ORGANIC LETTERS

2003
Vol. 5, No. 21
3899−3902

Lewis Acid-Mediated Reactions of Alkyl Azides with α,β-Unsaturated Ketones

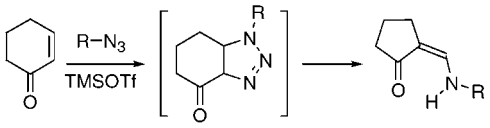
D. Srinivasa Reddy, Weston R. Judd, and Jeffrey Aubé*

Department of Medicinal Chemistry, 1251 Wescoe Hall Drive, Malott Hall, Room 4070, University of Kansas, Lawrence, Kansas 66045-7582

jaube@ku.edu

Received August 11, 2003

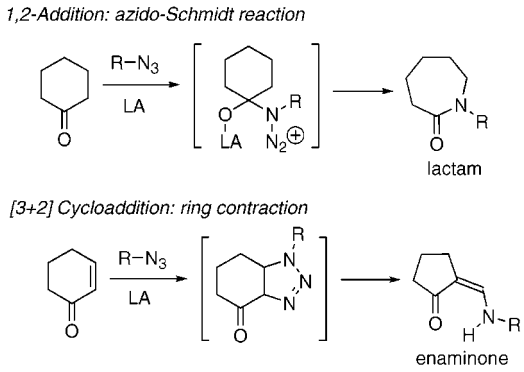
ABSTRACT



Alkyl azides react with saturated ketones upon treatment with Lewis acids to afford ring-expansion products through the azido-Schmidt reaction, but this reaction does not proceed when α,β-unsaturated ketones are used. In this study, alkyl azides were reacted with enones in the presence of Lewis acids to give enaminones (vinylogous amides), which formally involve a ring contraction reaction. The mechanism and scope of this reaction is discussed.

The chemistry of alkyl azides encompasses 1,3-cycloaddition or radical reactions as well as polar chemistry in which the azide plays the role of either electrophile or nucleophile.[1] About 10 years ago, we discovered that alkyl azides undergo Lewis acid-mediated reactions with ketones to give the corresponding lactams (the azido-Schmidt reaction; Scheme 1).[2] This reaction entails the initial addition of azide to an activated carbonyl group in a 1,2 fashion. In contrast, we have been unable to obtain Schmidt type ring expansion products from α,β-unsaturated ketones in either an inter- or intramolecular sense.[2d] In this paper we report that Lewis acids activate enones toward a facile [3 + 2] cycloaddition pathway, affording 1,2,3-triazolines. These intermediates are not observed, but in many cases rearrange in situ to furnish enaminones in an overall ring contraction process.

Scheme 1



This investigation began by examining the reactions of 2-cyclohexenone with simple alkyl azides. Thus, treatment of cyclohexenone with benzyl azide in the presence of TMSOTf afforded enaminone **1** as a crystalline material in

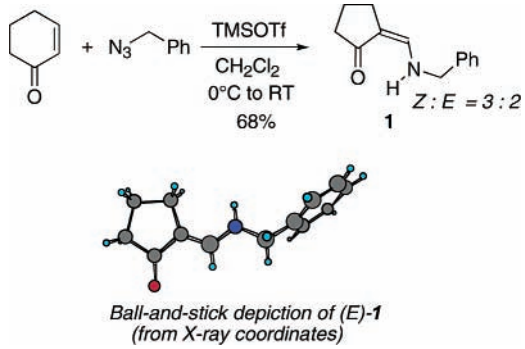
(1) For reviews and some recent leading references, see: (a) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley & Sons: London, 1971; pp 397−440 (b) Abramovich, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley & Sons: London, 1971; pp 221−329. (c) Kyba, E. P. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: Orlando, 1984; pp 2−34. (d) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368. (e) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521−5522. (f) Tingoli, M.; Tiecco, M.; Chianelli, D.; Balducci, R.; Temperini, A. *J. Org. Chem.* **1991**, *56*, 6809−6813. (g) Clive, D. L. J.; Etkin, N. *Tetrahedron Lett.* **1994**, *35*, 2459−2462. (h) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192−3193. (i) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2113-2116. (j) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030. (k) Mertens, A.; Lammertsma, K.; Arvanaghi, M.; Olah, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 5657−5660. (l) Khouki, M.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1986**, *27*, 1031−1034.

