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Water-promoted highly regio- and stereoselective synthesis of α-dehydro-β-amino esters and nitriles from Baylis–Hillman acetates

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ABSTRACT

The nucleophilic addition of amines to Baylis–Hillman acetates has been efficiently carried out in water at room temperature in the absence of any base, acid, or metal catalyst to produce α-dehydro-β-amino esters and nitriles. This procedure addresses a variety of aliphatic open-chain and cyclic amines and anilines. All the reactions are highly regio- and stereoselective, fast and high yielding.

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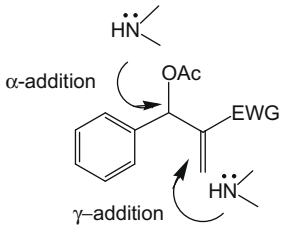
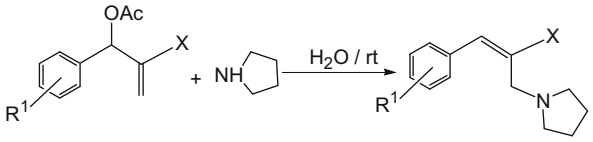
The Baylis–Hillman adducts constitute very useful and versatile synthons toward the synthesis of a variety of carbocycles, heterocycles, and biologically active molecules and thus have received considerable attention.[1] However, nucleophilic addition to Baylis–Hillman adducts having several active functionalities is also very complicated because of the regio- and stereochemical implications.[2] The reaction of an amine and an acetate of Baylis–Hillman adduct is a convenient route to the synthesis of α-dehydro-β-amino esters which are useful precursors to indenoquinoline derivatives, β-amino acids, β-lactams, and uracils.[3] However, in principle, a nucleophilic attack by an amine may take place at the γ- or at the α-carbon of BH adduct generating two regioisomers associated with two stereoisomers for each (Scheme 1). A number of procedures involving a variety of reagents such as ceric ammonium nitrate (THF, 65 °C, 3 h),[4a] AgOTf (CH_2Cl_2, reflux, 1–24 h),[4b] MeOH (rt, 4–18 h),[4c,d] $Pd(PPh_3)_4$ (THF, rt, 2 h),[4e] THF (reflux, 14–18 h),[4f] H_2O–MeOH (rt, 6–20 h),[4g] $LiClO_4$ (ether, rt, 5 h),[4h] K_2CO_3 (DMF, 40–50 °C, 3 h),[4i] Et_3N (THF, reflux, 30 h),[4j] and DABCO (THF/H_2O)[4k] have been developed for this reaction. Several of these procedures[4a,c,e,i] produced mixtures (regio/stereo) of products and majority of them involved organic solvents as reaction media and required long-reaction time. Moreover, the reactions of aliphatic cyclic amines are rarely addressed.[4e] Thus, an alternative simpler, more efficient and general and environment friendly method is appreciated.

The use of water as reaction medium for organic reactions has received wide acceptabilities[5] because of environmental concern, low cost and unique reactivity and selectivity that cannot be attained by organic solvents.[6] As a part of our continued activities[7] to explore the potential of water as promoter for organic transformations, we report here an efficient synthesis of α-dehydro-β-amino esters by the reaction of amines with Baylis–Hillman acetate adducts in water at room temperature without any catalyst in an aerobic atmosphere (Scheme 2).



Scheme 1. Potential centers of nucleophilic addition to BH acetate.



Scheme 2. Addition of amine to BH acetate in water.

