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Isomerization of the Baylis-Hillman adducts using amberlyst-15 as a heterogeneous reusable catalyst: a simple and efficient stereoselective synthesis of (*E*)-cinnamyl alcohol derivatives[†]

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The Baylis-Hillman adducts, 3-aryl-3-hydroxy-2-methylene-alkanoates and 3-aryl-3-hydroxy-2-methylene-alkanenitriles have been efficiently isomerized to the corresponding (*E*)-cinnamyl alcohols by treatment of the adducts with Ac_2O in the presence of Amberlyst-15 followed by hydrolysis of the intermediate acetates with K_2CO_3/MeOH. The first step occurs under solvent-free conditions and the catalyst has been found to be reusable.

Keywords: Baylis-Hillman adduct, cinnamyl alcohol, Amberlyst-15, isomerization, stereoselective synthesis, heterogeneous reusable catalyst

IPC: **Int**.**Cl**.^{8}**C07C**

The Baylis-Hillman reaction involves the coupling of activated vinylic system with electrophiles in the presence of a Lewis base (usually DABCO) as a catalyst[1]. The adducts of the reaction, 3-hydroxy-2-methylene-alkanoates (derived from acrylate esters) and 3-hydroxy-2-methylene-alkanenitriles (derived from acrylonitrile) have been utilized for the stereoselective synthesis of various polyfunctional molecules[1b, 2].

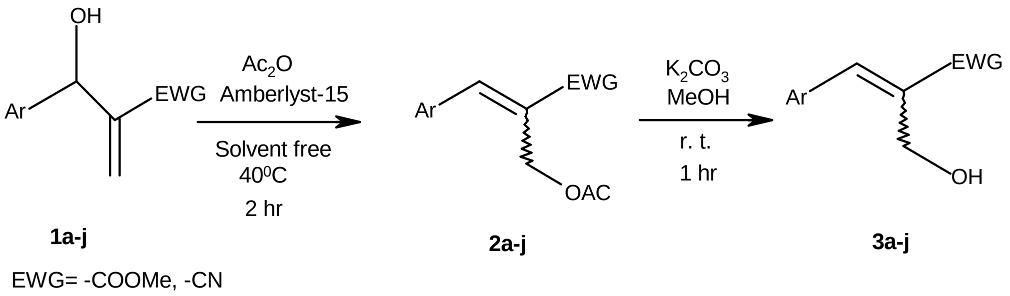
In continuation of our work[3] on the synthesis of trisubstituted alkenes we have observed that the Baylis-Hillman adducts generated from aromatic aldehydes can efficiently be isomerized into the corresponding cinnamyl alcohols. Various cinnamyl alcohols are important synthons for the synthesis of different biologically active molecules[4]. However, there are a limited number of methods for isomerization of the Baylis-Hillman adducts to form the cinnamyl alcohols. Some of the reported methods (bromination-formylation-hydrolysis[5a], bromination-acetylation-hydrolysis[5b] and treatment with DEAD/PPh_3 followed by hydrolysis[5c]) require two to three separate steps to get the desired products.

Some other methods[6a,b] have been mentioned for isomerization of only ester-containing adducts or of nitrile-containing adducts. CF_3COOH (a strong acid) was used[7] directly under reflux for 20 hr for isomerization of the Baylis-Hillman adducts but the yield of the products from the adducts derived from acrylonitriles were low (27-40%). Montmorillonite K-10 was also applied[8] for isomerization of the acetates of the Baylis-Hillman adducts under microwave irradiation. Though the conversion was attempted with an activated form of Baylis-Hillman adducts the catalyst did not work at room temperature and also at 40ºC even after 24 hr.

Recently, we develop an efficient isomerization of the Baylis-Hillman adducts **1** by treatment with Ac_2O in the presence of Amberlyst-15 at 40ºC under solvent-free conditions followed by hydrolysis of the intermediate acetates **2** with K_2CO_3/MeOH to produce the cinnamyl alcohols **3** (**Scheme I**).