(2) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (b) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637. (c) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226−7232. (d) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459. (e) Wrobleski, A.; Aubé, J. *J. Org. Chem.* **2001**, *66*, 886−889.

10.1021/ol0355130 CCC: $25.00
Published on Web 09/24/2003

68% yield (Scheme 2). The assigned structure was confirmed by X-ray crystallography.[3]

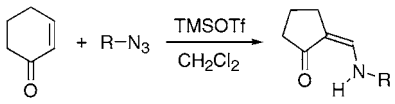
Scheme 2



Reactions of azides and enones are known to produce ring-contracted products or ring-expanded lactams thermally via triazoline intermediates.[4] There have also been reports on ring-contraction of enamines and enol ethers using arylsulfonyl azides.[5] In general, such reactions usually require heating to ca. 100 °C for 1,3-dipolar cycloaddition. In the present case, temperatures of 0 °C to rt are sufficient to activate the carbonyl group toward cycloaddition. Enaminones are versatile building blocks for the construction of various heterocycles[6] and natural products[7] and are often endowed with useful pharmacological properties.[8] Enaminones are generally prepared from 1,3-diketones and amines,[6a,9] and the present method could provide an alternative route to these useful materials.

Scanning a variety of Lewis acids for the above transformation, it was found that the first choice of TMSOTf was best, although $BF_3{\cdot}Et_2O$ and TFA also gave the same product. Other Lewis acids such as $TiCl_4$, triflic acid, $MeAlCl_2$, and $Yb(OTf)_3$ resulted in less than 10% conversion. Using TMSOTf, we then examined the reaction of cyclohexenone with a variety of alkyl azides (Table 1). The alkyl azides examined gave smooth ring contraction to furnish enaminones **2**−**7** in ca. 60−90% yields with the exception of azidocyclohexane (entry 7).

Table 1. Reaction of Cyclohexenone with Various Azides



entry	R	yield (%)	product (*Z*/*E* ratio)
1	$PhCH_2CH_2-$	93	**2** (2:1)
2	*n*-$C_6H_{13}-$	83	**3** (2:1)
3	*trans*-$PhCH{=}CHCH_2-$	76	**4** (3:2)
4	$EtO_2CCH_2CH_2-$	69	**5** (1:1)
5	*p*-$MeO(C_6H_4)CH_2-$	62	**6** (1:1)
6	$Cl(CH_2)_3-$	77	**7** (2:1)
7	*c*-$C_6H_{11}-$	20	**8** (2:1)

The *Z*,*E* ratio of each product was determined using ^{1}H NMR of the crude material. In general, the isomers were not separable, and enaminones with *Z* double-bond geometry were favored over the *E* isomers. The geometry was assigned based on spectroscopic (IR and ^{1}H NMR) trends throughout the series (Figure 1). To wit, the isomer that had the lower field NH proton and a higher field olefinic proton was assigned as the *Z* isomer.[10] In addition, the *Z* isomer has a lower $\nu_{C=O}$ compared to that measured for the *E* isomer. Intramolecular hydrogen bonding in the *Z* isomer could be responsible for the dramatic difference in the spectral data of the *Z* and *E* isomers.[11]

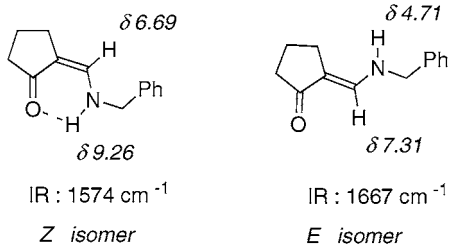


Figure 1. Characteristic spectral data of (*Z*)- and (*E*)-**1**.

