

Organic Reactions in Water: An Efficient Zinc-Mediated Stereoselective Synthesis of (*E*)- and (*Z*)-Trisubstituted Alkenes Using Unactivated Alkyl Halides

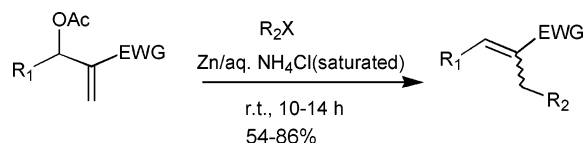
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ABSTRACT



Treatment of the acetyl derivatives of the Baylis–Hillman adducts 3-hydroxy-2-methylene-alkanoates and 3-hydroxy-2-methylene-alkanenitriles with unactivated alkyl halides in the presence of Zn in saturated aqueous NH_4Cl solution at room temperature afforded (*2E*)-2-substituted-alk-2-enoates in the first case and (*2Z*)-2-substituted-alk-2-enenitriles with high (*Z*)-selectivity in the second case.

The Baylis–Hillman reaction involving the coupling of activated vinylic systems with electrophiles under the catalytic influence of a tertiary amine, usually DABCO, is a useful carbon–carbon bond forming method in organic synthesis.¹ The adducts of the reactions, 3-hydroxy-2-methylene-alkanoates (derived from acrylate esters) and 3-hydroxy-2-methylene-alkanenitriles (derived from acrylonitrile), have been employed for stereoselective synthesis of different multifunctional molecules.² A trisubstituted alkene moiety has widely been found in various naturally occurring bioactive molecules including several important pheromones and antibiotics.³ The biological activity of these alkenes is highly dependent on their isomeric purity. Different trisubstituted alkenes with defined stereochemistry are also often utilized as the key intermediates in the synthesis

of other stereospecific compounds.⁴ Thus a few methods have been developed for the preparation of trisubstituted alkenes.^{4,5} To our knowledge, there is only one method⁶ developed to achieve (*E*)- and (*Z*)-selectivity involving activated Baylis–Hillman adducts using Grignard conditions.

During our efforts toward the synthesis of trisubstituted alkenes⁷ derived from Baylis–Hillman adducts, we envisaged that a metal-mediated alkylation in aqueous medium would smoothly substitute the Grignard conditions. There has been considerable recent attention in carbon–carbon bond formation in water with organometallics,⁸ particularly with zinc⁹ involving unactivated alkyl iodides. Although some reports

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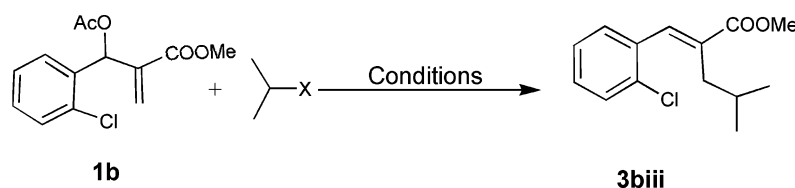
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Table 1. Optimization of the Reaction Conditions^a

entry	metal (equiv)	alkyl halide (equiv)	solvent	yield (%) ^b	side product (%) ^c
1	Zn (1.5)	<i>i</i> -PrI (1.5)	CH ₂ Cl ₂	0	0
2	Zn (1.5)	<i>i</i> -PrI (1.5)	dioxane	2	0
3	Zn (1.5)	<i>i</i> -PrI (1.5)	MeOH	5	0
4	Zn (1.5)	<i>i</i> -PrI (1.5)	H ₂ O	8	0
5	Zn (1.5)	<i>i</i> -PrI (1.5)	0.1 M aq NH ₄ Cl	38	tr
6	Zn (1.5)	<i>i</i> -PrI (1.5)	0.5 M aq NH ₄ Cl	58	tr
7	Zn (1.5)	<i>i</i> -PrI (1.5)	1 M aq NH ₄ Cl	63	5
8	Zn (1.5)	<i>i</i> -PrI (1.5)	saturated aq NH ₄ Cl	72	15
9	Zn (1.5)	<i>i</i> -PrI (1.5)	saturated aq NH ₄ Cl/dioxane (1:1)	68	17
10	Zn (1.5)	<i>i</i> -PrBr (1.5)	saturated aq NH ₄ Cl	52	24
11	Zn (3)	<i>i</i> -PrBr (4)	saturated aq NH ₄ Cl	56	20
12	Zn (2)	<i>i</i> -PrI (2)	saturated aq NH ₄ Cl	75	10
13	Zn (3)	<i>i</i> -PrI (4)	saturated aq NH ₄ Cl	86	<2
14	In (3)	<i>i</i> -PrI (4)	saturated aq NH ₄ Cl	0	0
15	Sm (3)	<i>i</i> -PrI (4)	saturated aq NH ₄ Cl	0	0
16	Zn (3)/Yb(OTf) ₃	<i>i</i> -PrI (4)	saturated aq NH ₄ Cl	85	<2

