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Z/E SELECTIVE SYNTHESIS OF β,β-DISUBSTITUTED AND (*Z*)-β-MONOSUBSTITUTED BAYLIS-HILLMAN ADDUCTS *VIA* ANIONIC ADDITIONS OF VINYLCUPRATES TO ALDEHYDES

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ABSTRACT: A new method has been developed for the synthesis of achiral β,β-disubstituted and (*Z*)-β-monosubstituted Baylis-Hillman adducts with excellent *Z/E* stereospecificity in some cases. The process involves the conjugate additions of R_2CuLi or RMgBr-CuBr-DMS to α,β-acetylenic esters and followed by additions of anionic α-(alkoxycarbonyl)vinyl]copper intermediates to aldehydes. The individual *Z*- and *E*- isomers of the resulting β-branched α-(hydroxylalkyl)acrylates can be separated by column chromatography in modest to excellent yield.

Baylis-Hillman adducts can be used as the building blocks for the synthesis of numerous chemically and biologically important molecules.[1-10] Unfortunately, the original Baylis-Hillman system has serious limitations, for example, the β-substituted acrylate olefins do not normally undergo the Baylis-Hillman reaction.[1,6&7] Therefore, alternative methods should be developed for synthesizing β-branched Baylis-Hillman adducts.[8-10] Recently, we developed a new method for the stereospecific synthesis of β-branched Baylis-Hillman

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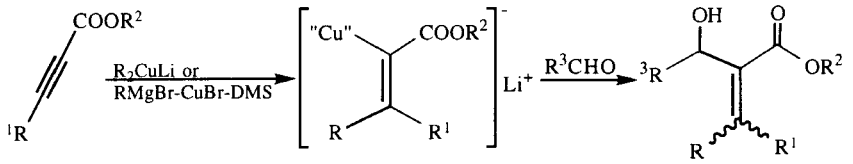
adducts in excellent *Z/E* selectivity,[8] which was achieved by forming anionic β-substituted [α-(alkoxycarbonyl)vinyl]aluminum intermediates and followed by their additions to aldehydes and ketones at low temperature. Here, we wish to describe a new method for synthesizing β,β-disubstituted and (*Z*)-β-monosubstituted α-(hydroxylalkyl)acrylates by using organocopper reagents.[11-13]

β-Branched anionic (α-carbethoxyvinyl)cuprate intermediates, which are derived from the conjugate addition of organocopper reagents to α,β-acetylenic esters, have been utilized for the synthesis of substituted α,β-unsaturated esters[14-16], divinyl ketones[17] and α,β-unsaturated lactones.[18] So far, the application of these intermediates to the synthesis of unusual Baylis-Hillman adducts has not been well documented. In 1983, an unique copper reagent, Li (α-carbethoxyvinyl)CuHex, was discovered for the synthesis of β,β-disubstituted and (*Z*)-β-monosubstituted α-(hydroxylalkyl)acrylates.[19] This method involves the addition reaction of Li (α-carbethoxyvinyl)CuHex with ketone to give (*Z*)-β-monosubstituted α-(hydroxylalkyl)acrylates in excellent yields. However, the same reaction using aldehydes as the electrophilic species gave the mixtures of two *E/Z* isomers which were not separable by column chromatography.

During our studies in developing new methods for the synthesis of unusual Baylis-Hillman adducts, we found that the common (α-carbethoxyvinyl)cuprates derived from the conjugate addition of organocopper reagents (R_2CuLi and RMgBr-CuBr-DMS) to α,β-acetylenic esters can react readily with aldehydes to give β,β-disubstituted and (*Z*)-β-monosubstituted α-(hydroxylalkyl)acrylates (Scheme 1). This processes can give (*Z*)-β-monosubstituted α-(hydroxylalkyl)acrylates with excellent *E/Z* selectivities in some cases (Table 1& 2). Both aromatic and nonaromatic α,β-acetylenic esters can be used as the substrates for the Michael addition and followed by carbonyl addition to aldehydes which was performed by using excess amount of aldehydes (1.25 equiv)



R^1 = H, Me, Ph; R^2 = Me, Et.; R = Me, Bu, Ph.

