Alternate, Easy and Practical Synthesis of Allylamines from Acetyl Derivatives of Baylis–Hillman Adducts Using Methanolic Ammonia[1]

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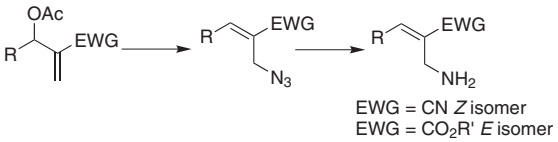
Abstract: A methanolic ammonia-mediated alternate, easy and practical stereoselective synthesis of allylamines from the acetyl derivatives of Baylis–Hillman adducts is described.

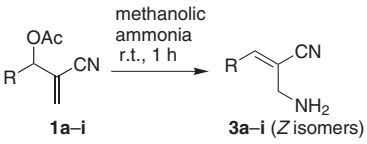
Key words: Baylis–Hillman, allylamine, methanolic ammonia, stereoselective



Scheme 1 Synthesis of allylamines from allylazides[4]

The Baylis–Hillman reaction is now a standard synthetic method to achieve the synthesis of several synthons, heterocycles and natural products.[2] In connection with our project on the synthesis of nitrogen-containing heterocyclic systems using Baylis–Hillman chemistry,[3] we were interested in the generation of allylamines from the acetyl derivatives of the Baylis–Hillman adducts in a synthetically practical fashion. Indeed we have earlier reported the stereoselective synthesis of such allylamines by carrying out reduction of the allylazides, obtained from the acetates of Baylis–Hillman adducts, using the Staudinger reaction (Scheme 1).[4] However, when this reaction is carried out on a large scale large quantities of triphenylphosphine oxide were generated. Additionally, the time consumed for the Staudinger reaction was 16 hours which made the synthesis lengthy. More recently, Das et al. described the ammonium acetate-assisted synthesis of similar allylamines in stereoselective fashion.[5] However, we have reinvestigated their synthetic protocol and reported that the products formed during the ammonium acetate-promoted reactions are not allylamines.[6] In view of these limitations, we probed for alternate options to obtain the allylamines directly from the acetyl derivative of the Baylis–Hillman products in a more practical fashion. During the exploratory studies we have discovered that methanol saturated with ammonia afford the desired allylamines efficiently from the acetates of Baylis–Hillman adducts in a short period and the reaction can be successfully carried out at multi-gram scales without generating any waste reagent. The details of our results are presented in this communication.

The starting substrates **1**,**2** for the study were generated according to the literature procedure.[7] Initially the acetyl derivative **1a** was treated in a closed vessel (screw cap vial or a flask capped with septum) with methanolic ammonia that was freshly prepared by passing ammonia gas in methanol. It was gratifying to observe that the reaction was complete within one hour (Scheme 2). The methanolic ammonia could be easily removed under vacuum on the rotary evaporator to furnish the crude allylamine **3a**, which was sufficiently pure to be utilized for further reactions. The structure of the amine was established unambiguously by comparison with a sample prepared by the azide route as shown in Scheme 1. In order to assess the general applicability of this synthetic methodology, acetyl derivatives of several Baylis–Hillman adducts of acrylonitrile **1a–j** were evaluated to afford the allylamines **3a–i** in good yields (Table 1). The ^{1}H NMR of the crude products conclusively indicated the reaction was stereoselective as only the *Z* isomer was present.[2a,8] Mechanistically, the NH_3 present in the methanol being nucleophilic attacks the double bond with subsequent migration of the double bond and concomitant loss of the acetyl group to afford the amine. More important, this synthetic methodology works efficiently even at multi-gram levels.



