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Tetrahedron Letters 45 (2004) 9225–9227
Tetrahedron Letters

An efficient stereoselective synthesis of (*E*)- and (*Z*)-trisubstituted alkenes from unactivated Baylis–Hillman adducts using $NaBH_4/CuCl_2{\cdot}2H_2O$☆

Biswanath Das,* Joydeep Banerjee, Anjoy Majhi and Gurram Mahender

Organic Chemistry Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 25 August 2004; revised 8 October 2004; accepted 14 October 2004

Abstract—A convenient and facile stereoselective synthesis of (*E*)- and (*Z*)-trisubstituted alkenes has been achieved by treatment of unactivated Baylis–Hillman adducts with $NaBH_4$ in the presence of $CuCl_2{\cdot}2H_2O$ at room temperature for 15 min.

Trisubstituted alkene moieties have been widely observed in several natural bioactive compounds including different pheromones and antibiotics.[1] The biological properties of these alkenes are highly dependent on their isomeric purity. Various trisubstituted alkenes with defined stereochemistry have also been used as key intermediates for the synthesis of other stereospecific compounds.[2] Thus a limited number of methods have been developed for stereoselective preparation of trisubstituted alkenes.[2,3] Here we present our efforts toward the synthesis of (*E*)- and (*Z*)-trisubstituted alkenes from the unactivated Baylis–Hillman adducts, 3-hydroxy-2-methylene-alkanoates **1** and 3-hydroxy-2-methylene-alkanenitriles **2**.

The Baylis–Hillman reaction involves the coupling of activated vinylic systems with electrophiles under the catalytic influence of a tertiary amine, usually DABCO.[4] The adducts **1** (derived from acrylate esters) and **2** (derived from acrylonitrile) have been utilized for stereoselective syntheses of various functionalized molecules.[4b,5] In continuation of our work[6] on the synthesis of trisubstituted alkenes derived from Baylis–Hillman adducts we have studied the effect of the reactions of these adducts with a combination of $NaBH_4$ and a metallic chloride.[7]

We initially observed that treatment of **1** with $NaBH_4$ alone afforded a mixture of trisubstituted alkene **3**, the corresponding 1,3-propane diol and the saturated alcohol in the approximate ratio of 5:2:3. Previously the reaction of **1** with $NaBH_4$ was reported[8] to yield the corresponding 1,3-propane diols as the major products. During the present study we first considered the reduction of **1b** (R = 2-Cl–C_6H_4 and EWG = –COOMe) with $NaBH_4$ in the presence of different metallic chlorides to examine the variation of yields of the products (Table 1). It was observed that $NaBH_4$ in combination with a metallic chloride (except with LiCl) afforded the trisubstituted alkene, **3b** as the major product along with the corresponding saturated alcohol in minor amounts (~5%). $CuCl_2$ is the metallic chloride of choice in terms

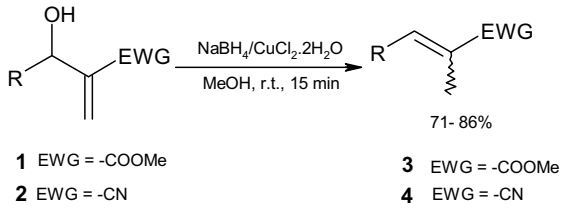
Table 1. Reduction of **1b** (R = 2-Cl–C_6H_4, EWG = –COOMe) with $NaBH_4$ in the presence of different metallic chlorides[a]

Entry	Metal ion	Isolated yield (%) of alkene[b]
1	Li^+	15
2	Cu^{2+}	82
3	Co^{2+}	70
4	Ni^{2+}	72
5	Zn^{2+}	7
6	Al^{3+}	12
7	In^{3+}	55
8	Ce^{3+}	68

[a] Treatment of **1b** (1 equiv) with $NaBH_4$ (1.5 equiv) and $CuCl_2{\cdot}2H_2O$ (1.5 equiv) in methanol at room temperature for 15 min.
[b] In entry 1 the corresponding 1,3-propane diol was the major product (76%); the corresponding saturated alcohol was formed as a minor product (~5%) in each case.

Keywords: Unactivated Baylis–Hillman adduct; (*Z*)- and (*E*)-Trisubstituted alkenes; $NaBH_4/CuCl_2{\cdot}2H_2O$; Metallic halides; Stereochemistry.
☆ Part 55 in the series, Studies on Novel Synthetic Methodologies.
* Corresponding author. Tel./fax: +91 40 7160512; e-mail: biswanathdas@yahoo.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.088



Scheme 1.

of the yield of the alkene (Scheme 1). The activity of $NiCl_2$, $CoCl_2$, and $CeCl_3$ in combination with $NaBH_4$ is somewhat weak while that of $ZnCl_2$ and $AlCl_3$ is poor. Reduction with $NaBH_4/InCl_3$ produced **3b** in 55% yield. However, due to the stronger reducing capacity,[9] $NaBH_4$ in the presence of LiCl produced the corresponding 1,3-propane diol as the major product (76%) along with **3b** (15%) and the saturated alcohol (9%).