^a Treatment of **1b** with isopropyl halide and metal at room temperature for 12 h. ^b Isolated yield of product **3biii**. ^c Isolated yield of the reduced side product.

on alkylation in aqueous conditions^{9a} are known, there is still a need to develop a method for stereoselective synthesis of (*E*)- and (*Z*)-trisubstituted alkenes with unactivated alkyl halides in water.¹⁰ The fact is that a highly reactive metal is required to break the C–X bond of an unactivated alkyl halide. Even if the desired organometallic intermediate is successfully generated by this reaction, various competing side reactions may occur. For examples, reduction of starting materials and the hydrolysis of an organometallic intermediate may be mentioned. Essentially, these difficulties have prevented the further development of aqueous organic reaction onto simple alkyl halides. Hence, there must be a fair balance between metal reactivity and side product conversion without severely compromising the yield of the desired alkylated product. Herein we wish to report an efficient alkylation on activated Baylis–Hillman adducts to produce trisubstituted alkenes in water. In the presence of zinc and saturated aqueous NH₄Cl, simple alkyl iodides reacted with activated Baylis–Hillman adducts at room temperature to yield (*E*)- and (*Z*)-trisubstituted alkenes with moderate to high yield and excellent stereoselectivity.

To achieve the suitable conditions of the above transformation, a series of experiments was carried out (Table 1). Treatment of **1b** (R₁ = 2-Cl-C₆H₄; EWG = -COOMe) with

isopropyl iodide (*i*-PrI) in the presence of Zn in CH₂Cl₂ afforded no product even after 12 h. Only a trace amount of the product was formed during the same period of time when the similar reaction was conducted in methanol, dioxane, or water. However, the rate and yield of the products were improved by the addition of aqueous solution of NH₄Cl, and the concentration of NH₄Cl was found to have a prominent effect. Thus the dry conditions of the reaction are not required. The role of water is significant here as the addition of NH₄Cl in other dry solvents such as dioxane and MeOH yielded only the trace quantity of the product. The yield of the trisubstituted olefin **3biii** was good (72%) in 12 h when saturated aqueous NH₄Cl solution and 1.5 equiv of alkyl iodide were used. However, a larger side product (15%, Table 1) led us to further optimize the conditions. To our expectation, increasing the amount of alkyl iodide (entry 13, Table 1) led to the formation of the alkylated product (**3biii**) almost exclusively (side product <2%). Thus, 4 equiv of alkyl iodide were used for R₁ = aryl (**3a–c**, **4a–b**, Table 2), whereas 5 equiv was needed when R₁ = alkyl (**3d–e**, **4c**, Table 2). It may be noted that the extended conjugation provided by the aromatic ring stabilizes the alkene and hence formed the products in high yield even with only a slight excess of the nucleophile. Metal reactivity toward the reaction was also studied and zinc (3 equiv entry 13, Table 1) was found to be the best choice. Samarium and indium, metals of current interest, failed to produce the product (Table 1). Addition of a lanthanide triflate [e.g., Yb(OTf)₃] along with saturated aqueous NH₄Cl did not effect the yield of the

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Table 2. Stereoselective Synthesis of (*E*)-2-Substituted Alk-2-enoates (**3**) and (*Z*)-2-Substituted Alk-2-ene-nitriles (**4**)

1: EWG= -COOMe				3: EWG= -COOMe	
2: EWG= -CN				4: EWG= -CN	
entry	R ₁	R ₂	time (h)	yield (%) ^a	<i>Z/E</i> ^b
3a	C ₆ H ₅	(i) <i>n</i> -Bu	10	74	0:100
		(ii) <i>n</i> -Hex	10	77	0:100
		(iii) <i>i</i> -Pr	10	84	0:100
3b	2-Cl-C ₆ H ₄	(i) <i>n</i> -Bu	12	73	0:100
		(ii) <i>n</i> -Hex	12	78	0:100
		(iii) <i>i</i> -Pr	12	86	0:100
3c	4-OMe-C ₆ H ₄	(i) Et	12	70	0:100
		(ii) <i>n</i> -Bu	12	75	0:100
		(iii) <i>i</i> -Pr	12	85	0:100
3d	<i>n</i> -C ₅ H ₁₁ ^c	(i) Et	14	54	0:100
		(ii) <i>n</i> -Pr	14	63	0:100
3e	2-C ₄ H ₉ ^c	(i) <i>i</i> -Pr	14	65	0:100
		(ii) <i>n</i> -Hex	14	62	0:100
4a	C ₆ H ₅	(i) <i>n</i> -Bu	12	78	88:12
		(ii) <i>n</i> -Hex	12	76	90:10
		(iii) <i>i</i> -Pr	12	80	94:6
4b	2-Cl-C ₆ H ₄	(i) <i>n</i> -Bu	12	76	89:11
		(ii) <i>n</i> -Hex	12	73	90:10
		(iii) <i>i</i> -Pr	12	77	95:5
4c	<i>n</i> -C ₃ H ₇ ^c	(i) <i>n</i> -Bu	14	58	80:20
		(ii) <i>n</i> -Hex	14	60	82:18

^a Isolated yield of products **3** (EWG = COOMe) and **4** (EWG = CN).

