Environmentally Benign Regio- and Stereoselective Synthesis of Functionalized Tertiary Amines

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The environmentally benign, regio- and stereoselective synthesis of functionalized tertiary amine **3** from acetates of Baylis-Hillman adducts with the aliphatic primary amines in the absence of any solvent and catalysts was reported.

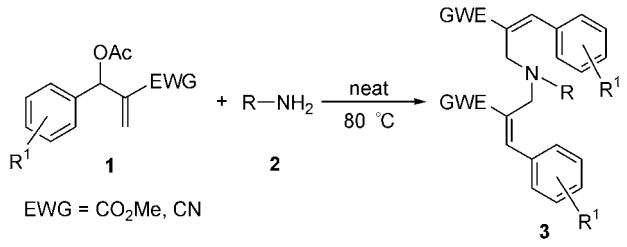
Keywords environmentally benign, regio- and stereoselective synthesis, functionalized tertiary amine, Baylis-Hillman adduct, aliphatic primary amine

Introduction

Tertiary amines are widely present in a variety of natural products and drugs.[1] Especially, tertiary amines are an extremely important class of compounds from the drug discovery perspective. Indeed no less than a quarter of registered drugs contain tertiary amines.[2] They are particularly common in drugs which are active within the central nervous system. The allylamine functionality is found in a wide range of biologically active compounds.[3] Allylamines are also valuable synthetic intermediates for the preparation of α- and β-amino acids, alkaloids, and aza-carbohydrate derivatives.[4] In addition, it is well known that structural and functional diversity plays an important role in the drug discovery process because they offer means for the structural derivatization. Consequently, the development of simple, convenient, and new methodologies for the synthesis of tertiary amines, in particular, the highly functionalized tertiary amines continues to be a challenging endeavor in synthetic organic chemistry.[5]

The Morita-Baylis-Hillman (MBH) reaction has become one of the powerful carbon-carbon bond forming methods in organic synthesis.[6] The MBH reaction provides molecules possessing hydroxy, alkenyl, and electron-withdrawing groups in close proximity, which makes it valuable in a number of stereoselective transformation processes.[7] Furthermore, many strategies/methodologies have been successfully employed in the syntheses of biologically active molecules and natural products.[8] In the past several years, we have paid much attention to the application of Baylis-Hillman adducts. And many excellent results were also demonstrated.[9] Recently, we also focused on searching more "green" or environmentally friendly chemical processes.[10] As a continuation of our interest in Baylis-Hillman and green chemistry, herein we wish to report the regio- and stereoselective synthesis of functionalized tertiary amines **3** via the reaction of acetates of Baylis-Hillman adducts **1** with aliphatic primary amines **2** under the catalyst- and solvent-free conditions (Scheme 1).

Scheme 1



Results and discussion

Our initial experiment was carried out with Baylis-Hillman adduct **1a** (R^1=phenyl, EWG=COOMe) and benzyl amine **2a** as model substrates. In a typical experiment, 3 mmol of **1a** was added to 1 mmol of **2a** under solvent- and catalyst-free conditions, and the mixture was then stirred at 80 ℃. To our delight, this model reaction finished within 3 h and the corresponding functionalized tertiary amine **3a** was afforded in 92% yield (Table 1, Entry 1). Furthermore, high *E*,*E*-selectivity was observed from the ^{1}H NMR spec-

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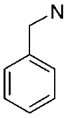
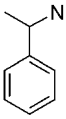
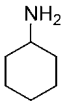
Table 1 Synthesis of functionalized tertiary amines[a]

