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Alternate, Easy and practical synthesis of allyl amines 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 allyl amines from the acetyl derivatives of Baylis-Hillman adducts is described.

Key words: Baylis-Hillman, allyl amine, methanolic ammonia, stereoselective.

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 generation of allyl amines from the acetyl derivatives of the Baylis-Hillman adducts in a synthetically practical fashion. Indeed we have earlier reported the stereoselective synthesis of such allyl amines by carrying out reduction of the allyl azides, obtained from the acetates of Baylis-Hillman adducts, using the Staudinger reaction (Fig. 1).[4] However, when this reaction is carried out on a large scale large quantities of triphenyl phosphine oxide were generated. Additionally, the time consumed for the Staudinger reaction was 16 h which made the synthesis lengthy. More recently, Das et al. described the ammonium acetate-assisted synthesis of similar allyl amines in stereoselective fashions.[5] However, we have reinvestigated their synthetic protocol and reported that the products formed during the ammonium acetate-promoted reactions are not allyl amines.[6] In view of these limitations, we probed for alternate options to obtain the allyl amines 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 allyl amines 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.

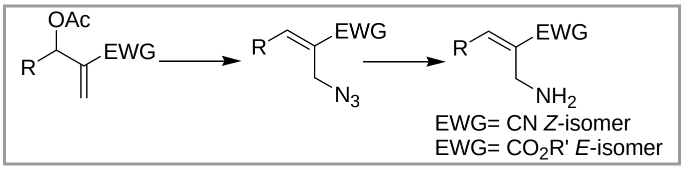
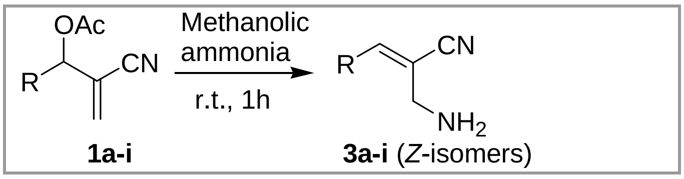


Fig. 1. Synthesis of allyl amines from allyl azides.[4]

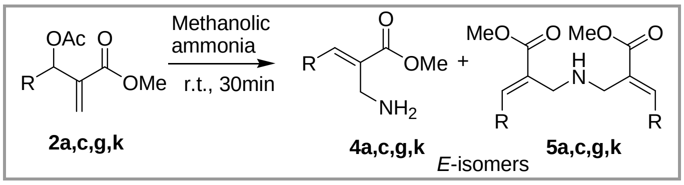
The starting substrates **(1-2)** for the study were generated according to the literature procedure.[7] Initially the acetyl derivative **1a** was treated in a closed vessel (screw cap vial or a flask capped with septum) with methanolic ammonia that was freshly prepared by passing ammonia gas in methanol. It was gratifying to observe that the reaction was complete within 1 h (Scheme 1). The methanolic ammonia could be easily removed under vacuum on the rotavapor to furnish the crude allyl amine **(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 Fig. 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 allyl amines in good yields **(3a-i)** (Table 1). The ^{1}H-NMR of the crude products conclusively indicated the reaction was stereoselective as only *Z*-isomer was present.[8,2a] 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.



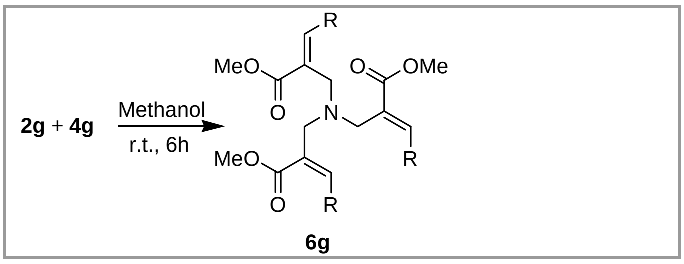
Scheme 1

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 min but the product contained a mixture of two compounds (Scheme 2, 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** while the polar compound was the desired amine derivative **4**.[9] As evident from ^{1}H-NMR the reaction was stereoselective for both products **4** and **5** since only *E*-isomers were afforded. 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

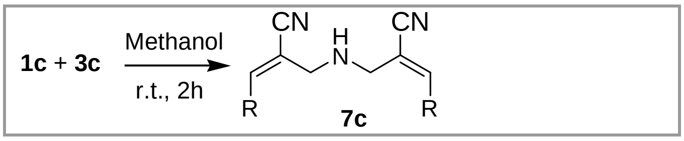
Michael addition on the acetyl derivative to yield the tertiary amine **6**. In order to provide the chemical evidence for the formation of product **4** in a representative reaction the acetyl derivative **2g** was subjected to Michael addition with the amine **4g** in methanol. Interestingly, this reaction was complete in 6 h and the product was the tertiary amine **6g** (Scheme 3). This product was similar in all respect (spectroscopically and R_t 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 2 h and the structure of the product was assigned as secondary amine **7c** (Scheme 4).



