Efficient Nitrogen Ring-Expansion Process Facilitated by in Situ Hemiketal Formation. An Asymmetric Schmidt Reaction

Vijaya Gracias, Gregory L. Milligan, and Jeffrey Aubé*

Department of Medicinal Chemistry, University of Kansas Lawrence, Kansas 66045-2506

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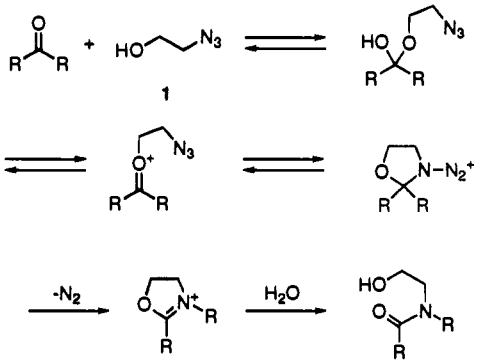
We recently reported an intramolecular version of the Schmidt reaction[1] in which hydrazoic acid was replaced by an alkyl azide connected to the reactive ketone.[2] This is an unusual example of intramolecularity because the analogous H^+-promoted intermolecular reaction does not succeed at all.[3] Given the potential utility of a general method for the intermolecular insertion of an *N*-alkyl group adjacent to a ketone, other conditions to effect the direct reaction of ketones with alkyl azides were examined. Of several Lewis acids tried, only $TiCl_4$ was effective.[4] However, this reaction turned out to be severely limited, with poor (<20%) yields being obtained when even modestly substituted cyclohexanones or, most curiously, cyclopentanones of any stripe were used. In addition, the need for such a strong Lewis acid could be a drawback in reactions of multifunctional substrates.

One immediately evident solution to this problem was to utilize a tethering substituent that would temporarily connect the two reactive groups and be subsequently removed.[5] Although meritorious, this approach would entail the addition of minimally two steps to a synthetic sequence in attaching and removing the tethering group. An alternative approach is suggested in Scheme 1. Utilization of an azido alcohol such as 2-azidoethanol (**1**) presents an activated ketone with two potential nucleophiles. Our previous work has shown that direct attack by azide is possible but only marginally effective. Instead, hemiketal formation could occur, followed by dehydration to generate the oxonium ion shown. At this point, intramolecular attack of the azide on the carbocation is possible, following our own precedent[2] and that of Pearson and co-workers.[6] Migration of one of the alkyl groups with concomitant loss of N_2 would then afford an iminium ether species that, upon addition of water, would give the formal product of direct insertion of the azide end of **1** into the ketone.

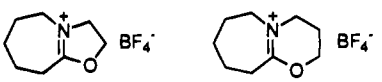
This idea was attractive because the tether which renders the ketone and azide intramolecular would be generated in situ and not require additional steps for its installation and removal. Previously, Boyer and co-workers had found that hydroxy azides could be reacted with aromatic aldehydes only, affording oxazolines or dihydrooxazines as the products in good yields; however, this H_2SO_4-promoted reaction failed with ketones.[7,8] These authors attributed the success of hydroxy azides relative to simple alkyl azides to greater acid stability of the former species (due to hydrogen bonding) and did not consider the

Scheme 1



mechanism shown above in Scheme 1.[9] Herein, we report that this strategy provides an effective and broad approach to multifunctional lactam synthesis and *that using chiral azido alcohols leads to the first known examples of an asymmetric Schmidt reaction.*

The examples shown in Table 1 are representative. Although several Lewis acids were found effective in this reaction, including trifluoroacetic acid, we have settled for the time being on $BF_3{\cdot}OEt_2$ as the most convenient promoter in terms of efficiency and ease of workup.[10] In each case, the yields of each product are superior to those obtained using simple alkyl azides;[4] in particular, note that cyclopentanones react to give N-substituted valerolactams in good to excellent yields throughout. Support for the mechanism shown in Scheme 1 arises from the fact that the reaction succeeds with substrates and promoters shown to be unsuccessful with simple alkyl azides;[4] in addition, a control experiment in which 3-azido-1-methoxypropane and cyclohexanone were submitted to these conditions gave only recovered starting materials. Also, intermediates **3** and **4** could be isolated (77, 78% yields) and characterized as their tetrafluoroborate salts after precipitation from the reaction mixture occasioned by the addition of cold THF.