Scheme 2 Synthesis of allylamines from Baylis–Hillman adducts (nitriles)

Once the objective to obtain the desired amine from the acetyl derivative of Baylis–Hillman product of acrylonitrile was accomplished we directed our attention towards the acetyl derivatives of Baylis–Hillman adducts of acrylates **2**. Similar reaction of methanolic ammonia with compound **2a** was complete within 30 minutes, but the product contained a mixture of two compounds (Scheme 3, Table 2). Based on the spectroscopic and analytical evidence, the structure assigned to the less polar compound on the TLC was that of the secondary amine **5**

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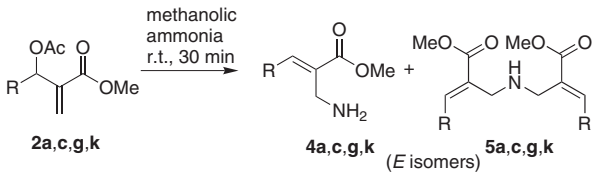
Table 1 Compounds **3a–i** Prepared

Product	R	Yield (%)	Appearance, mp (°C)	MS (ES+) *m/z*	IR (cm^{-1}) ν (C≡N), ν (NH_2)
3a	Ph	88	pale yellow solid, 108–110	159.00	2211, 3377
3b	2-ClC_6H_4	84	pale yellow solid, 106–108	193.30	2211, 3400
3c	4-ClC_6H_4	86	pale yellow solid, 102–104	193.31	2210, 3423
3d	2-FC_6H_4	88	yellow oil	176.93	2217, 3400
3e	4-FC_6H_4	82	white solid, 88–90	176.93	2215, 3406
3f	2-BrC_6H_4	86	white solid, 106–108	237.08	2244, 3374
3g	4-MeC_6H_4	88	white solid, 78–80	173.00	2211, 3437
3h	2-ClC_6H_4-isoxazol-5-yl	81	yellow oil	260.20	2223, 3397
3i	naphth-2-yl	85	white solid, 112–114	208.23	2212, 3410
3j	4-$OBnC_6H_4$	80	white solid, 140–142	264.31	2208, 3384

Table 2 Compounds **4-5a,c,f,g** Prepared

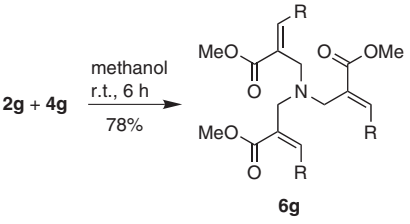
Product	R	Yield (%)		Appearance, mp (°C)		MS (ES+) *m/z*		IR (cm^{-1}) ν (CO_2Me and NH_2)	
		4	**5**	**4**	**5**	**4**	**5**	**4**	**5**
a	Ph	44	38	pale yellow sticky solid	yellow oil	192.07	366.13	1709, 3410	1710, 3332
c	4-ClC_6H_4	44	34	pale yellow oil	pale yellow solid, 100–102	225.93	393.00	1712, 3328	1712, 3403
f	2-BrC_6H_4	39	57	yellow oil	yellow solid, 80–82	271.87	366.13	1711, 3335	1712, 3430
g	4-MeC_6H_4	39	35	pale yellow sticky solid	white solid, 94–96	205.93	436.47	1711, 3412	1708, 3450

while the polar compound was the desired amine derivative **4**.[9] As evident from ^{1}H NMR data, the reaction was stereoselective for both products **4** and **5** since only *E* isomers were obtained. This observation was in contrast to reactions of compound **1** where no formation of analogous secondary amine was observed. The formation of compound **5** was confirmed by carrying out detailed mass spectral studies.[10] In principle, the product **5** could be generated by the reaction between the acetate **2** and the amine **4**. Further, the product **5** may again act as a nucleophile for the Michael addition on the acetyl derivative to yield the tertiary amine **6**.

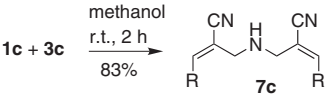


Scheme 3 Synthesis of allylamines from Baylis–Hillman adducts (esters)

In order to provide the chemical evidence for the formation of product **4** in a representative reaction the acetyl derivative **2g** was subjected to Michael addition with the amine **4g** in methanol. Interestingly, this reaction was complete in six hours and the product was the tertiary amine **6g** (Scheme 4). This product was similar in all respect (spectroscopically and t_R on HPLC) to the product obtained from the reaction between the acetyl derivative and ammonium acetate for corresponding substitution. Simultaneously, to evaluate a similar possibility in acetyl derivatives of Baylis–Hillman adducts of acrylonitrile, in a model reaction compound **1c** was reacted with the amine **3c**. Contrary to the findings with compound **2**, this reaction was complete in two hours and the structure of the product was assigned as the secondary amine **7c** (Scheme 5).



