A reinvestigation into the reaction of NH_4OAc with acetyl derivatives of Baylis-Hillman adducts: Formation of tertiary and secondary allyl amines instead of primary allyl amines[1]

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Abstract: A reinvestigation into the reaction between ammonium acetate and the acetyl derivatives of Baylis-Hillman adducts has led us to conclude that the products obtained are tertiary and secondary allyl amines and not the primary allyl amines. The unambiguous assignment of the structure of products using chemical and spectroscopic methods is described.

Key words: Baylis-Hillman, ammonium acetate, allyl amine, stereoselective.

Allyl amines are important synthons, which can be obtained in a convenient fashion employing Baylis-Hillman chemistry.[2] We have recently described the synthesis of these allyl amines from the acetates of Baylis-Hillman adducts utilizing methanolic ammonia.[3] This synthetic achievement successfully supplements our earlier reported protocol for the synthesis of such allyl amines from the respective azides.[4] Recently, Das et al. too have described the synthesis of allyl amines from the reaction between ammonium acetate and the acetates derived from the Baylis-Hillman adducts in anhydrous methanol.[5] However, we were intrigued by the fact that Das et al. could purify the allyl amines using hexane: EtOAc (4:1). In our hands we have been able to purify allyl amines always using $CHCl_3$: MeOH (1%) or neat EtOAc.

During our studies on reactions between acetates of Baylis-Hillman adducts and methanolic ammonia we have observed that the acetates of Baylis-Hillman adduct from acrylates invariably leads to a mixture of primary allyl amine **I** and the secondary allyl amine **II** (Fig. 1). On the contrary, similar reactions of acetates of Baylis-Hillman adducts of acrylonitrile furnish primary allyl amines **I** exclusively. Additionally, the primary allyl amines **I** are highly reactive and if treated with acetates further, lead to a tertiary amine **III** in case of acrylates and secondary allyl amine **II** in case of acrylonitrile. Compared to the polarity of the primary allyl amine, the secondary- and tertiary- allyl amines are relatively less polar. In view of these observations, we envisioned that during the use of excess of ammonium acetate it is likely that secondary and tertiary allyl amines (**II** and **III**) are formed instead of the primary allyl amines (**I**). Therefore we considered it worthwhile to investigate the claims of ammonium acetate-mediated preparation of allyl amines and our results are described in this communication.

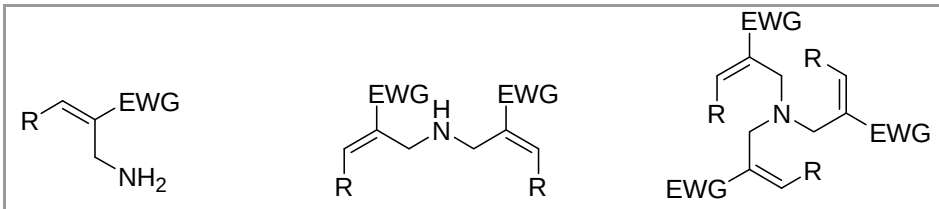
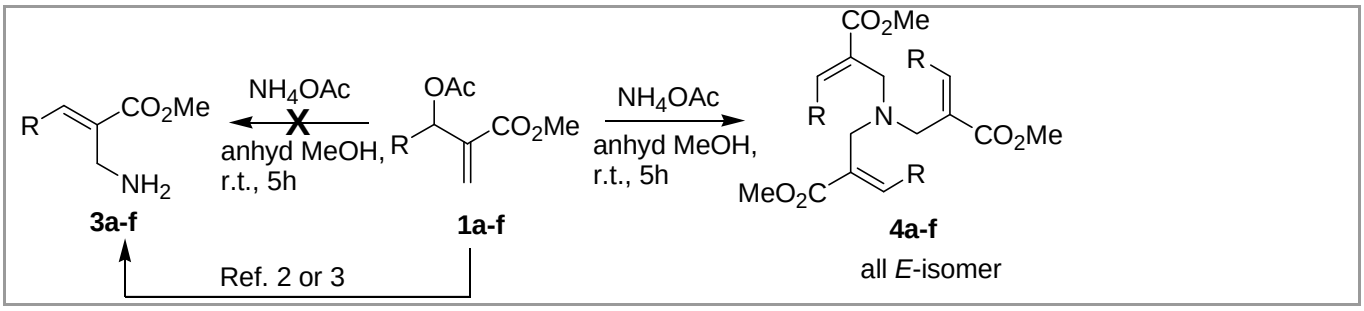