Scheme 2



Scheme 3



Scheme 4

In conclusion, we have described an easy, efficient, environmentally friendly, multi-gram, stereoselective procedure for the synthesis of allyl amines 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 allyl amines. The synthetic utility of these allyl amines will be a subject of our future communications.

Table 1 Characterisation data for compounds **3a-i**

Compd. No.	R	Yield (%)	Physical appearance, mp (°C)	Mass (ES+)	IR ν_{max} (CN and NH_2) cm^{-1}
3a	C_6H_5	88	Pale yellow solid, 108-110	159.00	2211, 3377
3b	2-Cl-C_6H_4	84	Pale yellow solid, 106-108	193.30	2211, 3400
3c	4-Cl-C_6H_4	86	Pale yellow solid, 102-104	193.31	2210, 3423
3d	2-F-C_6H_4	88	Yellow oil	176.93	2217, 3400
3e	4-F-C_6H_4	82	White solid, 88-90	176.93	2215, 3406
3f	2-Br-C_6H_4	86	White solid, 106-108	237.08	2244, 3374
3g	4-CH_3-C_6H_4	88	White solid, 78-80	173.00	2211, 3437
3h	2-Cl-C_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-OBn- C_6H_4	80	White solid, 140-142	264.31	2208, 3384

Table 2 Characterisation data for compounds **4-5a,c,g,k**

Compd. No.	R	Yield (%)		Physical appearance, mp (°C)		Mass (ES+)		IR ν_{max} (CO_2Me and NH_2) (cm^{-1})	
		4	**5**	**4**	**5**	**4**	**5**	**4**	**5**
a	C_6H_5	44	38	Pale yellow sticky solid	Yellow oil	192.07	366.13	1709, 3410	1710, 3332
c	4-Cl-C_6H_4	44	34	Pale yellow oil	Pale yellow solid, 100-102	225.93	393.00	1712, 3328	1712, 3403
g	4-CH_3-C_6H_4	39	35	Pale yellow sticky solid	White solid, 94-96	205.93	436.47	1711, 3412	1708, 3450
k	2-Br-C_6H_4	39	57	Yellow oil	Yellow solid, 80-82	271.87	366.13	1711, 3335	1712, 3430

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. 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 syste. The electrospray mass spectral studies were performed on a MICROMASS QUATTRO II triple quadrupole mass spectrometer. The samples (dissolved in methanol) were introduced into the ESI source through a syringe pump at the rate of 5µL/min. The ESI capillary was set at 3.5 kV and the cone voltage was variable (10V, 25V, 40V, 90v). The spectra were collected in 6 average scans. These allyl amines were found to have a very short shelf life and starts disintegrating within 24-48h. Therefore, only representative amines were subjected to microanalysis on a Elementar's Vario EL *III* microanalyzer. The amine **3h** was immediately utilized for further reactions, hence no ^{1}H-NMR is being provided.

General Procedure for the reaction of methanolic ammonia- To an appropriate acetyl derivative (1.0 g), 20 mL (approx) of freshly prepared methanolic ammonia solution (the solution can be stored in the fridge and works well for more than a month) was added 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 ambient temperature (no mixing or stirring is required). After the completion of reaction the excess solvent was evaporated. The crude product was purified by column chromatography over silica gel. A mixture of $CHCl_3$: MeOH (99:1, v/v) was used as eluent to obtain amines **3a-j**, while a mixture of hexane: EtOAc was used to obtain products **5a,c,g,k** (15% EtOAc) and **4a,c,g,k** (Neat EtOAc).

2-Aminomethyl-3-phenyl-acrylonitrile (3a)

^{1}H NMR (200 MHz, $CDCl_3$) δ= ^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.64 (s, 2H, $C\mathit{H}_2NH_2$), 3.77 (s, 2H, $CH_2N\mathit{H}_2$), 7.10 (s, 1H, =CH), 7.38-7.44(m, 3H, ArH), 7.72-7.77 (m, 2H, ArH); ^{13}CNMR (50 MHz, $CDCl_3$) δ= 21.8, 46.0, 129.3, 130.0, 13.7, 141.6, 145.1

2-Aminomethyl-3-(2-chloro-phenyl)-acrylonitrile (3b)

^{1}H NMR (200 MHz, $CDCl_3$) δ=3.62 (s, 2H, $C\mathit{H}_2NH_2$), 7.04 (s, 1H, =CH), 7.52-7.64 (m, 4H, ArH).