(3) Coincidently, a single crystal of the minor isomer (*E*)-**1** was picked from the mixture of *E*,*Z* isomers for X-ray analysis.

(4) (a) Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676−1678. (b) Schultz, A. G.; Ravichandran, R. *J. Org. Chem.* **1980**, *45*, 5008−5009. (c) Sha, C.-K.; Ouyang, S.-L.; Hsieh, D.-Y.; Hseu, T.-H. *J. Chem. Soc., Chem. Commun.* **1984**, 492−494. (d) Sha, C.-K.; Ouyang, S.-L.; Hsieh, D.-Y.; Chang, R.-C.; Chang, S.-C. *J. Org. Chem.* **1986**, *51*, 1490−1494. (e) Benati, L.; Calestani, G.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1381−1385. (g) Hansen, P. E.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 305−308. (h) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 71−77. (i) Benati, L.; Montevecchi, P. C.; Spagnolo, P.; Foresti, E. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2845−2850. (j) Molander, G. A.; Bibeau, C. T. *Tetrahedron Lett.* **2002**, *43*, 5385−5388.

(5) (a) Wohl, R. A. *Helv. Chim. Acta* **1973**, *56*, 1826−1828. (b) Wohl, R. A. *Tetrahedron Lett.* **1973**, 3111−3114. (c) Semenov, V. P.; Andreeva, T. D.; Ogloblin, K. A. *Zh. Org. Khim.* **1988**, *24*, 217−220. (d) Semenov, V. P.; Mishin, M. A.; Ogloblin, K. A. *Zh. Org. Khim.* **1988**, *24*, 2384−2388. (e) Semenov, V. P.; Ogloblin, K. A. *Zh. Org. Khim.* **1987**, *23*, 898−899. (f) Semenov, V. P.; Ogloblin, K. A. *Zh. Org. Khim.* **1988**, *24*, 2389−2397. (g) Xu, Y.; Wang, Y.; Zhu, S. *Synthesis* **2000**, 513−516.

(6) (a) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277−294. (b) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1997**, *67*, 207−343. (c) Cimarelli, C.; Palmieri, G. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 179−189.

(7) 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.

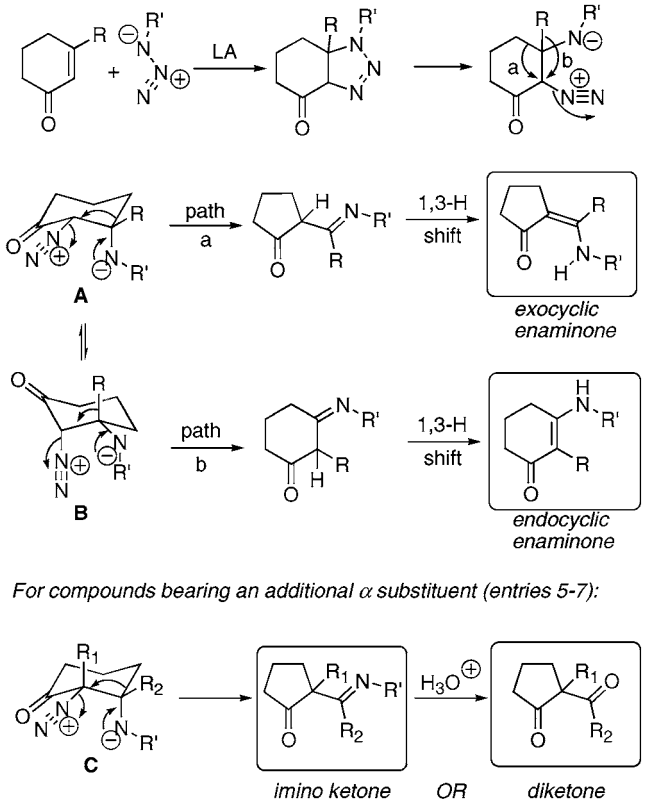
(8) (a) Scott, K. R.; Rankin, G. O.; Stables, J. P.; Alexander, M. S.; Edafiogho, I. O.; Farrar, V. A.; Kolen, K. R.; Moore, J. A.; Sims, L. D.; Tonnu, A. D. *J. Med. Chem.* **1995**, *38*, 4033−4043. (b) Edafiogho, I. O.; Alexander, M. S.; Moore, J. A.; Farrar, V. A.; Scott, K. R. *Curr. Med. Chem.* **1994**, *1*, 159−175. (c) Edafiogho, I. O.; Moore, J. A.; Alexander, M. S.; Scott, K. R. *J. Pharm. Sci.* **1994**, *83*, 1155−1170.