At the initiation of the programme the Baylis-Hillman adduct, **1a** (R= Ph, EWG= -COOMe) was treated with Ac_2O in the presence of various heterogeneous catalysts like montmorillonite K-10, KSF clay, HY-zeolite and Amberlyst-15 to study which will produce best the rearranged primary acetate, **2a** (**Table I**). Interestingly, the first three catalysts did not form the rearranged acetate at room temperature and even at 40ºC. On the other hand, Amberlyst-15 catalyzed the acetylation to form 61%

[†] Part 58 in the series, “Studies on novel synthetic methodologies”.



Scheme I

Table I—Acetylation of **1a** (Ar = Ph, EWG = -COOMe) using different heterogeneous catalysts

Entry	Catalyst	Conditions	Product	Yield (%)
1	Mont K-10	Neat, r. t., 2 hr	a	62
			b	0
		Neat, 40ºC, 4 hr	a	91
			b	0
2	KSF clay	Neat, r. t., 2 hr	a	63
			b	0
		Neat, 40ºC, 5 hr	a	86
			b	0
3	HY-Zeolite	Neat, r. t., 2 hr	a	54
			b	0
		Neat, 40ºC, 4 hr	a	71
			b	0
4	Amberlyst-15	Neat, r. t., 2 hr	a	61
			b	32
		Neat, 40ºC, 2 hr	a	8
			b	89

a : corresponding secondary acetate
b : rearranged primary acetate

of the secondary acetate and 32% of the primary acetate at room temperature while 8 and 89% of the secondary and primary acetates, respectively at 40ºC. Thus, we feel that Amberlyst-15 at 40ºC can properly be utilized to carry out the acetylation of the Baylis-Hillman adducts, **1** to the corresponding primary acetates, **2**. During our present study several 3-aryl-3-hydroxy-2-methylene-alkanoates, **1a-e** and 3-aryl-3-hydroxy-2-methylene-alkanenitriles, **1f-i** were converted into the corresponding cinnamyl alcohols, **3a-e** and **3f-i** respectively (**Table II**) following the reaction sequence shown in **Scheme I**. The conversion of **1** into **3** occurred smoothly. The intermediate acetates **2** were freed from the catalyst by dissolving in MeOH followed by filtration and subsequently these acetates were hydrolysed with K_2CO_3/MeOH. The yields of the cinnamyl alcohols **3** were very high (71-85%). The stereochemistry of **3** could easily be settled from the ^{1}H and ^{13}C NMR spectra of the compounds and the ratio of (*E*)- and (*Z*)- was determined from the ^{1}H NMR spectra of the crude products[6, 7]. It was observed that the cinnamyl alcohols were formed here with high (*E*)- selectivity (**Table II**).

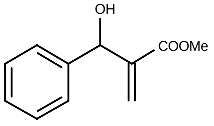
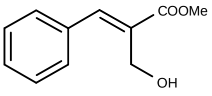
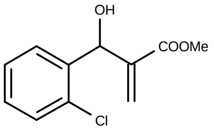
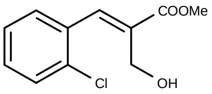
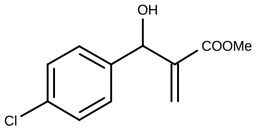
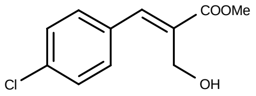
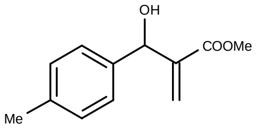
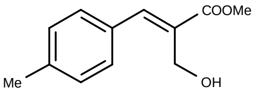
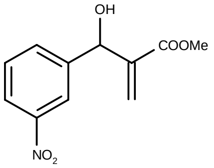
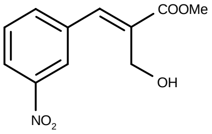
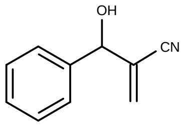
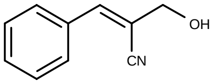
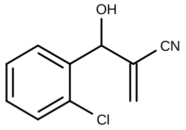
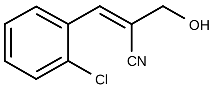
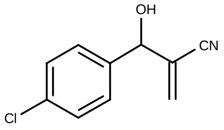
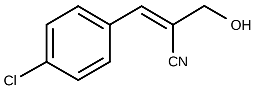
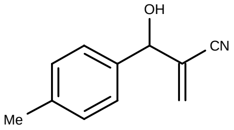
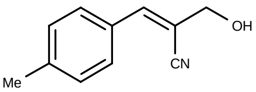
The plausible mechanism of the formation of the allyl primary acetates, **2** from the allyl secondary alcohol, **1** is shown in **Scheme II**. Compounds **2** are thermodynamically more stable than the acetates corresponding to compounds **1** and so the latter acetates rearranged facilely to form **2**.

