NI$) to α,β-acetylenic ketones followed by electrophilic coupling with aldehydes. *E*-β-Iodo Baylis–Hillman type ketones were also obtained by using $Et_2AlI$ as the promoter and the halogen source.[8] Afterwards, Lu and co-workers reported a method for the synthesis of β-iodo Baylis–Hillman esters and amides with *Z*-isomers as the major products.[9] The latter method also employed $(n\text{-Bu})_4NI$ as the halide source for the anionic conjugative addition, but used 1.2 equiv. of $ZnCl_4$ as the Lewis acid promoter.

Inspired by these previous studies, we and other groups have developed several methodologies for the synthesis of β-monosubstituted and β,β-disubstituted α-(hydroxyalkyl)acrylates, α-(aminoalkyl)acrylates and β-halo Baylis–Hillman ketones.[10–12] In our continuing development of new Baylis–Hillman-type processes, we are pleased to find that *Z*-β-iodo-α-(hydroxyalkyl)acrylates were obtained by mixing aldehydes, methyl propynoate and diethyl aluminium iodide in $CH_2Cl_2$. In this communication, we report this new procedure which is represented in Scheme 1 with results summarized in Table 1.

We initially attempted the three-component reaction of benzaldehyde, methyl propynoate and $TiCl_4$ (1.2 equiv.), but the success was very limited. However when $TiCl_4$ was replaced by $Et_2AlI$ as the halogen source and the Lewis acid promoter, the desired product was generated. The reaction was carried out at 0°C by adding $Et_2AlI$ dropwise into the mixture of aldehyde and methyl propynoate in $CH_2Cl_2$ under argon. Most reactions went to completion within 2 h as indicated by TLC or $^1H$ NMR analysis; good to high yields were realized for all examples that were examined.




**Scheme 1.**

*Keywords*: Baylis–Hillman adducts; diethyl aluminium iodide; methyl propynoate; β-iodo-α-(hydroxyalkyl)acrylates.
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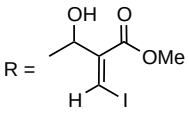
0040-4039/02/$ - see front matter 
PII: S0040-4039(02)01106-1

**Table 1.** Results of the $Et_2AlI$-mediated reaction for synthesis of β-iodo Baylis–Hillman adducts[13,14]

| Entry | Substrates | Products R =  | $Z/E$ selectivity (%)[a] | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Benzaldehyde | Phenyl-R | 94/6 | 88 |
| 2 | 4-Fluorobenzadehyde | 4-Fluorophenyl-R | 91/9 | 89 |
| 3 | 4-Chlorobenzadehyde | 4-Chlorophenyl-R | 95/5 | 85 |
| 4 | 2-Naphthaldehyde | 2-Naphthyl-R | 95/5 | 84 |
| 5 | *p*-Anisaldehyde | 4-Methoxybenzene-R | 95/5 | 95[c] |
| 6 | *p*-Tolualdehyde | *p*-Tolyl-R | 94/6 | 90 |
| 7 | Trimethylacetaldehyde | *tert*-Butyl-R | 93/7 | 76 |
| 8 | Acetophenone | *sec*-Phenethyl-R | 95/5 | 75[c] |
| 9 | Benzalacetone | 1-Phenyl-3-methyl-1-proene-R | 86/14 | 86[c] |

[a] Estimated by crude $^1H$ NMR determination.
[b] Yields after purification by column chromatography.
[c] Reaction for 4 h.

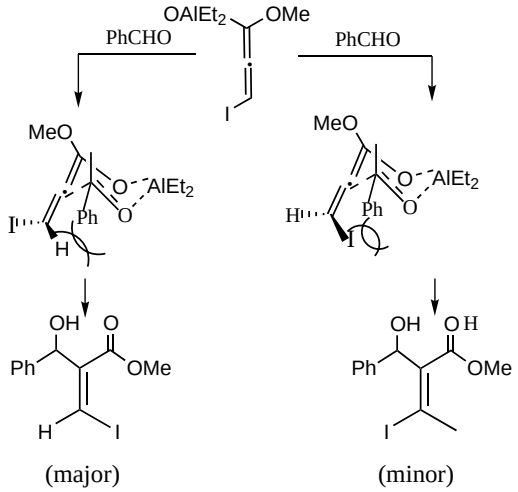
Dichloromethane provided the highest efficiency among the solvents tested in terms of yield and $Z/E$ selectivity when using benzaldehyde as the electrophilic acceptor. Diethyl ether gave rise to a lower yield of 65% within a 2 h reaction period, while benzene and toluene resulted in a poorer $Z/E$ selectivity with ratios of 80/20 and 76/24, respectively.

