Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8709–8711

An efficient synthesis of vinylogous carbamates from alkyl azides☆

Akundi Surya Prabhakar, Suthrapu Sashikanth, Padi Pratap Reddy and Praveen Cherukupally*

Research and Development Division, Dr. Reddy's Laboratories Ltd, Integrated Product Development, Bachupally, Hyderabad 500 055, AP, India

Received 13 August 2007; revised 26 September 2007; accepted 3 October 2007
Available online 6 October 2007

Abstract—An efficient one-pot synthesis of vinylogous carbamates is reported starting from alkyl azides by using NH_4Cl/Zn dust.

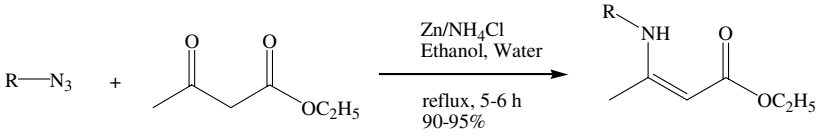
Vinylogous carbamates, also known as enaminoesters are versatile building blocks in the synthesis of various heterocycles,[1] natural products[2] (wortmannin-based probes for lipid and protein kinases) and are often endowed with useful pharmacological properties.[3] Recent reports show that these compounds are useful in peptidomimetics,[4] preparation of β-amino acids[5] and also in anti-HIV drugs[6] (MLN 1251). Vinylogous carbamates are generally prepared by the condensation of amines with β-ketoesters, with azeotropic removal of water, using expensive reagents, and some methods suffer from incomplete reaction and the use of hazardous solvents.[7] Recent reports described a one-pot synthesis of vinylogous carbamates from alkyl azides by hydrogenation,[8] which is expensive and needs special equipment on large scale.

In this Letter we describe the synthesis of various vinylogous carbamates starting from alkyl azides[9] and β-ketoesters in a one-pot procedure. This method has not been previously documented in aqueous media.[10]

A variety of alkyl azides were treated with ethyl acetoacetate in the presence of NH_4Cl/Zn dust/ethanol under reflux for 5–6 h to furnish the corresponding vinylogous carbamates in high yields (Table 1).[11,12] In all the cases we did not observe significant amounts of over reduced products or the intermediate amines. Reactions involving benzyl azides (Table 1, entries 3 and 6) did not undergo loss of the benzyl group, the corresponding vinylogous carbamates being obtained in good yields. In all the cases the products were isolated as mixtures of *Z*, *E*-isomers, which were not separable.

Products with *Z* double bond geometry were favoured over the *E*-isomer. It is postulated that intramolecular hydrogen bonding could be responsible for the observed equilibrium shift towards the *Z*-isomer.[13,14]

In conclusion, we have developed a simple, cost effective and green procedure for the synthesis of vinylogous carbamates starting from alkyl azides and β-ketoesters using NH_4Cl/Zn dust in ethanol (see Scheme 1).

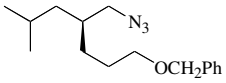
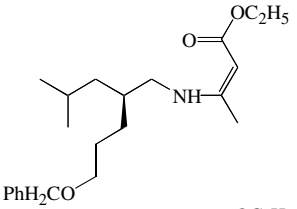
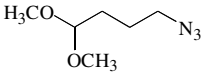
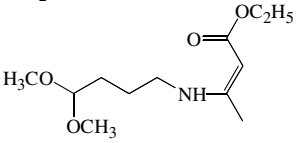
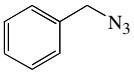
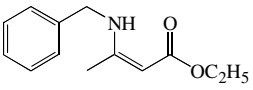
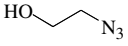
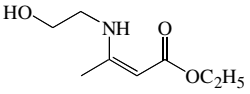
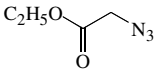
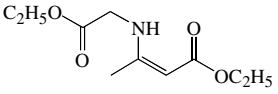
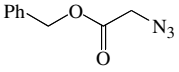
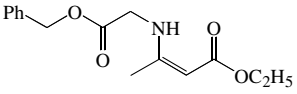
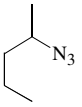
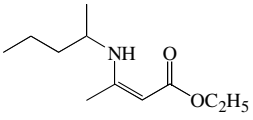
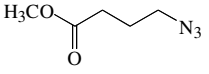
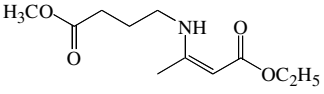
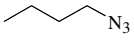
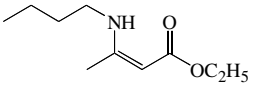