3 **4**

Substantial improvements in tolerance of the ring-expansion protocol to substitution adjacent to the ketone were also noted (Scheme 2). Interestingly, while the efficiencies were much better than those using the $RN_3/TiCl_4$ protocol (which only gave lactams in 10−20% yields, if at all), the regiochemistry of the reaction depended on the nature of the C-2 substituent. In

(1) Reviews of the Schmidt reaction: (a) Wolff, H. *Org. React. (N.Y.)* **1946**, *3*, 307−336. (b) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley and Sons: New York, 1963; Vol. 1; pp 457−591. (c) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley and Sons: London, 1971; pp 397−440. (d) Abramovich, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley and Sons: London, 1971; pp 221−329. (e) Kyba, E. P. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: Orlando, 1984; pp 2−34.

(2) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966.

(3) (a) Briggs, L. H.; De Ath, G. C.; Ellis, S. R. *J. Chem. Soc.* **1942**, 61−63. (b) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320−323.

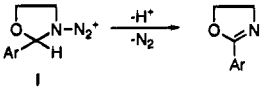
(4) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637.

(5) For a successful example of this strategy, see: Stork, G.; Chan, T. Y.; Brealt, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578−7579 and papers cited therein.

(6) (a) Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.* **1992**, *33*, 5291−5294. (b) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183−10194. (c) Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682−2684.

(7) (a) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951−954. (b) Boyer, J. H.; Canter, F. C.; Hamer, J.; Putney, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 325−327.

(8) Note that, with aldehydes, neutral products can be obtained from intermediates such as i by proton elimination, as contrasted to hydride migration.



i

(9) An intramolecular reaction of an alkyl azide connected by a thioether tether has been accomplished thermally: Schultz, A. G.; Ravichandran, R. *J. Org. Chem.* **1980**, *45*, 5008−5009.

(10) The reaction of cyclohexanone with **2** is representative. A solution of cyclohexanone (200 mg, 2.04 mmol) and 3-azido-1-propanol (247 mg, 2.44 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C. $BF_3{\cdot}Et_2$ (0.51 mL, 4.08 mmol) was added dropwise over 5 min. Immediate gas evolution was noted upon addition. The reaction was allowed to warm to room temperature over 30 min and was stirred for an additional 3 h. The solution was concentrated, 5 mL of saturated $NaHCO_3$ was added to the residual oil, and the mixture was stirred for 30 min. After concentration, an additional 100 mL of CH_2Cl_2 was added and the organic layer was separated, dried ($NaSO_4$), and concentrated to afford a colorless oil. Flash chromatography (EtOAc) gave 320 mg (90%) of 1-(3′-hydroxypropyl)-azepin-2-one as a clear oil.

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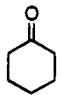
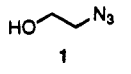
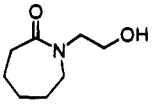
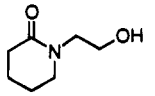
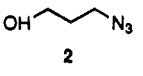
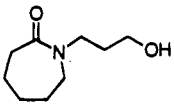
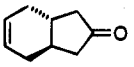
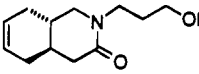
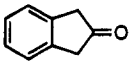
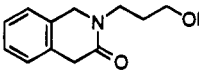
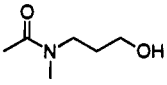
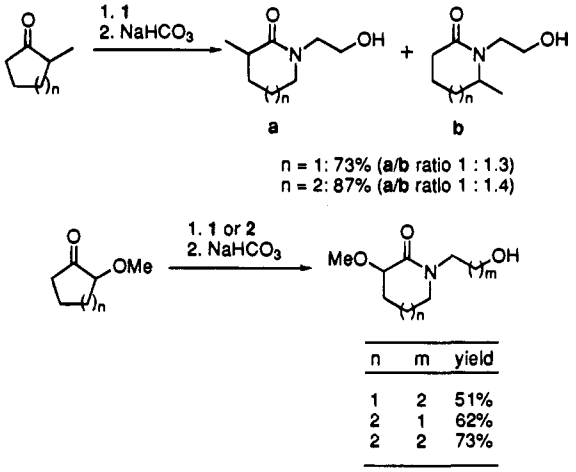
Table 1. Reactions of 2-Azidoethanol and 3-Azidopropanol with Symmetrical Ketones