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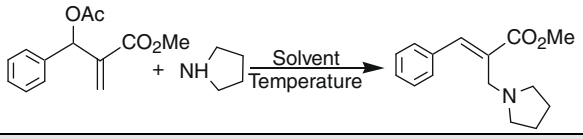
Table 1
Standardization of reaction conditions



Solvent	Temp (°C)	Time (h)	Yield (%)
DMF	60	2	55
DMF	rt	2	40
THF	rt	2	37
DCM	rt	2	70
MeOH	rt	2	90
MeOH	rt	0.2	65
H_2O	rt	2	99
H_2O	rt	0.5	95
H_2O	rt	0.2	93
Toluene	rt	2	30

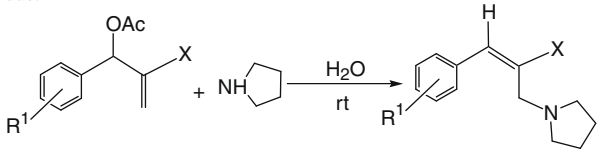
Reaction conditions: BH adducts (1 mmol), amine (1.5 mmol), solvent (2 ml) were stirred for required time period. Yield was calculated from comparison of ^{1}H NMR spectroscopy.

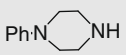
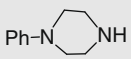
Water was found to be the best solvent compared to DMF, toluene, and THF in terms of reactivity (reaction time) and yield studied for a representative reaction with pyrrolidine (Table 1).

Several aliphatic open-chain and cyclic amines and anilines underwent reactions with a number of BH acetates bearing a variety of substituted aryl moieties by this procedure[8] to provide the corresponding α-dehydro-β-amino esters and nitriles. The results are summarized in Table 2. A wide variety of cyclic amines such as pyrrolidine, morpholine, pyrazines, and piperidines (Table 2, entries 1–11) are addressed in this procedure giving uniform results. The open-chain primary and secondary amines such as benzylamine and diisopropyl amine (Table 2, entries 12–14) and substituted anilines (Table 2, entries 15–17) also participated in this reaction without any difficulty, although the reactions of anilines are relatively sluggish compared to other reactions possibly because of their lower nucleophilicity. In all these reactions γ-products were obtained exclusively. Significantly, *E*-isomers were formed in the reactions of BH adducts bearing carboxylic ester moiety, whereas only *Z*-isomers were obtained from reactions of BH adducts containing nitrile functionality without any exception. The stereochemistry of the products was determined by comparison of the chemical shift (δ) value of the vinylic proton with the reported data for authentic compounds[4h] as well as by NOE experiments. A positive NOE (6%) between vinylic and allylic protons was found in case the product bears CN functionality (Table 2, entry 2), whereas the corresponding product containing CO_2Et (Table 2, entry 1) showed negligible enhancement (0.4%). NOESY experiment also indicated the proton–proton co-relationship between the vinylic proton and the allylic proton in case of product bearing CN moiety (Table 2, entry 2).

In general, the reactions are very clean and high yielding. All the reactions except for those with anilines are completed within

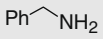
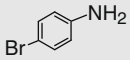
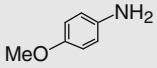
Table 2
Addition of amine to acetate of Baylis–Hillman adduct



Entry	R^1	X	Amine	*E*:*Z*	Time (min)	Yield[a] (%)	Ref.
1	H	CO_2Me		100:00	10	90	4h
2	H	CN		00:100	10	90	
3	4-Cl	CO_2Me		100:00	15	92	4h
4	4-Cl	CN		00:100	10	85	
5	4-Cl	CO_2Me		100:00	20	78	
6	H	CN		00:100	15	78	9
7	4-Cl	CN		00:100	15	80	
8	4-Cl	CO_2Me		100:00	20	82	
9	4-Cl	CN		00:100	15	86	
10	3-Br	CN		00:100	15	85	
11	4-OMe	CN		00:100	15	82	
12	3-Br	CN		00:100	20	90	

(*continued on next page*)

Table 2 (*continued*)

Entry	R^1	X	Amine	*E*:*Z*	Time (min)	Yield[a] (%)	Ref.
13	4-OMe	CN		00:100	20	88	
14	H	CO_2Me		100:00	30	70	4a
15	H	CO_2Me		100:00	90	75	4a
16	H	CO_2Me		100:00	90	70	
17	4-OMe	CN		00:100	75	80	

[a] Yields refer to those of pure isolated products characterized by spectroscopic data (IR, ^1H, ^{13}C NMR, and HR-MS).