The stereochemistry of the conversion can possibly be explained by considering the favourable transition state models **A** and **B**, which suggest the formation of (*E*)-cinnamyl alcohols predominantly in the present reaction.

The catalyst, Amberlyst-15 works under heterogeneous condition. It can easily be handled and removed from the reaction mixture. It was reused for three consecutive times after activation with a little variation of the yields of the acetates **2** (**Table III**).

In conclusion, we have developed a simple and efficient protocol for stereoselective synthesis of (*E*)-cinnamyl alcohols starting from Baylis-Hillman

Table II—Synthesis of cinnamyl alcohols*

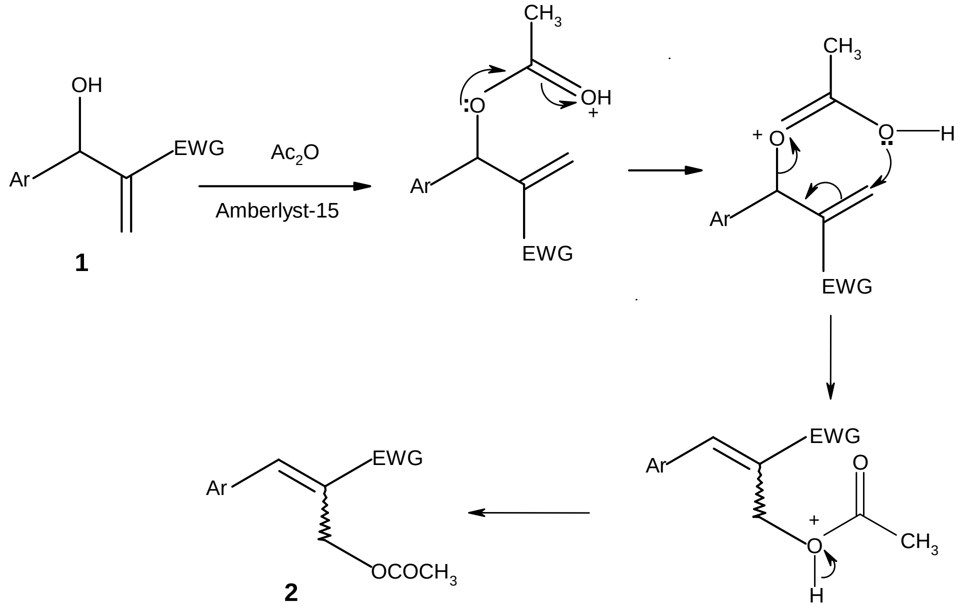
Entry	Baylis-Hillman adduct	Product	Overall yield (%)	*E*/*Z*	Ref.
a			85	92:8	6a
b			82	95:5	
c			79	90:10	6a
d			76	93:7	6a
e			71	91:9	
f			83	98:2	6b
g			80	96:4	7
h			77	92:8	6b
i			75	97:3	6b

*The structures of the products were settled from their spectral (IR, ^{1}H and ^{13}C NMR and MS) and analytical data

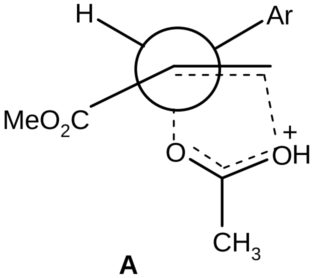
adducts containing both ester and nitrile moieties. The simple experimental procedure, utilization of a heterogeneous recyclable catalyst and high yields and stereoselectivity of the products are the advantages associated with the protocol. The application of the method for synthesis of some naturally occurring bioactive (*E*)-cinnamyl alcohols is under progress in our laboratory.