Scheme 1.

Keywords: Alkyl azide; Vinylogous carbamates.
☆DRL Publication No.: IPDOIPM-00080.
* Corresponding author. Tel.: +91 9963029500; fax: +91 40 44346431; e-mail: praveench@drreddys.com

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.10.013

Table 1. Reaction of azides with beta keto esters in presence of Zn/NH_4Cl

Entry	Azide	Product	Yield (%)
1			80
2			71
3			62
4			51
5			96
6			89
7			56
8			50
9			53

Acknowledgements

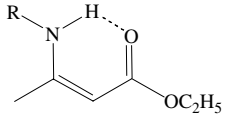
We thank the management of Dr. Reddy's Laboratories Ltd. for extending support to the work. Co-operation from project colleagues and the analytical department is highly appreciated.

References and notes

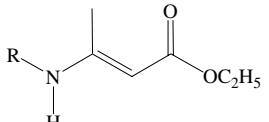
1. (a) Elassar, A. A.; El-Khai, A. A. *Tetrahedron* **2003**, *59*, 8463–8480; (b) Alan, C.; Spivey, A. C.; Srikaran, R.; Diaper, C. M.; David, J.; Turner, D. J. *Org. Biomol. Chem.* **2003**, *1*, 1638; (c) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277–294; (d) Cimarelli, C.; Palmieri, G. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 179–189; (e) Pawlak, J. M.; Khau, V. V.; Hutchinson, D. R.; Martinelli, M. J. *J. Org. Chem.* **1996**, *61*, 9055–9059.
2. Michael, J. P.; De Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979–988.
3. (a) Edafiogho, I. O.; Alexander, M. S.; Moore, J. A.; Farrar, V. A.; Scott, K. R. *Curr. Med. Chem.* **1994**, *1*, 159–175; (b) Edafiogho, I. O.; Moore, J. A.; Alexander, M. S.; Scott, K. R. *J. Pharm. Sci.* **1994**, *83*, 1155–1170.
4. (a) Smith, A. B.; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947–9962; (b) Smith, A. B.; Hirschmann, R.; Pasternak, A.; Akaishi, R.; Guzman, M. C.; Jones, D. R.; Keenan, T. P.;

Sprengeler, P. A.; Darke, P. L.; Emini, E. A.; Holloway, M. K.; Schleif, W. A. *J. Med. Chem.* **1994**, *37*, 215–218; (c) Smith, A. B.; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672–10674; (d) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568–6570.

