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Synthesis of stereochemically defined (*E*)-cinnamyl alcohol derivatives from the Baylis–Hillman adducts

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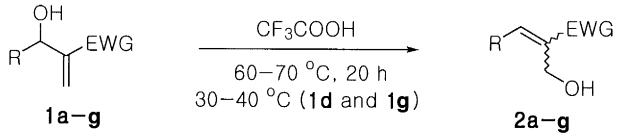
Abstract

The reaction of the Baylis–Hillman adducts **1a**–**g** and trifluoroacetic acid at 30–70°C gave the rearranged cinnamyl alcohols **2a**–**g** stereoselectively in moderate yields.

Keywords: allylic alcohols; Baylis–Hillman adducts; trifluoroacetic acid.

The Baylis–Hillman reaction is one of the most powerful carbon–carbon bond-forming methods in organic synthesis.[1] The Baylis–Hillman adducts, which are allylic alcohol derivatives, can be formed most often by the reaction of activated vinyls and carbonyl compounds.[1] Besides the usefulness of these Baylis–Hillman adducts themselves, further derivatization with various nucleophilic reagents toward synthetically useful compounds has been studied in depth by us and other groups.[2]



Scheme 1.

The Baylis–Hillman adducts **1** have secondary allylic alcohol functionality, which can be rearranged to the thermodynamically more stable primary allylic alcohols **2**. The synthesis of **2** which has cinnamyl alcohol moiety is important because it constitutes an important class of synthons for the synthesis of various biologically active molecules.[3] However, synthesis of **2** from **1** has been achieved by indirect three step method, that is a tandem bromination–formylation–hydrolysis.[4a–b] The Mitsunobu type reaction of the Baylis–Hillman adducts with appropriate carboxylic acid can also be used to form esters of the rearranged allylic alcohols.[4c] Quite recently, Basavaiah et al. have reported an aqueous sulfuric acid mediated isomerization of the nitrile-containing Baylis–Hillman adducts (vide infra).[4d]

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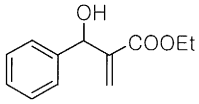
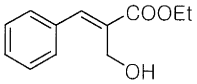
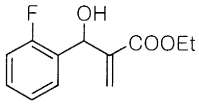
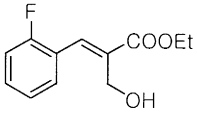
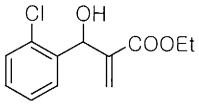
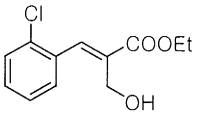
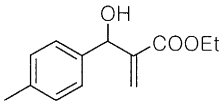
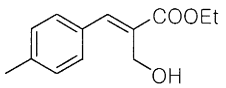
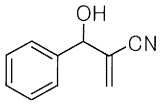
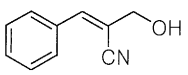
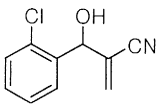
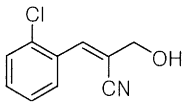
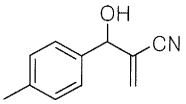
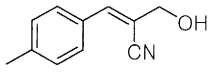
They obtained (*E*)-α-cyanocinnamyl alcohols in 52–68% isolated yields. However, there were no comments on the reaction of ester-containing Baylis–Hillman adducts.

Table 1
Synthesis of allylic alcohols **2a–g**[a]

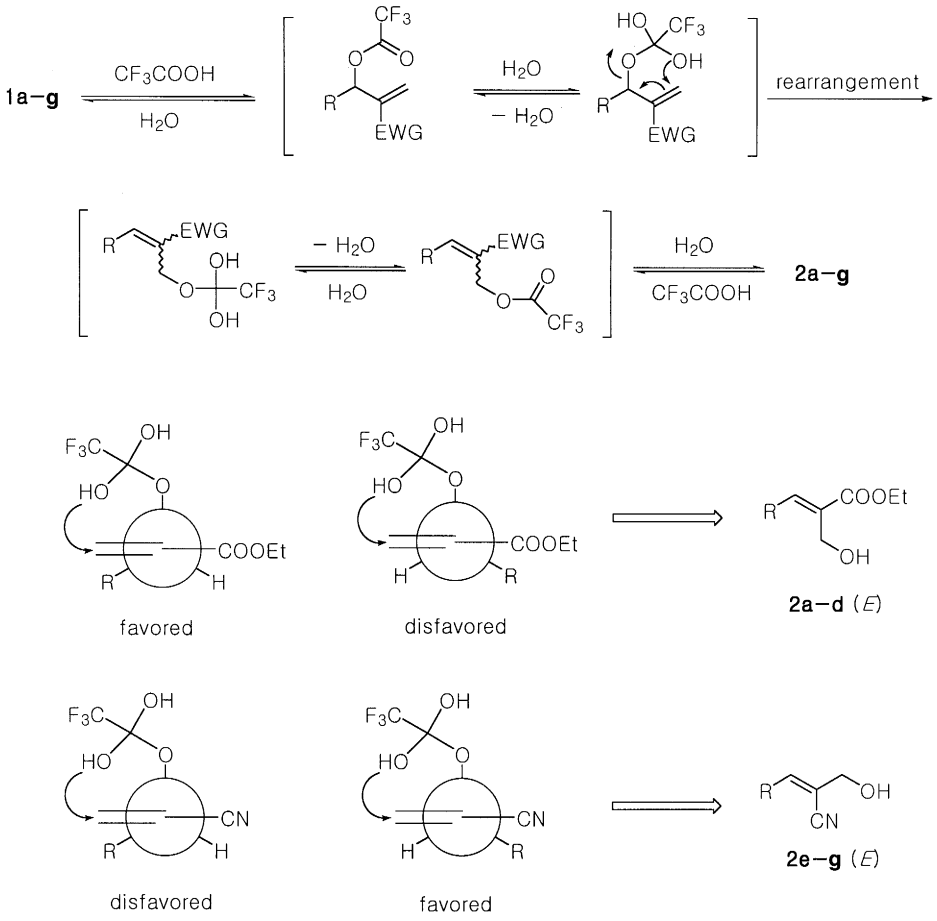
entry	B–H adducts (**1**)		products (**2**)[b]		yield (%)[c]
1		**1a**		**2a**(*E*)	51
2		**1b**		**2b**(*E*)	70
3		**1c**		**2c**(*E*)	72
4		**1d**		**2d**(*E*)	66
5		**1e**		**2e**(*E*)	27
6		**1f**		**2f**(*E*)	40
7		**1g**		**2g**(*E*)	31