Scheme 4 Formation of a tertiary amine during the synthesis of allylamines



Scheme 5 Model reaction of **1c** with **3c** affording a secondary amine

In conclusion, we have described an easy, efficient, environmentally friendly, multi-gram, stereoselective procedure for the synthesis of allylamines from the acetyl derivatives of the Baylis–Hillman adducts. The inexpensive reagent and simple reaction conditions makes this method an attractive option for generation of allylamines. The synthetic utility of these allylamines will be a subject of our future communications.

Melting points were determined in capillary tubes on a hot-stage apparatus containing silicon oil and are uncorrected. IR spectra were recorded using a Perkin-Elmer RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The FABMS were recorded on JEOL SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. The electrospray mass spectral studies were performed on a MICROMASS QUATTRO II triple quadrupole mass spectrometer. The samples (dissolved in MeOH) were introduced into the ESI source through a syringe pump at the rate of 5 μL/min. The ESI capillary was set at 3.5 kV and the cone voltage was variable (10 V, 25 V, 40 V, 90 V). The spectra were collected in 6 average scans. These allylamines were found to have a very short shelf life and start disintegrating within 24–48 h. Therefore, only representative amines were subjected to microanalysis on an Elementar's Vario EL *III* microanalyzer. The amine **3h** was immediately utilized for further reactions, hence no NMR data are given.

Reaction of Methanolic Ammonia with Baylis–Hillman Adducts 1 and 2; General Procedure

To an appropriate acetyl derivative **1** (1.0 g), was added freshly prepared methanolic ammonia solution (ca. 20 mL, the solution can be stored in the fridge and works well for more than a month) in a flask that was later capped with septum (or screw cap vial) so as to prevent the loss of ammonia. The flask was left at r.t. (no mixing or stirring was required). After the completion of reaction, the excess solvent was evaporated and the crude product was purified by column chromatography over silica gel. A mixture of $CHCl_3$–MeOH (99:1) was used as eluent to obtain amines **3a**–**j**, while a mixture of hexane–EtOAc was used to obtain products **5a**,**c**,**f**, **g** (15% EtOAc) and **4a**,**c**,**f**,**g** (neat EtOAc).

2-Aminomethyl-3-phenylacrylonitrile (3a)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.64 (s, 2 H, C*H*$_2$NH$_2$), 3.77 (s, 2 H, CH$_2$N*H*$_2$), 7.10 (s, 1 H, =CH), 7.38–7.44 (m, 3 H, ArH), 7.72–7.77 (m, 2 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8, 46.0, 129.3, 130.0, 13.7, 141.6, 145.1.

2-Aminomethyl-3-(2-chlorophenyl)acrylonitrile (3b)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.62 (s, 2 H, C*H*$_2$NH$_2$), 7.04 (s, 1 H, =CH), 7.52–7.64 (m, 4 H, ArH).

Aminomethyl-3-(4-chlorophenyl)acrylonitrile (3c)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.64 (s, 2 H, C*H*$_2$NH$_2$), 3.71 (s, 2 H, CH$_2$N*H*$_2$), 7.06 (s, 1 H, =CH), 7.35 (d, 2 H, *J* = 8.2 Hz, ArH), 7.69 (d, 2 H, *J* = 8.2 Hz, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 46.6, 129.6, 130.4, 132.0, 136.8, 142.3.

Anal. Calcd for $C_{10}H_9ClN_2$: C, 62.35; H, 4.71; N, 14.54. Found: C, 62.17; H, 4.55; N, 14.44.