(9) (a) Azzaro, M.; Geribaldi, S.; Videau, B. *Synthesis* **1981**, 880−881. (b) Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902−903. (c) Valduga, C. J.; Squizani, A.; Braibante, H. S.; Braibante, M. E. F. *Synthesis* **1998**, 1019−1022. (d) Stefane, B.; Polanc, S. *New J. Chem.* **2002**, *26*, 28−32.

(10) (a) Zhuo, J.-C. *Magn. Reson. Chem.* **1997**, *35*, 311−322. (b). Zhuo, J. C.; Schenk, K. *Helv. Chim. Acta* **1997**, *80*, 2137−2147.

These results show that, under Lewis acid activation, the enones are more activated for 1,3-dipolar cycloaddition than for nitrogen insertion into the carbonyl group. The mechanism formulated in Scheme 3 involves Lewis acid-mediated

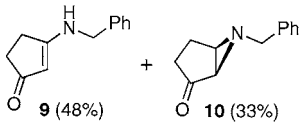
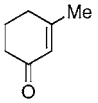
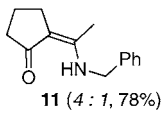
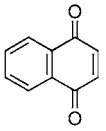
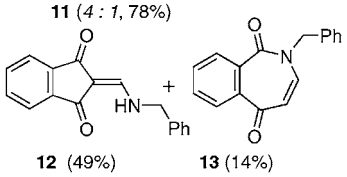
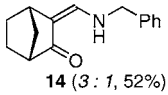
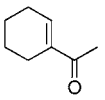
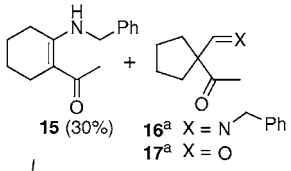
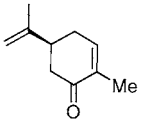
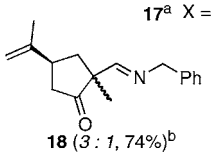
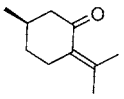
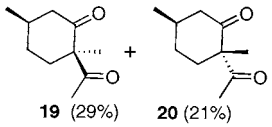
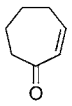
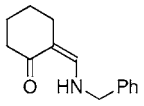
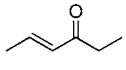
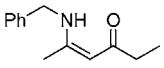
Scheme 3



regioselective 1,3-dipolar cycloaddition[12] of the alkyl azide onto the enone olefin as the first step to give the triazoline intermediate. Under the reaction conditions, the unstable triazoline intermediate undergoes decomposition to produce a zwitterionic species that can exist in either one of the two conformations (**A** or **B**). In conformer **A**, 1−2 bond migration onto the leaving diazonium species in an antiperiplanar fashion followed by 1,3-hydrogen shift leads to the ring-contracted exocyclic enaminone. In contrast, migration of the alkyl group in **B** onto the axial diazonium species results in formation of an endocyclic enaminone.