5. (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919; (b) Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7*, 355–361; (c) Tang, W.; Wang, W.; Yongxiang, C.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509–3511; (d) You, J.; Drexler, H. J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 913–916; (e) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571; (f) Pena, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553; (g) Wu, J.; Chen, X.; Guo, R.; Yeung, C.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 2490–2493; (h) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Borner, A. *Tetrahedron Lett.* **2000**, *41*, 2351–2355; (i) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084–6085; (j) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985–5986.
6. Drahl, C.; Cravatt, B. F.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5788–5809.
7. (a) Brandt, C. A.; da Silva, A. C. M. P.; Pancote, C. G.; Brito, C. L.; da Silvaria, M. A. B. *Synthesis* **2004**, 1557–1559; (b) Ahmad, R.; Khosropour, A. R.; Khodaei, M. M.; Kookhazadeh, M. *Tetrahedron Lett.* **2004**, *41*, 1725–1728; (c) Azzaro, M.; Geribaldi, S.; Videau, B. *Synthesis* **1981**, 880–881; (d) Stefane, B.; Polanc, S. *New J. Chem.* **2002**, *26*, 28–32.
8. (a) Reddy, D. S.; Vander Velde, D.; Aube, J. *J. Org. Chem.* **2004**, *69*, 1716–1719; (b) Reddy, D. S.; Rajale, Trideep V.; Shiva Kumar, K.; Iqbal, J. *Tetrahedron Lett.* **2005**, *46*, 979–982.
9. The alkyl azides were prepared from the corresponding bromides or mesylates using NaN_3.
10. (a) Lambert, P. H.; Vaultier, M.; Carrie, R. *J. Org. Chem.* **1985**, *50*, 5352–5356; (b) Langer, P.; Freifeld, I. *Chem. Commun.* **2002**, 2668–2669.
11. A mixture of 0.5 g alkyl azide (1 equiv), 0.34 g NH_4Cl (2 equiv), 0.8 g ethyl acetoacetate (1.2 equiv) and 0.2 g zinc (1 equiv) in ethanol (10 mL), and water (1.25 mL) was stirred for 3–5 h at reflux. After completion of the reaction (TLC), the reaction mixture was cooled to 25–35 °C, the zinc catalyst filtered and the filtrate distilled to dryness under reduced pressure. Ethyl acetate (20 mL) and water (20 mL) were added and the aqueous layer extracted twice more with ethyl acetate. The combined organic fractions were washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and distilled under reduced pressure to give the crude product, which was purified by column chromatography on silica gel to afford the pure product (eluent: ethyl acetate/hexane 15:85–40:60).
12. *Spectral data of selected compounds: Entry 3*: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3 (t, $J = 7.32$ Hz, 3H), 1.85 (s, 3H), 4.19 (q, $J = 7.32$ Hz, 2H), 4.4 (d, $J = 6.35$ Hz, 2H), 4.5 (s, 1H), 7.2–7.4 (m, 5H), 8.9 (br s, 1H). IR (neat, cm^{-1}): 1735 (C=O ester), 1648 (C=C), 3434 (NH), 2931 (CH aliphatic), 1497 (C=C aromatic). Mass (*m*/*z*): 219.28. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.32; H, 7.68, N, 6.26. *Entry 4*: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3 (t, $J = 7.34$ Hz, 3H), 1.82 (s, 3H), 3.4 (m, 2H), 3.75 (m, 1H), 4.2 (m, 4H), 4.5 (s, 1H), 8.7 (br s, 1H). Mass (*m*/*z*): 173.21. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.36; H, 8.68, N, 8.14. *Entry 6*: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3 (t, $J = 7.33$ Hz, 3H), 1.86 (s, 3H), 4.19 (m, 4H), 4.5 (s, 1H), 4.7 (s, 2H), 7.2–7.4 (m, 5H), 8.9 (br s, 1H). IR (neat, cm^{-1}): 1735 (C=O ester), 1648 (C=C), 3434 (NH), 2931 (CH aliphatic), 1497 (C=C aromatic). Mass (*m*/*z*): 277.32. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.86; H, 6.82, N, 5.14.
13. (a) Reddy, D. S.; Judd, W. R.; Aube, J. *Org. Lett.* **2003**, *5*, 3899–3902; (b) Gilli, P.; Bertolasi, V.; Pretto, L.; Lycka, A.; Gilli, G. *J. Am. Chem. Soc.* **2002**, *124*, 13554–13567; (c) Zhuo, J.-C. *Magn. Reson. Chem.* **1997**, *35*, 311–322.
14. Intramolecular hydrogen bonding in the *Z*-isomer could be responsible for shifting the equilibrium towards the *Z*-isomer.



Z isomer



E isomer