Previously the trisubstituted alkenes **3** were prepared from the unactivated Baylis–Hillman adducts **1** by treatment with a low-valent titanium reagent[10a] or SmI_2.[10b] In the first case the conversion was conducted under reflux and the yields (50 or <50%) were unsatisfactory. In the second case trisubstituted alkenes **3** were prepared along with 1,5-hexadiene derivatives at various temperatures, and at low temperature the yields of the former were poor.

In order to generate a series of trisubstituted alkenes the Baylis–Hillman adducts, 3-hydroxy-2-methylene-alkanoates **1** and 3-hydroxy-2-methylene-alkanenitriles **2** were treated with $NaBH_4/CuCl_2{\cdot}2H_2O$ in methanol.[11] The reaction was conducted for 15 min at room temperature. The trisubstituted alkenes (**3** and **4**, respectively) were formed in high yields (Table 2). The stereochemistry of the products was easily determined[4b] from the ^1H NMR spectra and the ratio of (*E*)- and (*Z*)-isomers was determined from the ^1H NMR spectra of the crude products. It was observed that the product **3** was formed with (*E*)-configuration while product **4** was obtained with high (*Z*)-selectivity (Table 2).

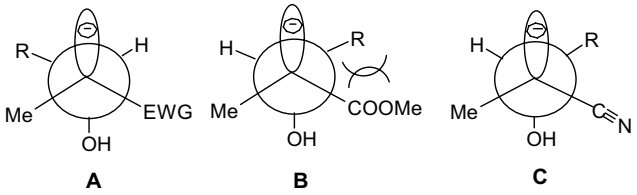
Table 2. Synthesis of (*E*)- and (*Z*)-trisubstituted alkenes **3** and **4** using $NaBH_4/CuCl_2{\cdot}2H_2O$[a]

Entry	R	EWG	Isolated yield[b] (%)	*E*:*Z*
3a	C_6H_5	COOMe	86	100:0
3b	2-Cl–C_6H_4	COOMe	82	100:0
3c	4-Cl–C_6H_4	COOMe	81	100:0
3d	2,4-Cl_2–C_6H_3	COOMe	78	100:0
3e	4-MeO–C_6H_4	COOMe	77	100:0
3f	CH_3–$CH(CH_3)$–CH_2–	COOMe	75	100:0
4a	C_6H_5	CN	83	12:88
4b	2-Cl–C_6H_4	CN	80	10:90
4c	4-Cl–C_6H_4	CN	78	14:86
4d	4-MeO–C_6H_4	CN	74	15:85
4e	*n*-C_4H_9	CN	71	18:82

[a] The structures of the alkenes were determined from their spectral (^1H NMR and MS) data.

[b] The corresponding saturated alcohol was formed as a minor product (~5%) in each case.

The stereochemistry of the reaction can possibly be explained by considering the transition state models **A**, **B**, and **C**. Transition state **A** is more favored than **B** when EWG = –COOMe and (*E*)-products are thus formed, exclusively. On the other hand, **C** is somewhat more favored than **A** when EWG = –CN, as –CN is linear and hence (*Z*)-products are formed predominantly.



In conclusion, we have developed a simple and efficient methodology for the stereoselective synthesis of (*E*)- and (*Z*)-trisubstituted alkenes from unactivated Baylis–Hillman adducts by treatment with $NaBH_4$ in the presence of $CuCl_2{\cdot}2H_2O$. The reducing system can easily be prepared from readily available and inexpensive reagents. The mild reaction conditions, experimental simplicity, short reaction time, and high yields as well as selectivity are the main advantages of the present protocol. The synthesis of some bioactive naturally occurring molecules applying this methodology is currently under progress in our laboratory.

Acknowledgements

The authors thank CSIR and UGC, New Delhi for financial assistance.

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11. General experimental procedure: The Baylis–Hillman adduct (**1** or **2**) (2 mmol) and $CuCl_2{\cdot}2H_2O$ (3 mmol) were dissolved in MeOH (5 mL) and the mixture stirred for 5 min. $NaBH_4$ (3 mmol) was added in small portions with stirring. A vigorous gas evolution occurred and the temperature of the mixture increased (35–40 °C). Stirring was continued for 15 min. Saturated aqueous NH_4Cl solution was added to neutralize the reaction mixture. The mixture was extracted with ether (3×10 mL), the combined organics dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to column chromatography over silica gel using 5% EtOAc in hexane as eluent to afford pure trisubstituted alkene. The spectroscopic data of two representative alkenes are given below.
3b: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.72 (1H, s), 7.41 (1H, dd, J = 8.0, 2.0 Hz), 7.32–7.20 (3H, m), 3.83 (3H, s), 1.98 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 168.5, 136.0, 134.1, 131.2, 130.4, 129.6, 129.4, 127.8, 126.4, 52.1, 14.0; EIMS: *m/z* 210, 212 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.71; H, 5.23. Found: C, 62.78; H, 5.28.
3f: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.76 (1H, t, J = 7.0 Hz), 3.70 (3H, s) 2.08 (2H, t, J = 7.0 Hz), 1.82 (3H, s), 1.71 (1H, m), 0.94 (6H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 168.4, 141.6, 130.8, 51.6, 31.9, 28.3, 22.5, 14.1; EIMS: *m/z* 156 ($M^{+\cdot}$); Anal. Calcd for $C_9H_{16}O_2$: C, 69.23; H, 10.26. Found: C, 69.14; H, 10.31.