A Practical and Stereoselective Synthesis of Cinnamyl Alcohols Bearing α-Cyano or α-Ester Functional Group from Baylis-Hillman Adducts

Ka Young Lee, Saravanan GowriSankar, and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
Received December 18, 2003

Key Words : Cinnamyl alcohols, Baylis-Hillman adducts, Sulfuric acid, Acetic anhydride

Cinnamyl alcohols bearing ester, acid, or nitrile functional group at the 2-position are very useful synthons for the synthesis of various biologically important compounds.[1]

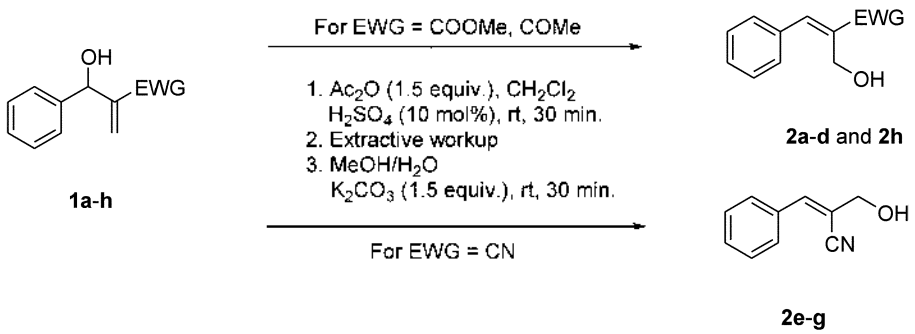
Synthesis of cinnamyl alcohol derivatives from the Baylis-Hillman adducts has been reported by us and other groups.[1-4] The conversion can be carried out directly by using 20% aqueous sulfuric acid (for the Baylis-Hillman adducts derived from acrylonitrile)[2] or trifluoroacetic acid (for the Baylis-Hillman adducts derived from acrylates).[3] Recently, Basavaiah and coworkers have reported the two-step, one-pot conversion method: TMSOTf-assisted conversion of Baylis-Hillman alcohol into the corresponding primary acetate with acetic anhydride and the following partial hydrolysis with K_2CO_3 in methanol.[1a]

In the above chemical transformation, the conversion of secondary acetate into the primary one is the key step. Rearrangement of secondary acetate into the primary one was conducted by following reaction conditions such as DABCO/THF/reflux,[5] montmorillonite K10 clay/microwave,[4] and TMSOTf (cat.)/CH_2Cl_2.[1a,6] Direct conversion of Baylis-Hillman alcohol into the corresponding primary acetate can be carried out by the Basavaiahs method: acetic anhydride in the presence of TMSOTf.[1a] However, TMSOTf is a moisture-sensitive and somewhat expensive reagent. During the preparation of Baylis-Hillman acetate, we found that the use of acetic anhydride in the presence of a catalytic amount of sulfuric acid in CH_2Cl_2 afforded directly the corresponding primary acetate in excellent yield.[7]

In these regards we envisioned that we could develop the more convenient and practical method to convert the Baylis-Hillman alcohol into the primary acetate or eventually to primary alcohol (Scheme 1 and Table 1).

The reaction of Baylis-Hillman adducts with acetic anhydride (1.5 equiv.) in the presence of sulfuric acid (10 mol%) gave the corresponding rearranged cinnamyl acetates quantitatively in dichloromethane at room temperature within 30 min (Actually, the cinnamyl acetate derivatives could be isolated in 92-95% yields.). In order to obtain the corresponding cinnamyl alcohols in a one-pot we tried some reaction conditions for the next partial hydrolysis. Addition of water to the reaction mixture (two-phase system) afforded the hydrolyzed cinnamyl alcohols in trace amounts. The use of THF instead of CH_2Cl_2 showed better results in the hydrolysis step. However, neither the acetylation in THF nor the subsequent acidic hydrolysis in aq. THF was efficient. As a next choice, we used methanol as solvent after the formation of rearranged acetate in CH_2Cl_2 and added K_2CO_3. However, this process showed incomplete reaction and produced some side products. Thus, we finally adapted the two-step procedure involving the well-known hydrolysis protocol, K_2CO_3 in methanol, after simple workup process of the primary acetates (vide infra).