^b Ratio was determined by ¹H NMR analysis. ^c Zn (4 equiv) and alkyl iodide (5 equiv) were used.

product. When using alkyl bromide instead of alkyl iodide, a much lower yield of the product was observed (Table 1).

During the current studies several 3-acetoxy-2-methylene-alkanoates (**1**) and 3-acetoxy-2-methylene-alkanenitriles (**2**) were treated¹¹ with various alkyl iodides in the presence of Zn in saturated aqueous NH₄Cl solution at room temperature to generate efficiently different trisubstituted alkenes (Tables 2). The stereochemistry of the trisubstituted alkenes derived from Baylis–Hillman adducts is well-documented.^{1b,12} The electron-withdrawing groups present in the adducts direct the stereochemistry of the products. When β-substituted acrylate esters were present in the adduct (**1**), the conversion afforded the olefins (**3**) with (*E*)-stereoselectivity exclusively,

(11) **General Experimental Procedure.** A suspension of a 3-acetoxy-2-methylene-alkanoate or a 3-acetoxy-2-methylene-alkanenitrile (3 mmol), alkyl iodide (12 mmol), and Zn powder (588 mg, 9 mmol) in saturated aqueous NH₄Cl solution (6 mL) was stirred for 10–14 h at room temperature. After the reaction was completed (monitored by TLC), EtOAc (15 mL) was added and shaken. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic portion was washed with brine (3 × 10 mL) followed by water (3 × 10 mL), dried, filtered, and concentrated. The residue was subsequently subjected to column chromatography over silica gel to afford pure trisubstituted alkene.

(12) Trisubstituted alkenes derived from Baylis–Hillman adducts having EWG = CN and R₂ = alkyl never produced (*Z*)-isomer solely. For example, see ref 6.

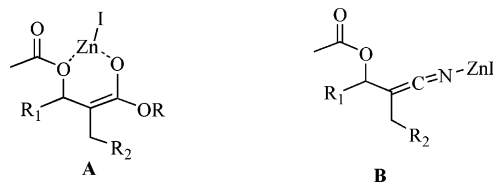
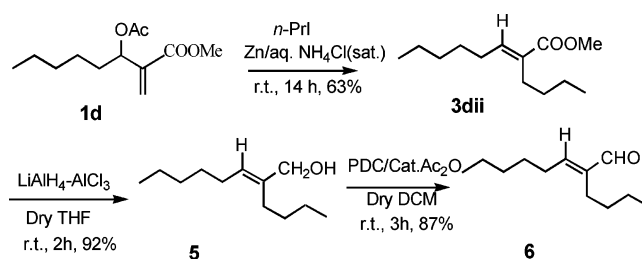


Figure 1. Possible intermediates to account for the observed stereoselectivity.

whereas when β-substituted acrylonitriles were present in the adduct (**2**), the olefins (**4**) were formed with high (*Z*)-stereoselectivity. The *Z/E* ratio was determined by ¹H NMR spectra of the crude products, and the structures and stereochemistry of the products were established from the spectral (IR, ¹H and ¹³C NMR, and MS) data of the pure compounds.^{11,13} Thus the present method can be utilized for the preparation of both the (*E*)- and (*Z*)-trisubstituted alkenes. The regioselective alkylation can be explained by a 1,4-addition type of mechanism involving a β-acetoxy elimination.^{5d,14} In the present case the reaction possibly involves the activation of the C–I bond of the alkyl iodide to form an alkylzinc species, which then undergoes the above mechanism on the acetyl derivatives of the Baylis–Hillman adducts. This mechanism explains the (*E*)-selectivity with ester (forming a chelated reaction intermediate, **A**, Figure 1) and (*Z*)-selectivity with nitriles (forming a nonchelated intermediate, **B**, Figure 1). However, an alternative mechanism for the reaction involving a single-electron transfer (SET) process¹⁵ could not be excluded. The methodology

Scheme 1



was successfully applied to the synthesis of (*E*)-2-butyloct-2-enal (**6**),^{3a,16} an alarm pheromone component of the African weaver ant, *Oecophylla longinoda*. Reduction of (*E*)-

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methyl-2-butyl-3-pentyl-propenoate (**3dii**) yielded the corresponding alcohol (**5**) in 92%. Upon oxidation with PDC the product **6** was furnished in 87% yield.

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Supporting Information Available: Analytical and spectral data of all prepared new compounds and experimental procedure for the synthesis of compound **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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