Entry	Amine **2**	R^1	EWG	Yield[b]/%	*E*,*E*/*E*,*Z*[c]
1		H	CO_2Me	92 (**3a**)	94∶6
2		4-Me	CO_2Me	88 (**3b**)	91∶9
3		4-Cl	CO_2Me	96 (**3c**)	86∶14
4	**1a**	H	CN	94 (**3d**)	89∶11
5		H	CO_2Me	97 (**3e**)	89∶11
6		4-Me	CO_2Me	96 (**3f**)	89∶11
7		4-Cl	CO_2Me	95 (**3g**)	83∶17
8		H	CN	92 (**3h**)	83∶17
9		H	CO_2Me	92 (**3i**)	83∶17
10		H	CN	93 (**3j**)	84∶16
11		H	CO_2Me	90 (**3k**)	80∶20
12		H	CN	94 (**3l**)	100∶0

[a] Reaction conditions: Baylis-Hillman adduct **1** (3 mmol), amine **2** (1 mmol), 80 ℃; [b] Isolated yields; [c] The ratio was determined by the ^{1}H NMR spectrum.

trum of **3a**. We have also performed a number of control experiments: (1) at room temperature, the reaction proceeded slowly in relatively low yields; (2) when the ratio of **1a** and **2a** was 2∶1, **3a** was obtained in 87% yield; (3) when the ratio of **1a** and **2a** was 1∶2, the mixture of secondary amine and tertiary amine was observed; (4) when the ratio of **1a** and **2a** was 1∶3, only secondary amine was observed; (5) significant solvent effect was observed in our experiments and solvent-free case was found to be the best choice. When THF and DMF were used as solvent in this reaction, the reaction time was increased and the desired product **3a** was isolated in relatively lower yields compared with the neat condition.

Encouraged by these experimental results, a series of aliphatic primary amines **2** were treated with Baylis-Hillman adducts **1** at 80 ℃ under catalyst- and solvent-free conditions. As shown in Table 1, various aliphatic primary amines underwent smooth conversion to corresponding functionalized tertiary amines **3** in good to excellent yields. And the good *E*,*E*-stereoselectivity was demonstrated in all cases and no side products were observed. In addition, to establish the generality of the present transformation, a series of aromatic amines were then tested with Baylis-Hillman adducts **1**. Aromatic amines also underwent smooth amination under same reaction conditions, however, no functionalized tertiary amines were observed. Only high yields of secondary amines were afforded.

In summary, we have developed an environmentally benign, facile, regio- and stereoselective synthesis of the functionalized tertiary amines **3** in excellent yields from acetates of Baylis-Hillman adducts with aliphatic primary amines in the absence of any solvent and catalyst. This procedure represents a very operationally simple yet powerful method for the construction of two carbon-nitrogen bonds and two carbon-carbon double bonds in one pot. Furthermore, the resulted functionalized tertiary amines **3** have reactive ester group, carbon-carbon double bond, cyano and tertiary nitrogen atom, which enable further modifications leading to molecular diversity. Thus the present method has potential to be applied in medicinal and synthetic chemistry. Studies on the broading scope of the reaction are currently in progress in our laboratory. We believe that our method will find its use in organic synthesis, especially in large-scale industrial preparation.

Experimental

Unless otherwise stated, all reagents were commercially purchased and used without further purification. Baylis-Hillman adducts were easily prepared by addition of aromatic aldehydes with methyl acrylate. The ^{1}H NMR spectra were recorded on Brucker AC-500 (500 MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. ^{13}C NMR spectra were measured with Brucker AC-125 spectrometer. EI-MS were determined with a HP5989B mass spectrometer. IR spectra were taken as KBr discs with a Bruck vector 22 spectrometer. Elemental analyses were performed on a Vario EL III element analyzer.

General procedure for the synthesis of functionalized tertiary amines (3) To a stirred solution of 1 mmol aliphatic primary amines **2**, 3 mmol of Baylis-Hillman adduct **1** was added. The resulting mixture was allowed to react at 80 ℃ for 3 h. Then, the reaction mixture was cooled to room temperature and purified by column chromatography using ethyl acetate and petroleum ether (V∶V=1∶15) as eluent to afford the corresponding product **3a—3l** in good to excellent yields. The products were identified by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analyses.