20 min at room temperature. The reactions of anilines (Table 2, entries 15–17) were carried out at 80 °C. Interestingly, the reactions of BH adducts bearing –CN moiety were rarely addressed in the literature.[4j,k] In a recent Letter by Yadav et al.[4k] only α-addition products were obtained using DABCO and Kim et al.[4j] reported only one reaction giving *Z*-isomer of γ-product for this type of aza-Michael reaction. Nevertheless, our procedure addressed a variety of BH adducts containing CN moiety giving *Z*-isomer of γ-products with a clear distinction from others. Without water, the neat reactions at room temperature were very sluggish and inconsistent. Thus, water plays an important role in this reaction. It is likely that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atoms of acetate and carboxylic ester moieties increasing the electrophilic character at the β-carbon and this facilitates the nucleophilic attack by amine followed by elimination of acetate group.

In conclusion, we have developed a mild and efficient method for the synthesis of α-dehydro-β-amino esters and nitriles by the reaction of amines and acetates of Baylis–Hillman adducts in water at room temperature without using any basic, acidic, or metal catalyst. The reactions provided only γ-addition products. The additions are also highly stereoselective providing (*E*)-isomers in case of BH adducts bearing carboxylic ester moiety and (*Z*)-isomers for adducts containing CN functionality. Certainly, the simple operation, high yields, fast reaction, excellent regio- and stereoselectivity of products, applicability to a variety of amines and BH adducts and green reaction conditions using water without any catalyst in aerobic atmosphere make this procedure more attractive for academia as well as industries.

Acknowledgments

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8. Representative experimental procedure for the aza-Michael addition of amine to Baylis–Hillman acetate adduct (Table 2, entry 1): A mixture of pyrrolidine (106 mg, 1.5 mmol) and Baylis–Hillman acetate, 2-(acetoxy-phenyl-methyl)-acrylic acid methyl ester (202 mg, 1 mmol) in water (2 mL) was stirred at room temperature in aerobic atmosphere for 10 min (TLC). The reaction mixture was extracted with ethyl acetate (2 × 10 mL) and the combined extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product which was purified by column chromatography over silica gel to provide a viscous liquid (190 mg, 90%), which was identified as 3-phenyl-2-pyrrolidine-1-yl-methyl-acrylic acid methyl ester by comparison of its ^1H NMR and ^{13}C NMR spectroscopic data with the reported values.[4h]
This procedure is followed for all the reactions listed in Table 2. The known products were easily identified by comparison of their spectroscopic data with those reported (see Table 1). The unknown compounds were characterized by their IR, ^1H NMR, ^{13}C NMR, and HR-MS spectroscopic data. These were provided below in order of their entries in Table 1.
3-Phenyl-2-pyrrolidin-1-ylmethyl-acrylonitrile (Table 1, entry 2): Yellow liquid; IR (neat) 2962, 2212, 1608, 1512, 1348, 1126, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80–1.86 (m, 4H), 2.61–2.65 (m, 4H), 3.39 (s, 2H), 7.12 (s, 1H), 7.38–7.40 (m, 3H), 7.74–7.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6 (2C), 53.7 (2C), 60.0, 109.4, 118.8, 127.0, 128.8 (2C), 129.0 (2C), 133.4, 144.7; HR-MS Calcd for $C_{14}H_{16}N_2$ $[M+H]^+$: 213.139; found: 213.131.
3-(4-Chloro-phenyl)-2-pyrrolidin-1-ylmethyl-acrylonitrile (Table 2, entry 4): Yellow liquid; IR (neat) 2882, 2218, 1615, 1240, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.77–1.81 (m, 4H), 2.50–2.58 (m, 4H), 3.36 (s, 2H), 7.06 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.6 (2C), 53.8 (2C), 59.9, 110.1, 118.5, 129.6 (2C), 130.1 (2C), 131.9, 136.0, 143.2; HR-MS Calcd for $C_{14}H_{15}N_2Cl$ $[M+H]^+$: 247.10; found: 247.09.
3-(3-Chloro-phenyl)-2-morpholin-4-ylmethyl-acrylic acid methyl ester (Table 2, entry 5): Yellow liquid; IR (neat) 3016, 2820, 1710, 1553, 1240, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (t, J = 4.2 Hz, 4H), 3.26 (s, 2H), 3.60 (t, J = 4.2 Hz,