[a]All reactions were carried out on a 2 mmol scale of **1a–g**. [b]^{1}H and ^{13}C NMR spectra indicate the absence of any *Z*-isomer. [c]Isolated yields of products after column chromatography.

In these contexts, we felt that it will be highly useful if the Baylis–Hillman adducts can be transformed directly into α-ethoxycarbonylcinnamyl alcohols in a stereoselective manner. After some trials we were able to develop a facile method using trifluoroacetic acid and report herein the preliminary results.

As shown in Scheme 1 and Table 1, the Baylis–Hillman adducts **1** in trifluoroacetic acid at 30–70°C for 20 h gave the rearranged allylic alcohols **2a–d** in 51–72% yields.[5] The rearrangement might proceed via the trifluoroacetate or its hydrate form as shown in Scheme 2. Subsequent in situ hydrolysis of the trifluoroacetate of rearranged alcohols gave **2a–d**.[5] The reaction of **1a** in acetic acid did not produce

2a at all. The reaction of **1d** in formic acid gave rearranged alcohol **2d** (8%, *E*) and the corresponding rearranged formate ester (75%, *E*) as the major products. The formate ester relative to the trifluoroacetate ester is much more resistant to hydrolysis.[6] Ester derivatives **1a**–**d** gave *E*-form allylic alcohols **2a**–**d** stereoselectively. We could not isolate *Z*-form isomer which might be present in trace amounts in the reaction mixtures.



Scheme 2.

The assignment of the *E*-*Z* stereochemistry was based on the ^{1}H NMR and ^{13}C NMR data of the published ones.[4,5]

However, in the cases of nitrile derivatives **1e**–**g** lower yields (27–40%) of **2e**–**g** (again *E*-form due to inversion of priority of the substituents) were obtained with some unidentified polar compounds. As mentioned earlier, Basavaiah et al. have reported the aqueous sulfuric acid mediated rearrangement of the nitrile-containing Baylis–Hillman adducts such as **1e** and **1g**.[4d] In order to compare the applicability of these two methods (Basavaiah's and ours), we examined the reaction of **1e** and **1a** in aqueous sulfuric acid. The reaction of **1e** in Basavaiah's conditions (20% aq. sulfuric acid, reflux, 4 h) gave 72% yield of stereochemically pure *E*-allylic alcohol derivative **2e**. However, ester derivative **1a** in aqueous sulfuric acid showed complex mixtures containing a low yield of **2a**. From these results, we think that the Basavaiah's method works well in nitrile-containing adducts (for *E*-selective nitriles) while the trifluoroacetic acid method works well with ester-containing adducts (for *E*-selective esters). Thus,

these two methods are thought to be complementary to each other for the preparation of stereochemically defined cinnamyl alcohols.

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5. General procedure for the preparation of **2**: a stirred solution of **1** (2 mmol) in CF_3COOH (2 mL) was heated to 60–70°C (30–40°C for **1d** and **1g**) during 20 h. The reaction mixture was poured into cold water and extracted with ether. The organic layers were washed with water, dried with $MgSO_4$, evaporated to dryness. Column chromatography on silica gel (EtOAc:hexane, 1:10) of the crude product mixtures gave pure **2**. Unhydrolyzed trifluoroacetate derivatives of **2** were hydrolyzed readily to **2** during separation by column chromatography. Some selected spectroscopic data of **2a** and **2e** are as follows. Compound **2a**: clear oil; IR (neat) 3465, 1713, 1640, 1277 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, *J*=7.2 Hz, 3H), 2.62 (brs, 1H, OH), 4.25 (q, *J*=7.2 Hz, 2H), 4.41 (s, 2H), 7.30–7.42 (m, 5H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.29, 57.97, 61.13, 128.55, 129.14, 129.54, 131.18, 134.56, 142.24, 167.97; mass (70 eV) *m/z* (rel. intensity) 55 (40), 77 (58), 131 (100), 132 (44), 133 (39), 160 (24), 177 (31), 206 (M^+, 17). Compound **2e**: clear oil; IR (neat) 3408, 2215, 1626, 1449, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (brs, 1H, OH), 4.42 (d, *J*=1.2 Hz, 2H), 7.21 (s, 1H), 7.40–7.45 (m, 3H), 7.73–7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 64.29, 110.53, 117.72, 128.84 (2C), 130.52, 132.95, 143.82; mass (70 eV) *m/z* (rel. intensity) 51 (51), 77 (50), 78 (55), 91 (60), 102 (31), 103 (36), 130 (100), 159 (M^+, 76).
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