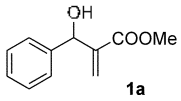
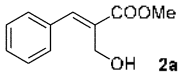
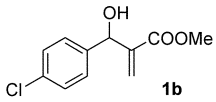
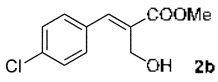
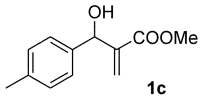
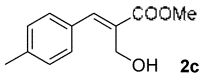
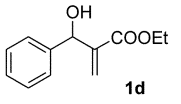
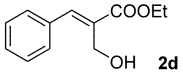
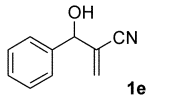
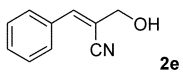
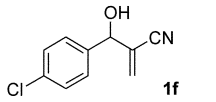
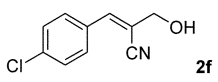
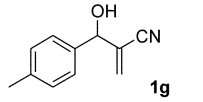
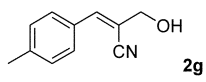
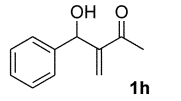
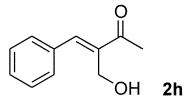
The representative examples are shown in Table 1. As shown in Table 1, the method can be applicable to both of the Baylis-Hillman adducts derived from acrylates or acrylonitrile. The yields are higher than the reported in all cases.[1-4] The formation of the cinnamyl alcohols is highly stereoselective (*E* for the ester and acetyl derivatives and *Z* for the nitrile analogs) as reported.[1-4] The method has some advantages over the previous methods: (1) higher yields in



Scheme 1

*Corresponding Author: Phone: +82-62-530-3381, e-mail: kimjn@chonnam.ac.kr

Table 1. Synthesis of cinnamyl alcohols **2a-h**

entry	substrate	products	yields (%)[a]
1	 **1a**	 **2a**	72 (61)[1a]
2	 **1b**	 **2b**	79 (69)[1a]
3	 **1c**	 **2c**	74 (60)[1a]
4[b]	 **1d**	 **2d**	67 (55)[3]
5	 **1e**	 **2e**	71 (27),[3] (60)[2]
6	 **1f**	 **2f**	78 (62)[2]
7	 **1g**	 **2g**	69 (31),[3] (68)[2]
8	 **1h**	 **2h**	82

[a]Reported yields in the parenthesis. [b]When we used ethanol instead of methanol, reaction time was 5 h.

all cases, (2) general applicability to the Baylis-Hillman adducts bearing nitrile, ester, and acetyl functional group, (3) short reaction time and mild reaction conditions, (4) the use of cheap and easily available reagent.

In summary, we have developed an efficient method transforming the Baylis-Hillman adducts into the corresponding cinnamyl alcohol derivatives via the simple operations: sulfuric acid-mediated simultaneous acetylation and rearrangement followed by partial hydrolysis protocol.

Experimental Section

General procedure for the synthesis of cinnamyl alcohols: To a well-stirred solution of Baylis-Hillman alcohol (2 mmol) and acetic anhydride (320 mg, 3 mmol) in CH_2Cl_2 (5 mL) at room temperature was added H_2SO_4 (20 mg, 10 mol%) and stirred for 30 min. TLC showed complete formation of the corresponding primary acetate. The reaction mixture was poured into cold water (30 mL) and extracted with ether (3 × 40 mL). The combined organic layer was washed with brine. After drying with $MgSO_4$ solvent was removed under reduced pressure. The crude reaction mixture was dissolved in aq. MeOH (H_2O/MeOH, 1 : 2, 5 mL), added K_2CO_3 (420 mg, 3 mmol), and stirred at room temperature for 30 min. After usual workup and purification by flash column chromatography (hexanes/ether, 4 : 1), we obtained cinnamyl alcohols. Compounds **2a-g** were identified by their reported ^{1}H NMR data.[1a,2,3] The spectroscopic data of the acetyl derivative **2h** are as follows. **2h**: IR (KBr) 3475, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 2.88 (br s, 1H), 4.46 (d, J = 4.8 Hz, 2H), 7.35-7.50 (m, 5H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.7, 57.2, 128.6, 129.4, 129.6, 134.4, 139.8, 143.1, 201.3.

Acknowledgments. This work was supported by the grant (R05-2003-000-10042-0) from the Basic Research Program of the Korea Science & Engineering Foundation. Spectroscopic data was obtained from the Korea Basic Science Institute, Kwangju branch.

References and Notes

1. (a) Basavaiah, D.; Padmaja, K.; Satyanarayana, T. *Synthesis* **2000**, 1662 and further references cited therein. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
2. Basavaiah, D.; Kumaragurubaran, N.; Padmaja, K. *Synlett* **1999**, 1630.
3. Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613.
4. (a) Shanmugam, P.; Singh, P. R. *Synlett* **2001**, 1314. (b) Shanmugam, P.; Rajasingh, P. *Chem. Lett.* **2002**, 1212.
5. Mason, P. H.; Emslie, N. D. *Tetrahedron* **1994**, *50*, 12001.
6. Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synthesis* **2000**, 545.
7. Unpublished results.