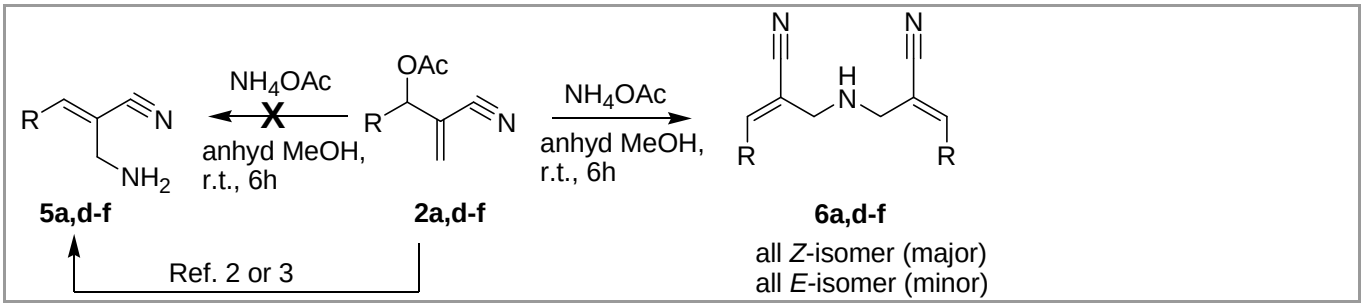
Figure 1. Representative prototypes of allyl amines

The procedure described by Das et al. was followed as closely as experimental details would permit. For both reactants **1** and **2** we have included several examples (Schemes 1 and 2). The products **4a-f** were obtained as *E*-isomer exclusively. On the other hand though the products **6a,d-f** were obtained as *Z*-isomer in major yield, minor quantities of *E*-isomer were also detected. The NMR of products **4a-f** and **6a, d-f** synthesized by us nearly matched the ones reported by Das et al.[6] Therefore, chemical and mass spectroscopic methods were employed to establish structures of these compounds.

The authentic samples of allyl amines **3** and **5** were prepared from the azide or methanolic ammonia route. A comparison of their physical and chemical properties with products **4** and **6** obtained from ammonium acetate is illustrated in Table 1 and 2. From several parameters mentioned in Table 1 and 2 it is clear that products afforded by the reaction of ammonium acetate are not primary allyl amines. The retention time of compounds **5** and **6** (*Z*-isomer) on RP-HPLC further support our results.[7] Chemically, primary allyl amines **3** and **5** reacted with acetates **1** and **2** to furnish products **4** and **6**, respectively. In order to obtain additional evidence for establishing the structure of products derived from ammonium acetates unambiguously, detailed mass spectroscopy of compounds **3**, **4**, **5** and **6** was carried out. In the FABMS of all compounds, the required molecular ion



Scheme 1



Scheme 2

Table 1 Comparison between the physicochemical and spectroscopic characterisation data of compounds **3** and **4**..

Compd No.	R (Yield (%)of **4** from NH_4OAc)	TLC (R_f) adsorbent-silica		Physical appearance, mp (°C)		Mass (FAB+) (M^++1) (Ratio of isotopic peak intensities)		IR ν_{max} CO_2Me and NH_2 (cm^{-1})	
		3[a]	**4**[b]	**3**	**4**	**3**	**4**	**3**	**4**
a	C_6H_5 (97)	0.4	0.5	Sticky pale yellow solid	White solid, 162-164	192	540	1709, 3410	1711
b	4-CH_3-C_6H_4 (99)	0.5	0.5	Sticky pale yellow solid	White solid, 130-132	206	582	1708, 3450	1708
c	2-Cl-C_6H_4 (98)	0.6	0.6	Yellow oil	White solid, 115-117	226, 228 (3:1)	642, 644, 646, 648 (27:27:9:1)	1710, 3410	1712
d	2-Br- C_6H_4 (96)	0.5	0.5	Yellow oil	White solid, 154-56	270, 272 (1:1)	774, 776, 778, 780 (1:3:3:1)	1711, 3335	1720
e	2-F- C_6H_4 (89)	0.6	0.6	Yellow oil	White solid, 138-140	210	594	1711, 3406125	1713
f	4-Cl-C_6H_4 (98)	0.6	0.6	Pale yellow oil	White solid, 142-144	226, 228 (3:1)	642, 644, 646, 648 (27:27:9:1)	1712, 3403	1714

[a]The mobile phase is $CHCl_3$:MeOH (96:4, v/v), [b]The mobile phase is Hexane: EtOAc (80:20, v/v).

Table 2 Comparison between the physicochemical and spectroscopic characterisation data of compounds **5** and **6**.