ketone	azide	product	yield
	 1		98%
	1		96%
	 2		90%
	2		88%
	2		80%
	2		86%

Scheme 2

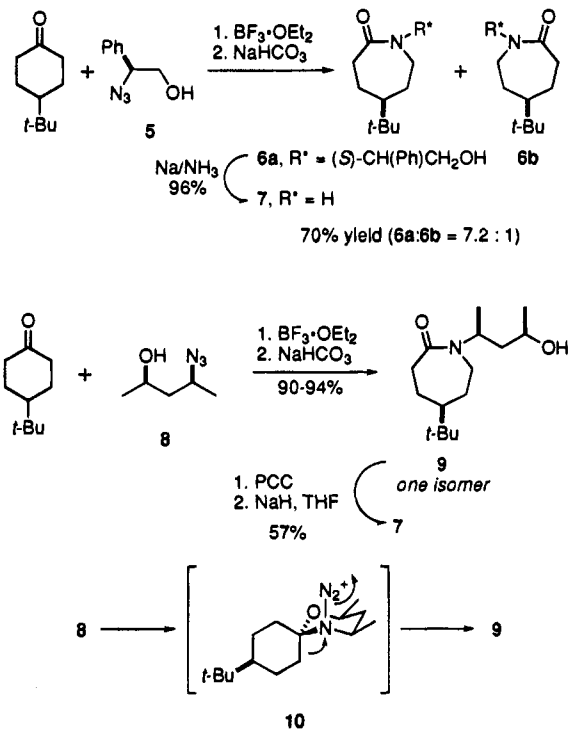


n	m	yield
1	2	51%
2	1	62%
2	2	73%

particular, whereas 2-methylcycloalkanones afforded mixtures of regioisomers, the 2-methoxy-substituted versions resulted in the isolation of product resulting from the migration of the less-substituted carbon. This is opposite to the regiochemistry generally observed in the classical Schmidt[1] or Beckmann[11] reactions.

Finally, two examples suffice to demonstrate the potential of this process in the asymmetric synthesis of chiral lactams. Although axially dissymmetric oximes can be resolved and subjected to stereoselective Beckmann reactions,[12] the only known asymmetric nitrogen insertion process able to differentiate the enantiotopic methylene groups in ketones like 4-*tert*-butylcyclohexanone utilizes oxaziridines (three reactions and two pots) and results in overall ratios of about 7.3:1.[13] As shown in Scheme 3, utilization of two readily available chiral azido alcohols[14] affords diastereotopic lactams in good yields and improved stereoselectivity. So far, the best results were

Scheme 3



observed with **8**: running the reaction at 0 °C and in pentane afforded lactam **9** as a single diastereomer in 90–94% isolated yield (as ascertained by 500 MHz NMR analysis[16]). Enantioselective lactam syntheses were completed by reductive removal of the chiral substituent on nitrogen or by the sequence shown for **8**.[17] Although detailed mechanistic proposals are premature, an intermediate such as **10**, arising from equatorial attack of azide onto the oxonium ion, would be expected to afford the observed product by migration of the pseudoaxial bond antiperiplanar to the departing N_2 substituent.

The utilization of an in situ tether in nitrogen ring-expansion reactions has been shown to greatly improve the scope and efficiency of these reactions. Current work is directed toward the application of this reaction in asymmetric synthesis, investigating the chemistry of the intermediate iminium ethers, and determining the scope of this asymmetric variant of the Schmidt reaction.

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Supporting Information Available: Experimental details and characterization data for new compounds including copies of ^1H and ^{13}C NMR spectra of **9** and **9b** (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(11) Gawley, R. E. *Org. React. (N.Y.)* **1988**, *35*, 1–420.
(12) (a) Lyle, R. E.; Lyle, G. G. *J. Org. Chem.* **1959**, *24*, 1679–1684. (b) Toda, F.; Akai, H. *J. Org. Chem.* **1990**, *55*, 4973–4974.
(13) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879–4891.
(14) (*S*)-2-Azido-2-phenylethanol was prepared by NaN_3 treatment of the commercially available (*R*)-styrene oxide, whereas commercially available (*R,R*)-2,4-pentanediol was subjected to the azide modification of the Mitsunobu reaction[15] to afford (2*S*,4*R*)-2-azido-4-hydroxypentane.
(15) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(16) Although we have not yet determined the diastereoselectivity of this reaction by HPLC or GC examination of the crude reaction mixture, the 90–94% yield of **9** obtained under the conditions noted represents diastereomerically pure material within the limits of 500 MHz NMR spectroscopy. An authentic sample of the C-5 epimer of **9** was obtained by running the reaction without solvent and at room temperature; under these conditions a 90% yield of **9** and 2% of its isomer **9b** (not shown) were isolated (see supporting information).
(17) The highest rotation that we have obtained for purified (*R*)-**7** is $[\alpha]_D$ = +16.4 (*c* 0.50, MeOH) (lit.[13] $[\alpha]_D$ = +14.7 (*c* 0.50, MeOH)). The reaction of 4-*tert*-butylcyclohexanone with **5** (ca. 84% ee by HPLC (Chiralcel OD)), followed by purification and Na/NH_3 treatment, afforded (*S*)-**7** with $[\alpha]_D$ = −14.6 (*c* 0.50, MeOH). The sequence involving azido alcohol **8** afforded (*S*)-**7** with $[\alpha]_D$ = −16.2 (*c* 0.50, MeOH).