Scheme 1. New synthesis of Unusual Baylis-Hillman Adducts Using (α-Carbethoxyvinyl)cuprate

at -78 °C. Two individual *Z*- and *E*- isomers of several resulting *tri*- and *tetra*-substituted olefinic esters can be easily separated by column chromatography.

It is interesting to note that R_2CuLi-derived anionic (α-carbethoxyvinyl)cuprates in THF solution do not undergo addition reactions with aldehydes even at room temperature, whereas, the same intermediates in diethyl ether solution can be almost completely consumed when reacting with aldehydes at -78°C. Moreover, the anionic (α-carbethoxyvinyl)cuprates derived from RMgBr-CuBr-DMS in both ether and THF solution can react with aldehydes at the same temperature. It has been previously pointed out by Corey that the nature of the solvent influences the stereoselectivity of cuprate addition to α,β-acetylenic esters, and there is an equilibrium between the *cis* and *trans* enolates in ether solution at a significant rate, even at -78°C.[14] To explain the excellent stereoselectivity of the resulting (*Z*)-β-monosubstituted α-(hydroxylalkyl)acrylates (Table 1 & 2), a mechanistic process similar to that of literature can be employed.[19] The carbonyl additions of vinylcuprates to aldehydes are controlled by stereo and kinetic effects. The aldehyde approaches the anionic center from the less hindered hydrogen side of the allenoate. The present low temperature system seems able to enhance these effects in controlling the stereoselectivity. It can also explain the *Z*/*E* selectivity of the original RHexCuLi-aldehyde reaction system which was conducted at higher temperature.

The steric effects of two terminal groups of allenoate are responsible for the poor *Z/E* selectivity of the resulting β,β-disubstituted Baylis-Hillman adducts (Table 1 and 2).

The typical procedures are demonstrated by the synthesis of β-methyl β-phenyl α-(hydroxylalkyl)acrylate (**4**) by using Me_2CuLi (procedure 1) and using PhMgBr-CuBr-DMS (procedure 2) respectively. Procedure 1: Into dry flask with a magnetic stirring bar was charged with CuI (415 mg, 2.1 mmol) and freshly distilled diethyl ether (10 mL). The flask was flushed with nitrogen, and was cooled to 0 °C before a solution of methyllithium in diethyl ether (1.4 M, 2.86 mL, 4.0 mmol) was added dropwise. The resulting homogeneous gray solution was stirred for 30 min at 0 °C, and then cooled to -78 °C using a dry ice-acetone bath. Into the resulting mixture was added the solution of ethyl phenylpropiolate (0.34 mL, ca 2.0 mmol) in diether ether (2 mL) by syringe over 10 min. The resulting mixture was stirred at -78 °C for 2 h before benzaldehyde (0.25 mL, ca. 2.5 mmol) was added. The reaction mixture was stirred at -78 °C for additional 2 h and at 0 °C for 1 h. The reaction was finally quenched by dropwise addition of 1N aqueous hydrochloric acid solution. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were each washed with saturated sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (EtOAc /hexane, 1/9, v/v) provided two individual isomers of β-methyl β-phenyl α-(hydroxylalkyl)acrylate (**4**, 0.190 g, *Z*- isomer of **4**, 0.293 g, combined yield 82.5 %) as a light yellow oil.

Procedure 2: A nitrogen flushed dry flask was charged with CuBr-DMS (416 mg, 2.0 mmol) and freshly distilled ether (10 mL). The flask was cooled to -23 °C before a solution of phenylmagnesium bromide in diether ether (3.0 M, 0.7 mL,