4H), 3.74 (s, 3H), 7.28 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2 (2C), 53.0 (2C), 53.6, 66.9, 128.6 (2C), 131.8 (2C), 133.7, 135.2, 142.6, 168.7; HR-MS Calcd for $C_{15}H_{18}ClNO_3$ $[M+H]^+$: 296.105; found: 296.107.

3-(4-Chloro-phenyl)-2-morpholin-4-ylmethyl-acrylnitrile (Table 2, entry 7): Yellow liquid; IR (neat) 2816–2960 (broad), 2214, 1749, 1492, 1114, 1012 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (t, J = 4.3 Hz, 4H), 3.23 (s, 2H), 3.71 (t, J = 4.3 Hz, 4H), 7.03 (s, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.5 (2C), 63.1, 67.1 (2C), 109.2, 117.2, 129.5 (2C), 130.5 (2C), 131.9, 136.9, 144.2; HR-MS Calcd for $C_{14}H_{15}ClN_2O$ $[M+H]^+$: 263.095; found: 263.196.

3-(4-Chloro-phenyl)-2-(4-phenyl-piperazin-1-ylmethyl)-acrylic acid methyl ester (Table 2, entry 8): Yellow liquid; IR (neat) 2830, 2250, 1610, 1240, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (t, J = 4.5 Hz, 4H), 3.19 (t, J = 4.5 Hz, 4H), 3.41 (s, 2H), 3.84 (s, 3H), 6.92 (d, J = 8.1 Hz, 2H), 7.23–7.31 (m, 3H), 7.37 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.3 (2C), 52.1 (2C), 52.6, 53.3, 116.2 (2C), 119.8, 126.0, 128.6 (2C), 129.2 (2C), 131.9 (2C), 133.8, 135.2, 142.7, 151.3, 168.8; HR-MS Calcd for $C_{21}H_{23}ClN_2O_2$ $[M+H]^+$: 371.152; found: 371.174.

3-(4-Chloro-phenyl)-2-(4-phenyl-piperazin-1-ylmethyl)-acrylonitrile (Table 2, entry 9): Low melting yellow solid; mp 48 °C; IR (KBr) 2829, 2212, 1597, 1492, 1222, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (t, J = 4.2 Hz, 4H), 3.41 (t, J = 4.2 Hz, 4H), 3.49 (s, 2H), 7.03–7.12 (m, 3H), 7.26 (s, 1H), 7.42–7.48 (m, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.0 (2C), 52.6 (2C), 62.2, 108.8, 116.1 (2C), 118.2, 119.8, 129.0 (4C), 130.1 (2C), 131.5, 136.2, 143.8, 151.0; HR-MS Calcd for $C_{20}H_{20}ClN_3$ $[M+H]^+$: 338.142; found: 338.141.

3-(3-Bromo-phenyl)-2-piperidin-1-ylmethyl-acrylonitrile (Table 2, entry 10): Yellow liquid; IR (neat) 2937, 2214, 1560, 1469, 1215, 1111, 995, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–1.45 (m, 2H), 1.56–1.58 (m, 4H), 2.42–2.45 (m, 4H), 3.20 (s, 2H), 7.01 (s, 1H), 7.22–7.27 (m, 1H), 7.45–7.48 (m, 1H), 7.71–7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 26.2 (2C), 54.5 (2C), 63.2, 111.0, 118.6, 123.1, 127.4, 130.7, 132.2, 133.4, 135.8, 143.4; HR-MS Calcd for $C_{15}H_{17}BrN_2$ $[M+H]^+$: 305.065; found: 305.064.