2-Aminomethyl-3-(2-fluorophenyl)acrylonitrile (3d)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.67 (s, 2 H, C*H*$_2$NH$_2$), 7.06–7.18 (m, 3 H, 1 H, =CH, 2 H, ArH), 7.37–7.46 (m, 2 H, ArH).

2-Aminomethyl-3-(4-fluorophenyl)acrylonitrile (3e)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.68 (s, 2 H, C*H*$_2$NH$_2$), 7.07 (s, 1 H, =CH), 7.17–7.26 (m, 2 H, ArH), 7.37–7.43 (m, 2 H, ArH).

2-Aminomethyl-3-(2-bromophenyl)acrylonitrile (3f)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.52 (s, 2 H, C*H*$_2$NH$_2$), 7.25 (s, 1 H, =CH), 7.30–7.42 (m, 2 H, ArH), 7.84 (d, 2 H, *J* = 8.4 Hz, ArH).

2-Aminomethyl-3-(4-methylphenyl)acrylonitrile (3g)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, ArC*H*$_3$), 3.62 (s, 2 H, C*H*$_2$NH$_2$), 7.05 (s, 1 H, =CH), 7.25 (d, 2 H, *J* = 8.2 Hz, ArH), 7.65 (d, 2 H, *J* = 8.2 Hz, ArH).

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.49; H, 6.90; N, 16.00.

2-Aminomethyl-3-(naphth-2-yl)acrylonitrile (3i)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.69 (s, 2 H, C*H*$_2$NH$_2$), 7.02 (s, 1 H, =CH), 7.26 (s, 2 H, ArH), 7.51–7.55 (m, 2 H, ArH), 7.82–7.98 (m, 3 H, ArH).

2-Aminomethyl-3-(4-phenoxymethylphenyl)acrylonitrile (3j)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.55 (s, 2 H, C*H*$_2$NH$_2$), 5.10 (s, 2 H, OCH$_2$), 6.98–7.02 (m, 3 H, 1 H, =CH, 2 H, ArH), 7.39–7.42 (m, 5 H, ArH), 7.72 (d, 2 H, *J* = 8.0 Hz, ArH).

2-Aminomethyl-3-phenylacrylic Acid Methyl Ester (4a)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.64 (s, 2 H, C*H*$_2$NH$_2$), 3.89 (s, 3 H, CO_2CH_3), 4.19 (s, 2 H, CH$_2$N*H*$_2$), 7.36–7.42 (m, 5 H, ArH), 7.97 (s, 1 H, =CH).

2-Aminomethyl-3-(4-chlorophenyl)acrylic Acid Methyl Ester (4c)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.51 (s, 2 H, C*H*$_2$NH$_2$), 3.71 (s, 3 H, CO_2CH_3), 7.12 (d, 2 H, *J* = 8.1 Hz, ArH), 7.54 (d, 2 H, *J* = 8.1 Hz, ArH), 7.85 (s, 1 H, =CH).

2-Aminomethyl-3-(2-bromophenyl)acrylic Acid Methyl Ester (4f)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.08 (s, 2 H, C*H*$_2$NH$_2$), 3.76 (s, 3 H, CO_2CH_3), 7.15–7.23 (m, 2 H, ArH), 7.39–7.44 (m, 1 H, ArH), 7.52–7.57 (m, 1 H, ArH), 7.85 (s, 1 H, =CH).

Anal. Calcd for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 48.86; H, 4.50; N, 5.15.

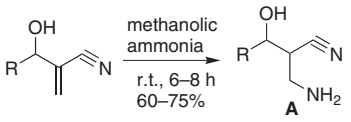
2-Aminomethyl-3-(4-methylphenyl)acrylic Acid Methyl Ester (4g)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, ArC*H*$_3$), 3.72 (s, 2 H, C*H*$_2$NH$_2$), 3.85 (s, 3 H, CO_2CH_3), 4.40 (s, 2 H, CH$_2$N*H*$_2$), 7.22 (d, 2 H, *J* = 8.3 Hz, ArH), 7.38 (d, 2 H, *J* = 8.3 Hz, ArH), 7.80 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 37.6, 52.7, 129.8, 129.9, 132.5, 140.1, 143.9, 168.2, 177.4.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.95; H, 7.07; N, 6.83.