Experimental Section

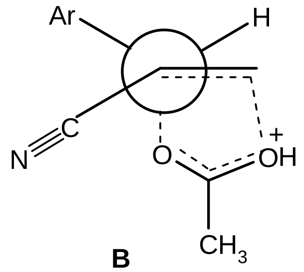
IR spectra were recorded on a Perkin-Elmer RX1 FR-IR spectrophotometer; ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard; and mass spectra in a VG Micromass 7070 H (70 eV). Column chromatography was performed with silica gel (100-200 mesh) and TLC with silica gel GF$_{254}$.



Scheme II



A



B

Typical experimental procedure

To a mixture of Baylis-Hillman adduct (5 mmoles) and Ac$_2$O (7 mmoles) Amberlyst-15 (30% w/w of the adduct) was added. The neat reaction mixture was stirred and heated at 40ºC for 2 hr. MeOH (3 × 5 mL) was added and filtered to recover the catalyst which could be reused. K$_2$CO$_3$ (15 mmoles, 2.07 g) was added to the reaction mixture which was stirred for 1 hr at room temperature. MeOH was removed under reduced pressure and the residue was diluted with water (10 mL) followed by extraction with Et$_2$O (3 × 10 mL). The solvent was evaporated and the residue was purified by column chromatography using EtOAc 10% in hexane to obtain cinnamyl alcohol derivative.

The spectral (IR, ^{1}H and ^{13}C NMR and MS) and analytical data of the unknown compounds are given below.

Methyl-(2*E*)-2-(hydroxymethyl)-3-(2-chlorophenyl)-propenoate (3b, Table II). Viscous; IR (KBr): 3478, 2951, 1718, 1471, 1437, 1219, 1107, 1020, 771 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.86 (1H, s), 7.57 (1H, dd, *J* = 8.0, 2.0 Hz), 7.41 (1H, dd, *J* = 8.0, 2.0 Hz), 7.32-7.25 (2H, m), 4.32 (2H, s), 3.88 (3H, s); ^{13}C NMR (CDCl$_3$): δ 168.0, 139.3, 134.2, 132.5, 130.9, 130.3, 129.6, 128.9, 126.8, 58.0, 52.3; EI-MS: m/z (%) 228 (M$^{+\cdot}$, 1), 226 (M$^{+\cdot}$, 3), 191 (100), 165 (12), 131 (17), 101 (15); Anal. Calcd. for $C_{11}H_{11}ClO_3$: C, 58.27; H, 4.86%. Found: C, 58.33; H, 4.81%.

Methyl-(2*E*)-2-(hydroxymethyl)-3-(3-nitrophenyl)-propenoate (3e, Table II). Viscous; IR (KBr): 3450, 2923, 2854, 1717, 1530, 1460, 1351, 1238, 743 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 8.30 (1H, s), 8.21 (1H, dd, *J* = 8.0, 2.0 Hz), 7.86 (1H, dd, *J* = 8.0, 2.0 Hz), 7.79 (1H, d, *J* = 2.0 Hz), 7.62 (1H, t, *J* = 8.0 Hz), 4.33 (2H, s), 3.84 (3H, s); ^{13}C NMR (CDCl$_3$): δ 167.9, 148.2, 140.0, 135.1, 132.2, 129.5, 129.0, 124.6, 123.5, 57.7, 52.4; EI-MS: m/z (%) 237 (3), 208 (8), 178 (7), 149 (45), 103 (22); Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.64%. Found: C, 55.62; H, 4.72%.

Acknowledgements

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