# A Facile Zn-mediated Stereoselective Synthesis of (*E*)- and (*Z*)-Trisubstituted Alkenes from Baylis–Hillman Adducts in Water and Its Application[1]

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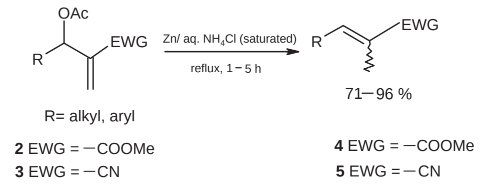
A simple and efficient stereoselective synthesis of (*E*)- and (*Z*)-trisubstituted alkenes has been accomplished by treatment of the acetyl derivatives of the Baylis–Hillman adducts with Zn in saturated aq. NH$_4$Cl solution under reflux. The method has been utilized for the preparation of the two chiral insect pheromones, dominicalure-I and dominicalure-II, of the lesser grain borer *Rhyzopertha dominica* (F).

Baylis–Hillman reaction is an important synthetic utility in recent years.[2] The adducts of the reaction, 3-hydroxy-2-methylenealkanoates (derived from acrylate esters) and 3-hydroxy-2-methylenealkanenitriles (derived from acrylonitriles) have been utilized for the stereoselective synthesis of various polyfunctional molecules.[2b,3] These adducts also represent useful intermediates for the synthesis of trisubstituted alkenes. Many naturally occurring bioactive compounds including different pheromones and antibiotics contain trisubstituted alkene moiety.[4] The biological property of these alkenes is highly dependent on their isomeric purity.[5,6] As for an example, (*S*)-(+)-1-methylbutyl-(*E*)-2-methyl-2-pentenoate (dominicalure-I) (**1a**) and (*S*)-(+)-1-methylbutyl-(*E*)-2,4-dimethyl-2-pentenoate (dominicalure-II) (**1b**), the aggregation pheromones of lesser grain borer *Rhyzopertha dominica* (F)[5] (Figure 1) contain stereodefined *trans*-double bond.

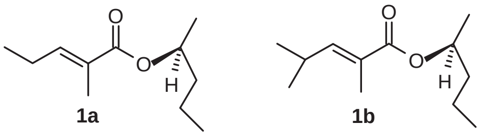
Baylis–Hillman adducts have been considered as simple synthones for stereoselective synthesis of trisubstituted alkenes.[7] However, to our knowledge, there is no method reported earlier for the synthesis of 2-methylalk-2-enoates and 2-methylalk-2-enenitriles from Baylis–Hillman adducts or their derivatives in aqueous medium. Moreover, the reported methods for the conversions of the adducts into these alkenes are associated with certain disadvantages such as utilization of expensive reagent,[7b,7d,7f,7g] limitation of applicability,[7d–7g] unsatisfactory yields,[7b,7d,7g] weak stereoselectivity,[7b,7d,7g] and formation of mixture of products.[7g]

In recent years, the application of water as a reaction medium is encouraged due to economic and environmental considerations.[8,9] We have observed that the acetyl derivatives of the Baylis–Hillman adducts (**2** and **3**) on treatment with Zn in saturated aq NH$_4$Cl solution under reflux were smoothly converted into (*E*)- and (*Z*)-trisubstituted alkenes (**4** and **5**, respectively) (Scheme 1).



**Scheme 1.**

These alkenes (**4** and **5**) were obtained as minor side products during our earlier work on zinc-mediated reactions of **2** and **3** with unactivated alkyl halides.[9] We envisaged that, without applying alkyl halides in the reaction mixture the minor side products would be emerged as desired sole products. Thus, to our expectation, we could successfully transform the liability of one reation into an asset in the present case. In fact, the present reaction of **2** and **3** with Zn in saturated aq NH$_4$Cl solution afforded only the trisubstituted alkenes **4** and **5** in (*E*)- and (*Z*)-forms (Table 1). The stereochemistry of the alkenes was directed by the electron-withdrawing groups present in the adducts. Thus, the acetyl derivatives of the adducts **2** containing ester group produced the alkenes **4** with (*E*)-stereoselectivity exclusively. On the other hand, the acetyl derivatives of the adducts **3** with nitrile moiety afforded alkenes **5** with high (*Z*)-selectivity. The *Z*/*E* ratio was determined by $^1$H NMR spectra of the crude products and the structures and stereochemistry of the products were derived from the spectral (IR, $^1$H and $^{13}$C NMR, and MS) data of the pure compounds.