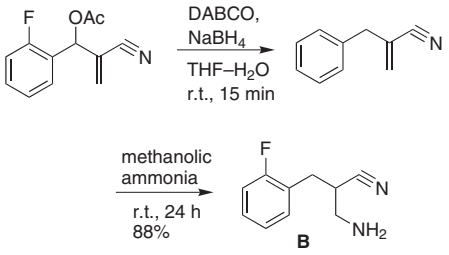
Note added in proof

The Baylis–Hillman adducts obtained by reaction between aldehydes and acrylonitrile react with ammonia to afford the 1,3-aminoalcohol **(A)** in good yields (Scheme 6).



Scheme 6

On the other hand, the allyl derivatives obtained from the reaction between the acetates of Baylis–Hillman adducts and sodium borohydride in the presence of DABCO in aqueous medium also react with ammonia to yield the corresponding amines **(B)** in excellent yields (Scheme 7).



Scheme 7

Acknowledgment

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References

(1) CDRI Communication No. 6786.
(2) (a) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627. (c) Cho, H. I.; Lee, S. W.; Lee, K.-J. *J. Heterocycl. Chem.* **2004**, *41*, 799. (d) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org Chem.* **2004**, *69*, 7379. (e) Lee, C. G.; Lee, K. Y.; GowriSankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 7409. (f) Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369. (g) Shanmugam, P.; Rajasingh, P. *Synlett* **2005**, 939. (h) Hong, W. P.; Lee, K.-J. *Synthesis* **2005**, 33. (i) Li, J.; Wang, X.; Zhang, Y. *Synlett* **2005**, 1039. (j) Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 1327. (k) Ramachandran, P. V.; Burghardt, T. E.; Reddy, M. V. R. *Tetrahedron Lett.* **2005**, *46*, 2121. (l) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493.
(3) (a) Singh, V.; Saxena, R.; Batra, S. *J. Org. Chem.* **2005**, *70*, 353. (b) Pathak, R.; Roy, A. K.; Batra, S. *Synlett* **2005**, 848. (c) Pathak, R.; Roy, A. K.; Kanojiya, S.; Batra, S. *Tetrahedron Lett.* **2005**, *46*, 5289.
(4) Patra, A.; Roy, A. K.; Batra, S.; Bhaduri, A. P. *Synlett* **2002**, 1819.
(5) Das, B.; Mahender, G.; Chowdhury, N.; Banerjee, J. *Synlett* **2005**, 1000.
(6) Singh V., Pathak R., Kanojiya S., Batra S.; *Synlett*; **2005**, 2465.
(7) (a) Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Bhaduri, A. P. *Synthesis* **2001**, 276. (b) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723.
(8) (a) Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr.* **1989**, 403. (b) Lee, J. L.; Chung, Y. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2000**, *21*, 843. (c) Batra, S.; Roy, A. K.; Patra, A.; Bhaduri, A. P.; Surin, W. S.; Raghavan, S. A. V.; Sharma, P.; Kapoor, K.; Dikshit, M. *Bioorg. Med. Chem.* **2004**, *12*, 2059.
(9) During extensive exploratory studies on the Baylis–Hillman derivatives we have observed that reaction between acetyl derivatives of Baylis–Hillman adducts and primary amines (ca 1–1.5-fold) always lead to tertiary amines (Figure 1) as the major product. However, the formation of such an amine can be reduced by using excess amine (ca. 4-fold) and adding acetyl derivative slowly under cold conditions.

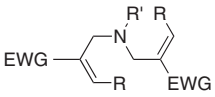

Figure 1 Structure of tertiary amines formed in the reaction of primary amines with Baylis–Hillman adducts.

(10) Several experiments using ESI mass spectrometry technique in the presence of NH_4OH and/or NH_4OAc (5–6 mM) were carried out to establish the exact molecular weight of products.