Both aromatic and aliphatic aldehydes were suitable electrophilic acceptors in this reaction, as shown in Table 1. For aromatic aldehydes, substitution of an electron-withdrawing group on the aromatic ring resulted in no obvious effect on the reaction efficiency. However, an electron-donating group attached to the aromatic aldehyde reduced the reaction rate. When *p*-anisaldehyde (entry 5, Table 1) was employed as the electrophilic acceptor, the reaction needed 4 h to generate product of more than 90% yield, with only 80% of *p*-anisaldehyde converted to product within 2 h. Both aromatic ketone and aliphatic ketone substrates can be employed as electrophilic acceptors, although they did result in lower reaction efficiencies (entries 8 and 9, respectively). The reaction temperature appears to affect the $Z/E$ selectivity as well as the rate of the reaction. For example, when benzaldehyde was used as the electrophilic acceptor, the reaction did not go to completion at −78°C even when the reaction time was extended to 24 h, however, the $Z/E$ selectivity was improved to 98/2.

The $Z/E$ selectivities listed in Table 1 were measured by $^1H$ NMR spectroscopic analyses of the crude product mixture. In all cases, the α-proton signals for *Z* and *E* isomers were clearly distinguishable with the proton for the *Z* isomer upfield relative to the proton for the *E* isomer. Isomers could be readily separated by flash chromatography and the geometries for the two isomers of the benzaldehyde reaction were confirmed by ROSEY NMR experiments. For the *Z* isomer, vinyl-proton irradiation resulted in α-proton enhancement, whereas, for the *E* isomer, vinyl proton irradiation resulted in methoxyl proton enhancement.

To explain the high $Z/E$ stereoselectivity of this new system, a cyclic transition state model proposed by Kishi can be invoked.[7] In their system, not only the $(n\text{-Bu})_4NI/TiCl_4$ combination but also $Et_2AlI$ and $TiI_4$ were employed for the reaction. The exclusive *Z* stereoselectivity of β-iodo Baylis–Hillman ketones was obtained at −78°C, while the high *E*-stereoselectivity was observed at 0°C. By using a cyclic transition state model, they suggested the *Z*-stereoisomer was the kinetically controlled product, while the *E*-stereoisomer was the thermodynamically controlled product. In the system we report here, the *Z*-isomer was favoured under all reaction conditions tested. These results suggest that the kinetic control plays a significant role in determining the geometric selectivity at 0°C (Scheme 2). This is in contrast to a previously reported $TiCl_4$-mediated reaction carried out at room temperature in which *E* isomers were predominantly obtained;[12] a process believed to be under thermodynamic control.

In summary, an efficient synthetic method for β-iodo-α-(hydroxyalkyl)acrylates has been developed. The new




**Scheme 2.**

protocol utilizes diethyl aluminium iodide as the iodine anion source, and concurrently as a Lewis acid promoter under relatively mild conditions. This new reaction system provides extensive functionalization of acrylate olefins with high chemical yields and geometric selectivity.

## Acknowledgements

We thank D. Purkiss for expert NMR support. Financial support was provided by the Robert A. Welch Foundation (D-1478 and D-1361).