Compd. No.	R (Yield (%)of **6** from NH_4OAc)	TLC (R_f) adsorbent -silica (HPLC[c] (T_R in min)		Physical appearance, mp (°C)		Mass (FAB+) (M^++1) (Ratio of isotopic peak intensities)		IR ν_{max} CN and NH_2/NH (cm^{-1})	
		5[a]	**6**[b]	**5**	**6**	**5**	**6**	**5**	**6**
a	C_6H_5 (85)	0.5 (11.4)	0.5 (20.56)	Pale yellow solid, 108-110	Colorless oil	159	300	2212, 3374	2214, 3346
d	2-Br- C_6H_4 (86)	0.4 (14.2)	0.4 (22.9)	White solid, 106-108	Colorless oil	237, 239 (1:1)	456, 458, 460 (1:2:1)	2244, 3374	2232, 3435
e	2-F- C_6H_4 (87)	0.5 (11.7)	0.5 (20.8)	Yellow oil	Yellow oil	177	336	2214, 3405	2217, 3345-
f	4-Cl-C_6H_4 (85)	0.6 (9.0)	0.6 (14.77)	Pale yellow solid, 102-104	Pale yellow solid, 80-82	193, 195 (3:1)	368, 370, 372 (100:65:10)	2210, 3423	2211, 3403 -

[a]The mobile phase is $CHCl_3$:MeOH (96:4, v/v) [b]The mobile phase is Hexane: EtOAc (80:20, v/v), [c]The HPLC were carried out on an Agilent 1100 system having a DA detector (λ_{max} = 220 nm, 254 nm used for this study) using a gradient run of 10-100% acetonitrile in water containing 0.1% TFA over 30 min on a RP-18e column (250 X 4.6 mm) having a particle size of 5μm

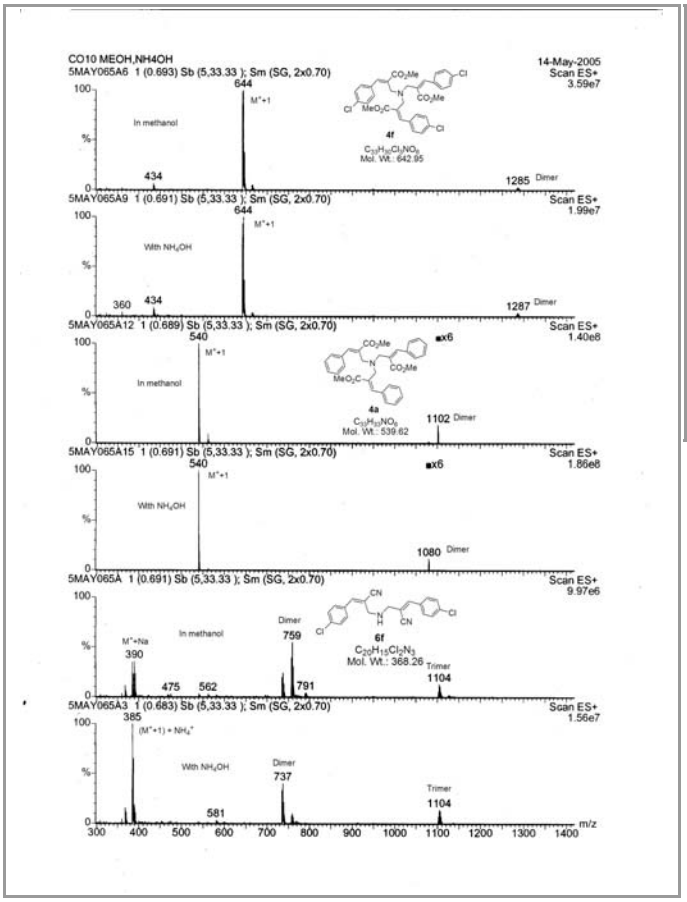


Figure 2. ES-Mass spectra of compounds **4f**, **4a** and **6f** in methanol and with NH_4OH (5 mM) at cone voltage= 10V

peak was present. The presence of molecular ion peaks for required isotopic cluster in the mass spectra of compounds containing 2 or 3 halogen atoms (chloro or bromo, **4c,d,f** and **6d,f**) provided additional evidence for the existence of products as sec- and tert-amines. In the ESI, mass spectra were first recorded in solvent (methanol) and subsequently in the presence of ammonium hydroxide (5mM) Fig. 2. In a representative example, when compound **4f** was subjected to EI-MS (70eV) the molecular ion peak was observed at 432 amu instead of 641 amu (Fig 3). This indicated that under EI conditions, the compound undergoes fragmentation. To confirm this fact, the ESMS of few derivatives were recorded at different cone voltages.[8] It was found at high cone voltage (90V) compounds **4a-f** undergo fragmentation and therefore the molecular ion peak was not observed.

Contrary to observation of Das et al., in our hands 4.0 eq. of ammonium acetate was found sufficient to take the reaction to completion without affecting the duration of the reaction and yields of products.

Thus, our results prove unambiguously that the products formed during the reaction between the acetyl derivatives of Baylis-Hillman adducts and ammonium acetate are tertiary allyl amines in case of acrylates and secondary allyl amines in case of acrylonitrile and not the primary allyl amines.