Compound **3a**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.79 (s, 2H), 7.52 (d, J=7.5 Hz, 4H), 7.26—7.17 (m, 11H), 3.70 (s, 6H), 3.54 (s, 4H), 3.50 (s, 2H); IR (KBr) v: 3059, 3026, 2948, 2843, 1707, 1622, 1576 cm^{-1}; MS (EI) m/z: 456 (M^++1). Anal. calcd for $C_{29}H_{29}NO_4$: C 76.46, H 6.42, N 3.07; found C 76.71, H 6.38, N 2.96.

Compound **3b**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.77 (s, 2H), 7.44 (d, J=8.0 Hz, 4H), 7.25—7.21 (m, 5H), 6.98 (d, J=8.0 Hz, 4H), 3.69 (s, 6H), 3.55 (s, 4H), 3.52 (s, 2H), 2.30 (s, 6H); IR (KBr) v: 3026, 2949, 2850, 1707, 1609, 1511 cm^{-1}. Anal. calcd for $C_{31}H_{33}NO_4$: C 76.99, H 6.88, N 2.90; found C 77.16, H 6.79, N 2.83.

Compound **3c**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.72 (s, 2H), 7.44 (d, J=8.5 Hz, 4H), 7.31—7.15 (m, 5H), 7.12 (d, J=8.5 Hz, 4H), 3.71 (s, 6H), 3.50 (s, 4H), 3.49 (s, 2H); IR (KBr) v: 3061, 2949, 2845, 1708, 1623, 1590 cm^{-1}; MS (EI) m/z: 523 (M^+). Anal. calcd for $C_{29}H_{27}Cl_2NO_4$: C 66.42, H 5.19, N 2.67;

found C 66.53, H 5.32, N 2.59.

Compound **3d**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.78 (d, J=8.0 Hz, 4H), 7.46—7.23 (m, 11H), 7.23 (s, 2H), 3.80 (s, 2H), 3.52 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 147.1, 137.3, 133.0, 130.5, 129.8, 129.0, 128.8, 127.50, 124.70, 118.7, 108.1, 57.3, 48.9; IR (KBr) v: 3053, 3025, 2920, 2828, 2212, 1622, 1573, 1492 cm^{-1}; MS (EI) m/z: 389 (M^+). Anal. calcd for $C_{27}H_{23}N_3$: C 83.26, H 5.95, N 10.79; found C 83.51, H 5.82, N 10.64.

Compound **3e**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.78 (s, 2H), 7.42 (d, J=7.5 Hz, 4H), 7.25—7.27 (m, 11H), 3.97 (q, J=7.0 Hz, 1H), 3.68 (s, 6H), 3.54 (s, 2H), 3.41 (s, 2H), 1.27 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MH_z) δ: 169.4, 142.0, 141.9, 141.8, 141.5, 135.1, 131.2, 130.1, 128.7, 126.7, 78.8, 57.3, 54.5, 51.9, 10.1; IR (KBr) v: 3058, 3026, 2948, 1714, 1625, 1576 cm^{-1}. Anal. calcd for $C_{30}H_{31}NO_4$: C 76.73, H 6.65, N 2.98; found C 76.59, H 6.71, N 3.02.

Compound **3f**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.72 (s, 2H), 7.29 (d, J=8.0 Hz, 4H), 7.22—6.99 (m, 9H), 3.94 (q, J=7.0 Hz, 1H), 3.72 (s, 1H), 3.62 (s, 6H), 3.49 (s, 1H), 3.38 (d, J=12.5 Hz, 2H), 2.31 (s, 6H), 1.28 (d, J=7.0 Hz, 3H); IR (KBr) v: 3026, 2948, 2843, 1712, 1608, 1511 cm^{-1}. Anal. calcd for $C_{32}H_{35}NO_4$: C 77.24, H 7.09, N 2.81; found C 77.41, H 6.87, N 2.93.