3-(4-Methoxy-phenyl)-2-piperidin-1-ylmethyl-acrylonitrile (Table 2, entry 11): Yellow liquid; IR (neat) 2920, 2224, 1550, 1420, 1156, 1008, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37–1.41 (m, 2H), 1.51–1.58 (m, 4H), 2.38–2.41 (m, 4H), 3.14 (s, 2H), 3.76 (s, 3H), 6.85 (d, J = 8.7 Hz, 2H), 6.93 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 25.7 (2C), 53.8 (2C), 55.2, 63.1, 105.4, 114.0 (2C), 119.2, 126.0, 130.5 (2C), 144.5, 161.0; HR-MS Calcd for $C_{16}H_{20}N_2O$ $[M+H]^+$: 257.165; found: 257.167.

3-(3-Bromo-phenyl)-2-[(diisopropylamino)-methyl]-acrylonitrile (Table 2, entry 12): Low melting yellow solid, mp 40 °C, IR (KBr) 2964, 2212, 1560, 1471, 1383, 1202, 1180, 956, 783 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 12H), 2.89–2.98 (m, 2H), 3.26 (s, 2H), 7.06 (s, 1H), 7.12–7.17 (m, 1H), 7.34–7.37 (m, 1H), 7.62–7.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (4C), 48.9 (2C), 50.1, 115.6, 118.6, 123.1, 127.2, 128.3, 130.5, 132.5, 136.2, 141.0; HR-MS Calcd for $C_{16}H_{21}BrN_2$ $[M+H]^+$: 321.096, 323.094; found: 321.096, 323.092.

2-[(Diisopropylamino)-methyl]-3-(4-methoxy-phenyl)-acrylonitrile (Table 2, entry 13): Yellow liquid; IR (neat) 2960, 2214, 1604, 1512, 1305, 1265, 1182, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, J = 6.6 Hz, 12H), 3.05–3.10 (m, 2H), 3.37 (s, 2H), 3.83 (s, 3H), 6.93 (d, J = 8.7 Hz, 2H), 7.12 (s, 1H), 7.75 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (4C), 48.2 (2C), 49.7, 55.3, 110.3, 114.1 (2C), 119.3, 126.6, 130.4 (2C), 142.0, 160.8; HR-MS Calcd for $C_{17}H_{24}N_2O$ $[M+H]^+$: 273.196; found: 273.196.

2-[(4-Bromo-phenylamino)-methyl]-3-phenyl-acrylic acid methyl ester (Table 2, entry 16): Low melting solid, mp 49 °C; IR (KBr) 3394, 1708, 1593, 1494, 1232, 1105, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 4.10 (s, 2H), 6.37 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 7.40 (m, 5H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.9, 52.5, 109.6, 115.1 (4C), 128.9 (2C), 129.5 (2C), 131.8, 134.7, 143.0, 143.1, 146.5, 168.0; HR-MS Calcd for $C_{17}H_{16}BrNO_2$ $[M+H]^+$: 346.044; found: 346.043.

2-[(4-Methoxy-phenylamino)-methyl]-3-p-tolyl-acrylonitrile (Table 2, entry 17): Yellow liquid; IR (neat) 3392, 3016, 2208, 1620, 1514, 1236, 1035, 819, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.72 (s, 3H), 3.98 (s, 2H), 6.62 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 7.11 (s, 1H), 7.18 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 48.7, 55.4, 107.9, 114.3 (2C), 114.7 (2C), 118.3, 128.6 (2C), 129.3 (2C), 130.3, 140.5, 140.6, 143.3, 152.4; HR-MS Calcd for $C_{18}H_{18}N_2O$ $[M+H]^+$: 279.149; found: 279.149.

9. Eagen, M. C.; Cromwell, N. H. *J. Org. Chem.* **1974**, *39*, 3863–3865.