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13. Typical procedure (Table 1, entry 1): A dry standard-glass test tube (150×22 mm) with a stir bar placed at the bottom was flushed with nitrogen and cooled to 0°C. Into the tube, freshly distilled dichloromethane (5.0 mL), benzaldehyde (0.1 mL, 1.0 mmol) and methyl propynoate (0.12 mL, 1.3 mmol) were added. The mixture was stirred at 0°C for 5 min. and then a solution of diethylaluminium iodide in toluene (25 wt% solution in toluene, 1.2 mL, 1.2 mmol) was added dropwise via syringe in ca. 5 min. The resulting homogeneous yellow solution was stirred for 2 h at 0°C. The reaction was quenched by dropwise addition of 2N aqueous hydrochloric acid. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic layers were then washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (hexane:EtOAc, 10/1, v/v) to provide products **1***Z* (263 mg, 83% yield) and **1***E* (17 mg, 5.3% yield) (combined yields, 88%), both colourless oils.
14. The physical data of all products: **1***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.91 (d, $J=5.5$ Hz, 1H), 3.72 (s, 3H), 5.54 (dd, $J=5.5$, 1.5 Hz, 1H), 7.27 (d, $J=1.5$ Hz, 1H), 7.30–7.36 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 51.9, 76.0, 87.1, 126.5×2, 128.3, 218.6×2, 140.0, 145.1, 166.3; IR (neat): $\nu_{max}=3443$, 3063, 2950, 1714; MS (CI, $CH_4$): $m/z$ (%) 318.1 $[M]^+$; HRMS calcd for 318.1110; found: 318.1105. **1***E*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.72 (s, 3H), 4.20 (d, $J=11.4$ Hz, 1H), 5.83 (d, $J=11.4$ Hz, 1H), 7.26–7.44 (m, 5H), 8.14 (s, 1H). Compound **2**: colourless oil (299 mg, 89% combined yields); **2***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.93 (d, $J=6.0$ Hz, 1H), 3.72 (s, 3H), 5.52 (dd, $J=6.0$, 1.5 Hz, 1H), 7.00–7.06 (m, 2H), 7.28–7.32 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 51.9, 73.9, 87.1, 115.4, 115.7, 128.4, 135.8, 144.9, 160.8, 164.1, 166.2; IR (neat): $\nu_{max}=3499$, 3071, 2952, 1731. Compound **3**: colourless oil (300 mg, 85% combined yields); **3***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.23 (d, $J=6.0$ Hz, 1H), 3.72 (s, 3H), 5.48 (dd, $J=6.0$, 1.4 Hz), 7.22–7.32 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 51.9, 75.4, 87.7, 127.8×2, 128.8×2, 134.1, 138.5, 144.6, 166.1; IR (neat): $\nu_{max}=3453$, 3068, 2958, 2359, 1720; MS (CI, $CH_4$): $m/z$ (%) 352.5 $[M]^+$; HRMS calcd for 352.5558; found: 352.5551. Compound **4**: colourless oil (309 mg, 84% combined yields); **4***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.04 (d, $J=6.0$ Hz, 1H), 3.70 (s, 3H), 5.69 (dd, $J=6.0$, 1.5 Hz, 1H), 7.29 (s, 1H), 7.47–7.50 (m, 3H), 7.80–7.84 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 51.9, 76.1, 87.5, 124.2, 125.6, 126.3×2, 127.6, 128.1, 128.5, 133.1×2, 137.3, 145.0, 166.3; IR (neat): $\nu_{max}=3447$, 3055, 2949, 1715. Compound **5**: colourless oil (330 mg, 95% combined yields); **5***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.06 (d, $J=6.0$ Hz, 1H), 3.69 (s, 3H), 3.77 (s, 3H), 5.45 (dd, $J=6.0$, 1.5 Hz, 1H), 6.83–6.86 (d, $J=6.0$ Hz, 2H), 7.19–7.22 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 51.9, 55.2, 75.6, 86.4, 114.0×2, 127.9×2, 132.1, 145.4, 159.5, 166.4; IR (neat): $\nu_{max}=$ 3448, 3001, 2950, 2835, 1718. Compound **6**: colourless oil (399 mg, 90% combined yields); **6***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.32 (s, 3H), 3.07 (d, $J=6.0$ Hz, 1H), 3.68 (s, 3H), 5.46 (dd, $J=6.0$, 1.5 Hz, 1H), 7.11–7.20 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 21.1, 51.8, 75.8, 86.7, 126.4×2, 129.3×2, 137.0, 138.1, 145.2, 166.3; IR (neat): $\nu_{max}=3450$, 3024, 2949, 1713. Compound **7**: colourless oil (226 mg, 76% combined yields); **7***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (s, 9H), 2.68 (d, $J=6.0$ Hz, 1H), 3.82 (s, 3H), 4.25 (dd, $J=6.0$, 1.4 Hz, 1H), 7.07 (s, 1H);

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 25.5×3, 36.0, 51.9, 82.5, 85.6, 145.4, 167.9; IR (neat): $\nu_{max}$ = 1716, 1614. Compound **8**: colourless oil (249 mg, 75% combined yields); **8***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.70 (s, 3H), 3.67 (s, 3H), 3.80 (s, 1H), 7.11 (s, 1H), 7.25–7.42 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 28.7, 51.9, 77.8, 83.8, 125.0×2, 127.5, 128.3×2, 144.6, 150.1, 168.1; IR (neat): $\nu_{max}$ = 3484, 1726. Compound **9**: colourless oil (308 mg, 86% combined yields); **9***Z*: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.60 (s, 3H), 3.15 (s, 1H), 3.83 (s, 3H), 6.27 (d, $J$ = 18.0 Hz, 1H), 6.68 (d, $J$ = 18.0 Hz, 1H), 7.04 (d, $J$ = 0.9 Hz, 1H), 7.25–7.39 (m, 5H); IR (neat): $\nu_{max}$ = 3506, 2953, 1714.