Compound **3g**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.68 (s, 2H), 7.32—7.14 (m, 13H), 3.94 (q, J=7.0 Hz, 1H), 3.74 (s, 1H), 3.65 (s, 6H), 3.47 (s, 1H), 3.33 (d, J=12.5 Hz, 2H), 1.28 (d, J=6.5 Hz, 3H); IR (KBr) v: 3061, 3027, 2949, 2845, 1713, 1625, 1591 cm^{-1}. Anal. calcd for $C_{30}H_{29}Cl_2NO_4$: C 66.92, H 5.43, N 2.60; found C 66.73, H 5.61, N 2.64.

Compound **3h**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.77 (d, J=8.0 Hz, 4H), 7.47—7.38 (m, 11H), 7.29 (s, 2H), 4.13 (q, J=7.0 Hz, 1H), 3.52 (d, J=1.0 Hz, 2H), 3.43 (d, J=1.0 Hz, 2H), 1.50 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MH_z) δ: 145.1, 141.6, 137.3, 133.0, 130.5, 129.8, 129.0, 128.8, 127.50, 124.70, 118.7, 58.7, 49.1, 11.2; IR (KBr) v: 3059, 2930, 2839, 2212, 1623 cm^{-1}. Anal. calcd for $C_{28}H_{25}N_3$: C 83.34, H 6.24, N 10.41; found C 83.52, H 6.19, N 10.33.

Compound **3i**: viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.73 (s, 2H), 7.47 (d, J=1.5 Hz, 4H), 7.32—7.30 (m, 6H), 3.70 (s, 6H), 3.53 (s, 4H), 2.37 (m, 1H), 1.66—0.97 (m, 10H); IR (KBr) v: 3058, 3025, 2927, 2852, 1714, 1624 cm^{-1}. Anal. calcd for $C_{28}H_{33}NO_4$: C 75.14, H 7.43, N 3.13; found C 75.33, H 7.59, N 2.92.

Compound **3j**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.77 (d, J=8.0 Hz, 4H), 7.75 (s, 2H), 7.41—7.39 (m, 6H), 3.51 (s, 4H), 2.63 (m, 1H), 1.94—1.25 (m, 10H); IR (KBr) v: 3058, 3025, 2927, 2852, 1714, 1624 cm^{-1}. Anal. calcd for $C_{26}H_{27}N_3$: C 81.85, H 7.13, N 11.01; found C 81.73, H 7.35, N 10.87.

Compound **3k**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.72 (s, 1H), 7.50—7.14 (m, 10H), 6.84 (s, 1H), 3.76 (s, 3H), 3.70 (s, 2H), 3.46 (s, 3H), 3.30 (s, 2H), 1.15 (s, 9H); IR (KBr) v: 3057, 3024, 2970, 2839, 1717, 1639 cm^{-1}. Anal. calcd for $C_{26}H_{31}NO_4$: C 74.08, H 7.41, N 3.32; found C 73.84, H 7.53, N 3.47.

Compound **3l**: Viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.70 (s, 2H), 7.69 (d, J=1.0 Hz, 2H), 7.35—7.34 (m, 8H), 3.55 (s, 4H), 1.23 (s, 9H); IR (KBr) v: 3059, 3026, 2970, 2823, 2211, 1623 cm^{-1}. Anal. calcd for $C_{24}H_{25}N_3$: C 81.09, H 7.09, N 11.82; found C 80.76, H 7.13, N 11.72.

References

1 (a) Rao, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkatateswaelu, Y.; Rosser, R. M.; Faulkner, D. J.; Chen, M. H. M.; Clary, J. *J. Am. Chem. Soc.* **1984**, *106*, 7983.
(b) Daranas, A. H.; Fernandez, J. J.; Gavln, J. A.; Norte, M. *Tetrahedron* **1999**, *55*, 5539.
(c) Bleicher, L. S.; Cosford, N. D. P. *J. Org. Chem.* **1999**, *64*, 5299.
(d) Agosti, A.; Britto, S.; Renaud, P. *Org. Lett.* **2008**, *10*, 1417.