2.1 mmol) was added dropwise. The resulting yellow slurry mixture was stirred at -23 °C for 5 min and at 0 °C for 30 min. The flask was then cooled to -78 °C using a dry ice-acetone bath. Into the resulting mixture was added the solution of ethyl 2-butynoate (ca 0.118 mL, 1.0 mmol) in diether ether (2 mL) dropwise via syringe over 10 min. The resulting slurry mixture was stirred at -78 °C for 3 h before benzaldehyde (0.23 mL, ca. 2.2 mmol) was added. The reaction mixture continued stirring at -78 °C for 4 h and at 0 °C for 1 h. The reaction was quenched by dropwise addition of 1N aqueous hydrochloric acid solution. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were each washed with saturated sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (EtOAc /hexane, 1/9, v/v) provided two individual isomers of β-methyl β-phenyl α-(hydroxylalkyl)acrylate (**4**, 0.096 g, *Z*- isomer of **4**, 0.201 g, combined yield 50.5%) as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): **4**, δ 0.61 (t, J = 7.1 Hz, 3 H), 2.25 (s, 3H), 3.68 (dd, J = 14.2 Hz, 7.1 Hz, 2 H), 4.06 (br d, J = 8.0 Hz, 1 H), 5.82 (br d, J = 7.2 Hz, 1 H), 7.20- 7.49 (m, 10 H); *Z*- isomer of **4**, δ 1.05 (t, J = 7.1 Hz, 3 H), 2.36 (s, 3H), 3.77 (d, J = 10.5 Hz, 1 H), 4.06 (m, 2 H), 5.34 (d, J = 10.4 Hz, 1 H), 7.19- 7.40 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$): **4**, δ 13.1, 21.3, 60.4, 71.5, 125.7, 126.8, 127.3, 127.5, 128.1, 128.3, 128.4, 132.0, 142.2, 143.3, 145.4, 169.6; *Z*- isomer of **4**, δ 13.9, 23.6, 60.6, 71.9, 125.2, 126.8,

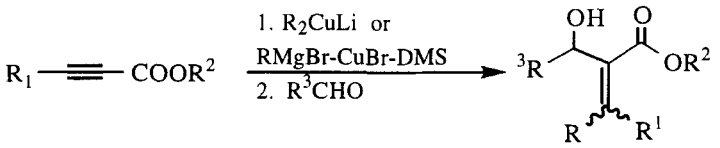
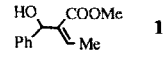
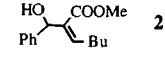
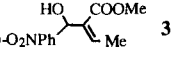
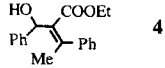
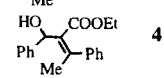
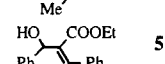
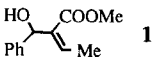
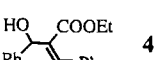
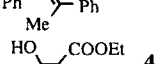


Table 1. Synthetic Results for β-Branched Baylis-Hillman Adducts by Use of R_2CuLi

R^1	R^2	R^3	R	Product		^{1}H-NMR (δ) of β-H (CH-OH)	*Z/E* [a]	Yield (%)[b]
H	Me	Ph	Me		**1**	5.44	95/1	69.0
H	Me	Ph	Bu		**2**	5.43	95/1	51.0
H	Me		Me		**3**	7.15	only *Z*	44.4
Me	Et	Ph	Ph		**4**	5.77	3.8/1	88.0
Ph	Et	Ph	Me		**4**	5.77	1.54/1	82.5
Me	Et	Ph	Bu		**5**	5.26	1/1	97.0[c]

[a] Z/E ratios were estimated by ^{1}H NMR. [b] Combined yields of two isomers after column chromatography. [c] Two isomers were not separable by column chromatography

Table 2. Synthetic Results of β-Branched Baylis-Hillman Adducts by Use of RMgBr-CuBr-DMS

R^1	R^2	R^3	R	Product		*Z/E* [a]	Yield (%)[b]
H	Me	Ph	Me		**1**	10/1	50.1
Me	Et	Ph	Ph		**4**	2.1/1	50.5
Ph	Et	Ph	Me		**4**	1.4/1	50.0

[a] Z/E ratios were estimated by ^{1}H NMR. [b] Combined yields of two isomers after column chromatography.

127.0, 127.7, 128.0, 128.5, 130.7, 141.6, 142.8, 148.9, 168.6. MS (EI) **4**, *m/z* 296.2 (296.4 calcd for $C_{19}H_{20}O_3$).

In conclusion, the new process described in this paper provides a convenient approach to (*Z*)-β-monosubstituted and β, β-disubstituted α-

(hydroxylalkyl)acrylates. This process can complement the previously developed method in which the scope is limited by the availability of various alkyl propiolate derivatives.[8] The individual *Z* and *E* stereoisomers of the most of the resulting β-disubstituted α-(hydroxylalkyl)acrylates can be separated by column chromatography.

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