**1a** **1b**

**Figure 1.**

**Table 1.** Stereoselective synthesis of (*E*)-2-methylalk-2-enoates (**4**) and (*Z*)-2-methylalk-2-enenitriles (**5**)

| Entry | R | Time/h | Yield/%[a] | *E*/*Z* ratio[c] |
|---|---|---|---|---|
| **4a** | $C_6H_5$ | 2.5 | 91 | 100:0 |
| **4b** | 2-Cl-$C_6H_4$ | 1 | 95 | 100:0 |
| **4c** | 4-Cl-$C_6H_4$ | 1.5 | 96 | 100:0 |
| **4d** | 4-OMe-$C_6H_4$ | 3 | 89 | 100:0 |
| **4e** | 3,4-$(MeO)_2$-$C_6H_3$ | 3.5 | 75 | 100:0 |
| **4f** | 2,4-$Cl_2$-$C_6H_3$ | 2 | 87 | 100:0 |
| **4g** | $CH_3$-$CH(CH_3)$-$CH_2$ | 4 | 78[b] | 100:0 |
| **4h** | *n*-$C_7H_{15}$ | 4.5 | 76[b] | 100:0 |
| **5a** | $C_6H_5$ | 4 | 79 | 10:90 |
| **5b** | 2-Cl-$C_6H_4$ | 2.5 | 83 | 9:91 |
| **5c** | 4-Cl-$C_6H_4$ | 3.5 | 86 | 13:87 |
| **5d** | 4-OMe-$C_6H_4$ | 4 | 77 | 15:85 |
| **5e** | *n*-$C_4H_9$ | 4.5 | 74[b] | 17:83 |
| **5f** | *n*-$C_7H_{15}$ | 5 | 71[b] | 22:78 |

[a] Isolated yield of products **4** (EWG= –COOMe) and **5** (EWG= –CN). [b] Zn powder (4.5 equiv.) was used while in other case Zn powder (3 equiv.) was required. [c] Ratio was determined by $^1$H NMR analysis.

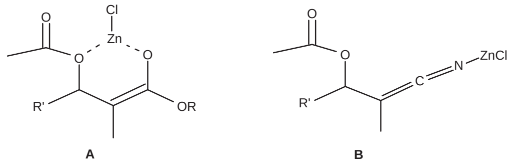
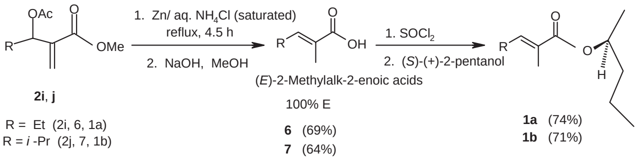


**Figure 2.** Possible intermediates to account for the observed stereoselectivity.



**Scheme 2.**

The regioselective reduction of **2** into **4** can possibly be explained by proposing the reaction to proceed via the formation of the intermediates **A** (Figure 2). This intermediate may arise by an initial SET to the conjugated enone moiety of **2** followed by protonation and the second SET process. A similar mechanism of the regioselective reduction of **3** into **5** can be proposed by involving the intermediate **B** (Figure 2). This mechanism explains the (*E*)-selectivity with ester (forming a chelated reaction intermediate, **A**) and (*Z*)-selectivity with nitriles (forming a non-chelated intermediate, **B**).

We have applied the developed methodology to achieve the synthesis of (*S*)-(+)-1-methylbutyl-(*E*)-2-methyl-2-pentenoate (dominicalure-I) (**1a**) and (*S*)-(+)-1-methylbutyl-(*E*)-2,4-dimethyl-2-pentenoate (dominicalure-II) (**1b**), the aggregation pheromones of lesser grain borer *Rhyzopertha dominica* (F).[5] The acetyl derivatives of Baylis–Hillman adducts, methyl 3-acetoxy-2-methylenepentanoate (**2i**), and methyl 3-acetoxy-2-methylene-4-methylpentanoate (**2j**), were treated with Zn (4.5 equiv.) in saturated aqueous $NH_4Cl$ solution under reflux followed by hydrolysis of the intermediate enoates[10] with methanolic NaOH in one pot to obtain (*E*)-2-methylpent-2-enoic acid (**6**), and (*E*)-2,4-dimethylpent-2-enoic acid (**7**), respectively. These two compounds (**6** and **7**) on treatment with $SOCl_2$, were converted into their corresponding acid chlorides which were then separately reacted with (*S*)-(+)-2-pentanol to form (*S*)-(+)-1-methylbutyl (*E*)-2-methyl-2-pentenoate (dominicalure-I) (**1a**) and (*S*)-(+)-1-methylbutyl (*E*)-2,4-dimethyl-2-pentenoate (dominicalure-II) (**1b**), respectively[11] (Scheme 2).

In conclusion, this methodology describes a convenient and efficient stereoselective synthesis of (*E*)- and (*Z*)-trisubstituted alkenes from acetyl derivatives of the Baylis–Hillman adducts in eco-friendly aqueous medium. The reagents are less expensive and the experimental procedure is simple. The products are formed in high yields in short reaction times. The stereoselectivity of the rection, especially with 3-hydroxy-2-methylenealkanoates is impressive. The process has successfully been applied for the synthesis of two chiral insect pheromones, (*S*)-(+)-1-methylbutyl (*E*)-2-methyl-2-pentenoate (dominicalure-I) (**1a**) and (*S*)-(+)-1-methylbutyl (*E*)-2,4-dimethyl-2-pentenoate (dominicalure-II) (**1b**), the aggregation pheromones of lesser grain borer *Rhyzopertha dominica* (F).

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10 The intermediate enoates were not isolated to avoid tedious work-up and unwanted product loss.

11 The target molecules **1a** and **1b** were both obtained as colorless oil with 74 and 71% yields, respectively with respect to their corresponding (*E*)-2-methylalk-2-enoic acid. Our spectral and optical data of these compounds are in agreement with literature data.[5a,5b]

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