2 This estimate was obtained by searching the World Drugs Index (Derwent Information Ltd.) for compounds with a tradename which also contain a tertiary amine group.

3 (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
(b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

4 (a) Burgess, K.; Liu, L.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758.
(b) Ito, K.; Akashi, S.; Saito, B.; Katsuki, T. *Synlett* **2003**, 1809.
(c) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126.
(d) Liu, H.; Liang, X.; Sohoel, H.; Buelow, A.; Bols, M. *J. Am. Chem. Soc.* **2001**, *123*, 5116.

5 (a) Sreedhar, B.; Reddy, P. S.; Prakash, B. V.; Ravindra, A. *Tetrahedron Lett.* **2005**, *46*, 7019.
(b) Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5086.
(c) Wei, C.; Li, C. *J. Am. Chem. Soc.* **2003**, *125*, 9584.
(d) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.
(e) Murai, T.; Toshio, R.; Mutoh, Y. *Tetrahedron* **2006**, *62*, 6312.
(f) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588.
(g) Yang, S.; Hsu, Y.; Gan, K. *Tetrahedron* **2006**, *62*, 3949.
(h) Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017.
(i) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323.
(j) Akamatsu, H.; Kusumoto, S.; Fukase, K. *Tetrahedron Lett.* **2002**, *43*, 8867.
(k) Singh, V.; Pathak, R.; Kanojiya, S.; Batra, S. *Synlett* **2005**, 2465.
(l) Klemarczyk, P. *Polymer* **2001**, *42*, 2837.
(m) Akssira, M.; Guemmout, F. E.; Bauchat, P.; Foucaud, A. *Can. J. Chem.* **1994**, *72*, 1357.

6 (a) Ciganek, E. *Org. Reactions* **1997**, *51*, 201.

(b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
(c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

7 (a) Ramachandran, P. V.; Madhi, S.; Bland-Berry, L.; Reddy, M. V. R.; O'Donnel, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 13450.
(b) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Organometallics* **2005**, *24*, 762.
(c) Chung, Y. M.; Gong, J. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2001**, *42*, 9023.
(d) Singh, V.; Saxena, R.; Batra, S. *J. Org. Chem.* **2005**, *70*, 353.
(e) Patra, A.; Roy, A. K.; Batra, S.; Bhaduri, A. P. *Synlett* **2002**, 1819.

8 (a) Radha Krishna, P.; Nasingam, M.; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 4773.
(b) Rodgen, S. A.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3913.
(c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
(d) Brzezinski, L. J.; Rafel, S.; Leahy, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 4317.
(e) Wori, M.; Kuroda, S.; Dekura, F. *J. Am. Chem. Soc.* **1999**, *121*, 5591.
(f) Trost, B. M.; Thiel, O. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2003**, *125*, 13155.

9 (a) Li, S. Y.; Li, J.; Jia, X. *Synlett* **2007**, 1115.
(b) Zhao, P.; Li, J.; Jia, X. *Synlett* **2008**, 932.
(c) Li, J.; Wang, X. X.; Zhang, Y. M. *Tetrahedron Lett.* **2005**, *46*, 5233.
(d) Li, J.; Wang, X. X.; Zhang, Y. M. *Synlett* **2005**, 1039.
(e) Li, J.; Qian, W. X.; Zhang, Y. M. *Tetrahedron* **2004**, *60*, 5793.

10 (a) Jia, X.; Huang, Q.; Li, J.; Li, S.; Yang, Q. *Synlett* **2007**, 806.
(b) Wang, G.; Li, C.; Li, J.; Jia, X. *Tetrahedron Lett.* **2009**, *50*, 1438.

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