Aminomethyl-3-(4-chloro-phenyl)-acrylonitrile (3c)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.64 (s, 2H, $C\mathit{H}_2NH_2$), 3.71(s, 2H, $CH_2N\mathit{H}_2$), 7.06 (s, 1H, =CH), 7.35 (d, 2H, *J* = 8.2 Hz, ArH), 7.69 (d, 2H, *J* = 8.2 Hz, ArH); ^{13}CNMR (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-fluoro-phenyl)-acrylonitrile (3d)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.67 (s, 2H, $C\mathit{H}_2NH_2$), 7.06-7.18 (m, 3H, 1H, =CH, 2H, ArH), 7.37-7.46 (m, 2H, ArH).

2-Aminomethyl-3-(4-fluoro-phenyl)-acrylonitrile (3e)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.68 (s, 2H, $C\mathit{H}_2NH_2$), 7.07 (s, 1H, =CH), 7.17-7.26 (m, 2H, ArH), 7.37-7.43 (m, 2H, ArH).

2-Aminomethyl-3-(2-bromo-phenyl)-acrylonitrile (3f)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.52 (s, 2H, $C\mathit{H}_2NH_2$), 7.25 (s, 1H, =CH), 7.30-7.42 (m, 2H, ArH), 7.84 (d, 2H, *J*= 8 4 Hz, ArH).

2-Aminomethyl-3-p-tolyl-acrylonitrile (3g)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 2.38 (s, 3H, $ArCH_3$), 3.62 (s, 2H, $C\mathit{H}_2NH_2$), 7.05 (s, 1H, =CH), 7.25 (d, 2H, *J*= 8.2 Hz, ArH), 7.65 (d, 2H, *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-(4-phenoxymethyl-phenyl) acrylonitrile (benzyloxy) (3i)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.55 (s, 2H, $C\mathit{H}_2NH_2$), 5.10 (s, 2H, OCH_2), 6.98-7.02 (m, 3H, 1H, =CH, 2H, ArH), 7.39-7.42 (m, 5H, ArH), 7.72 (d, 2H, *J*= 8.0 Hz, ArH).

2-Aminomethyl-3-naphthalen-2-yl-acrylonitrile (3j)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.69 (s, 2H, $C\mathit{H}_2NH_2$), 7.02 (s, 1H, =CH), 7.26 (s, 2H, ArH), 7.51-7.55 (m, 2H, ArH), 7.82-7.98 (m, 3H, ArH).

2-Aminomethyl-3-phenyl-acrylic acid methyl ester (4a)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.64 (s, 2H, $C\mathit{H}_2NH_2$), 3.89 (s, 3H, CO_2Me), 4.19 (s, 2H, $CH_2N\mathit{H}_2$), 7.36-7.42 (m, 5H, ArH), 7.97 (s, 1H, =CH).

2-Aminomethyl-3-(4-chloro-phenyl)-acrylic acid methyl ester (4c)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.51 (s, 2H, $C\mathit{H}_2NH_2$), 3.71 (s, 3H, CO_2Me), 7.12 (d, 2H, *J*= 8.1 Hz, ArH), 7.54 (d, 2H, *J*= 8.1 Hz, ArH), 7.85 (s, 1H, =CH);

2-Aminomethyl-3-p-tolyl-acrylic acid methyl ester (4g)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 2.38 (s, 3H, $ArCH_3$), 3.72 (s, 2H, $C\mathit{H}_2NH_2$), 3.85 (s, 3H, CO_2Me), 4.40 (s, 2H, $CH_2N\mathit{H}_2$), 7.22 (d, 2H, *J*= 8.3 Hz, ArH), 7.38 (d, 2H, *J*= 8.3 Hz, ArH), 7.80 (s, 1H, =CH)

^{13}CNMR (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.

2-Aminomethyl-3-(2-bromo-phenyl)-acrylic acid methyl ester (4k)

^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.08 (s, 2H, $C\mathit{H}_2NH_2$), 3.76 (s, 3H, CO_2Me), 7.15-7.23 (m, 2H, ArH), 7.39-7.44 (m, 1H, ArH), 7.52-7.57 (m, 1H, ArH), 7.85 (s, 1H, =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.

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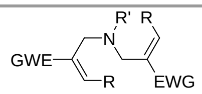
(9) It will be worth mentioning that during extensive exploratory studies on the Baylis-Hillman derivatives we have observed that reaction between acetyl derivative of Baylis-Hillman adducts and primary amines (ca 1-1.5 fold) always lead to tertiary amine (shown below) as the major product. However, the formation of such amine can be reduced by using excess amine (ca 4 folds) and adding acetyl derivative slowly under cold conditions.



Tertiary amine

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