Various enones were then surveyed toward their reaction with benzyl azide in the presence of TMSOTf (Table 2). Many examples gave ring-contraction products (enaminones) as occurred with cyclohexenone (entries 2−4 and 8). Cyclopentenone gave two different products in 81% overall yield, with the endocyclic enaminone **9** being the major one and the aziridine derivative **10**[13] being the minor one. Another

Table 2. Reactions of Benzyl Azide with Various Enones

entry	enone	product(s) (*Z* : *E* ratio, yield)
1		 **9** (48%) + **10** (33%)
2		 **11** (*4* : *1*, 78%)
3		 **12** (49%) + **13** (14%)
4		 **14** (*3* : *1*, 52%)
5		 **15** (30%) **16**[a] X = N Ph **17**[a] X = O
6		 **18** (*3* : *1*, 74%)[b]
7		 **19** (29%) + **20** (21%)
8		 **21** (*9* : *1*, 78%)
9		 **22** (49%)

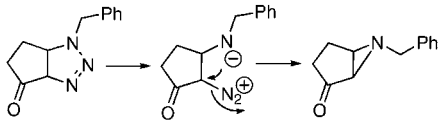
[a] Compounds were identified in crude NMR but not isolated. [b] Crude yield; stereochemistry unassigned.

manifold is possible for ketones bearing an additional substituent at the α carbon (see **C** in Scheme 3). Entries 5−7 show products with new quaternary centers in which the intermediates formed during ring contraction were mechanistically prohibited from forming enaminones via 1,3-H shift. In the case of (+)-pulegone, a diastereomeric mixture of *β*-diketones **19** and **20**[14] was isolated in 50% yield (entry

(11) Gilli, P.; Bertolasi, V.; Pretto, L.; Lycka, A.; Gilli, G. *J. Am. Chem. Soc.* **2002**, *124*, 13554−13567.

(12) (a) Huisgen, R.; Szeimies, G.; Moebius, L. *Chem. Ber.* **1966**, *99*, 475−490. (b) Broeckx, W.; Overbergh, N.; Samyn, C.; Smets, G.; L'Abbe, G. *Tetrahedron* **1971**, *27*, 3527−3534. (c) Texier, F.; Carrie, R. *Bull. Soc. Chim. Fr.* **1971**, 4119−4128.

(13) Formation of aziridine **10** can be explained by the following mechanism.



7) in which the imine obtained from methyl migration was hydrolyzed to give β-diketones under the reaction conditions. Also note that imines obtained in entries 5 and 6 were not isolated in pure form due to their instability. We also tried the reaction of benzyl azide with an acyclic enone, which gave enaminone **22** as the only isolated product (entry 9). In contrast, reaction of benzyl azide with methyl crotonate gave no desired product under the same conditions. Our experimental results showed that "path a" is favored over "path b" in our proposed mechanism (see Scheme 3) in all cases except cyclopentenone, which can be attributed to the strain factor in going from a 5- to a 4-membered ring. It is noteworthy that a formal Schmidt lactam product **13** (from ring expansion) was observed only in the case of naphthoquinone out of all the substrates tried.

This study establishes why enones fail in the Schmidt reactions of alkyl azides. Unlike simple carbonyls, which have only one mode of reactivity, enones can react at the carbonyl group in a 1,2 fashion or at the double bond. In the latter case, 1,4-addition (i.e., conjugate addition) or other kinds of double-bond reactivity are possible. Our study shows that azides react with Lewis acid-activated enones in the well-known [3 + 2] cycloaddition mode rather than in the Schmidt reaction mode. Furthermore, these reactions occur at temperatures well below those needed for analogous thermal reactions. Finally, we have established a range of further reactions possible for the 1,2,3-triazolines formed, at least one of which—ring contraction to afford enaminones—is likely to be of some synthetic interest. Further studies of alternative modes of azide reactivity are underway in these laboratories.

Acknowledgment. We thank the National Institutes of Health (GM-49093) for the support of this work and Doug Powell for the X-ray crystallographic structure.

Supporting Information Available: Experimental details and characterization data for all new compounds and details pertaining to the X-ray structure of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0355130

(14) Reusch, W.; Anderson, D. F.; Johnson, C. K. *J. Am. Chem. Soc.* **1968**, *90*, 4988−4993.