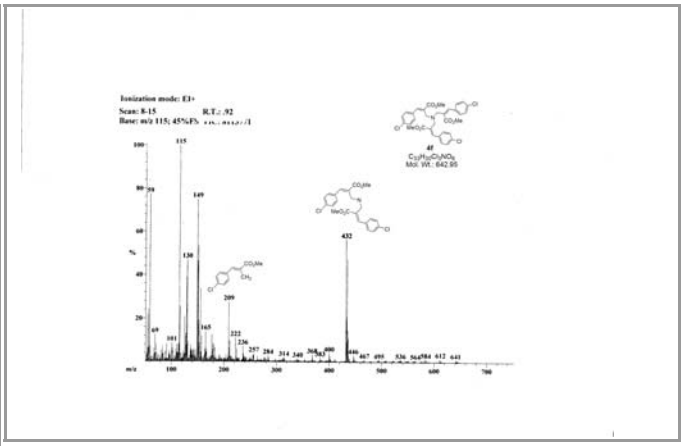


Figure 3. EI-Mass spectrum of compound **4f**.

Acknowledgments

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(6) Representative data: **2-({Bis-[3-(2-chloro-phenyl)-2-methoxycarbonyl-allyl]-amino}-methyl)-3-(2-chloro-phenyl)-acrylic acid methyl ester (4c)**- ^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.12 (s, 6H, 3 X CH_2N), 3.74 (s, 9H, 3 X CO_2Me), 7.12-7.25 (m, 6H, 3 X 2ArH), 7.35 (d, 3H, J= 7.7 Hz, 3 X 1ArH), 7.46 (d, 3H, J= 7.1Hz, 3 X 1ArH), 7.92 (s, 3H, 3 X =CH); ^{13}CNMR (50 MHz, $CDCl_3$) δ= 50.0, 52.4, 127.0, 129.9, 130.3, 131.6, 131.9, 133.9, 134.4, 140.2, 168.8.Anal. Calcd. for $C_{33}H_{30}Cl_3NO_6$: C, 61.65; H, 4.70; N, 2.25. Found: C, 61.54; H, 4.79; N, 2.18. **2-({Bis-[3-(2-bromo-phenyl)-2-methoxycarbonyl-allyl]-amino}-methyl)-3-(2-bromo-phenyl)-acrylic acid methyl ester (4d)**- ^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.07 (s, 6H, 3 X CH_2N), 3.76 (s, 9H, 3 X CO_2Me), 7.15-7.23 (m, 6H, 3 X 2ArH), 7.39-7.44 (m, 3H, 3 X 1ArH), 7.52-7.57 (m, 3H, 3 X 1ArH), 7.85 (s, 3H, 3 X =CH); ^{13}CNMR (50 MHz, $CDCl_3$) δ= 49.8, 52.5, 124.4, 127.6, 130.3, 131.7, 133.0, 135.8, 142.3, 168.8. Anal. Calcd. for $C_{33}H_{30}Br_3NO_6$:C, 51.06; H, 3.90; N, 1.80. Found: 51.33; H, 4.21; N, 2.05. **2-[(2-Cyano-3-phenyl-allylamino)-methyl]-3-phenyl-acrylonitrile (6a)**- ^{1}H NMR (300 MHz, $CDCl_3$) δ= 3.66 (s, 4H, 2 X $C\underline{H}_2NH$), 7.17 (s, 2H, 2 X =CH), 7.36-7.50 (m, 6H, 2 X 3ArH), 7.77-7.79 (m, 4H, 2 X 2ArH). Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 79.95; H, 5.59; N, 14.14. **3-(4-Chloro-phenyl)-2-{[3-(4-chloro-phenyl)-2-cyano-allylamino]-methyl}-acrylonitrile (6f)**- ^{1}H NMR (200 MHz, $CDCl_3$) δ= 3.64 (s, 6H, 3 X CH_2N), 7.14 (s, 2H, 2 X =CH), 7.40 (d, 4H, *J*= 8.4 Hz, 2 X 2ArH), 7.71 (d, 4H, *J*= 8.4 Hz, 2 X 2ArH), ^{13}CNMR (50 MHz, $CDCl_3$) δ= 52.5, 110.6, 118.5, 129.6, 130.5, 131.9, 136.9,

143.5. Anal. Calcd. for $C_{20}H_{15}Cl_2N_3$: C, 65.23; H, 4.11; N, 11.41. Found: 65.33; H, 4.49; N, 11.08.

(7) The products of series **4** were poorly soluble in methanol, therefore we did not attempt to compare their HPLC with the corresponding amine.

(8) The electrospray mass spectra were recorded 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.