ORGANIC LETTERS

2003
Vol. 5, No. 4
583−585

Epoxide-Initiated Electrophilic Cyclization of Azides: A Novel Route for the Stereoselective Construction of Azabicyclic Ring Systems and Total Synthesis of (±)-Indolizidine 167B and 209D†

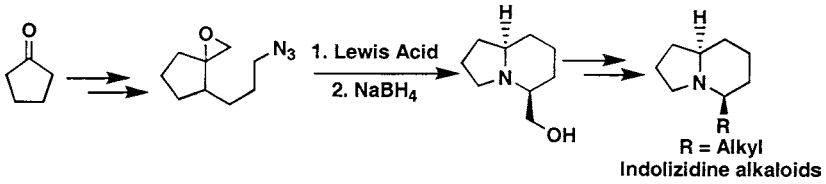
P. Ganapati Reddy, Babu Varghese,‡ and Sundarababu Baskaran*

Department of Chemistry, Indian Institute of Technology, Madras, Chennai-600036, India

sbhaskar@iitm.ac.in

Received December 27, 2002

ABSTRACT



A novel and general method for the stereoselective construction of 5-hydroxymethyl azabicyclic ring skeletons based on epoxide initiated electrophilic cyclization of azides has been developed and applied in the synthesis of (±)-indolizidine 167B and 209D with an overall yield of 16.5% and 17.8%, respectively. The efficiency of this methodology is further exemplified in the synthesis of azepine skeleton via tandem cation–olefin–azide cyclization.

Cation-induced cyclization is one of the most powerful techniques used in the synthesis of polycyclic frameworks.[1] With the advent of more efficient cation terminators, the importance of the epoxide-initiated electrophilic cyclization in the stereoselective synthesis of natural products is expanding rapidly.[2] In recent years, azide has gained remarkable attention as a cation terminator, since the subsequent skeletal rearrangement (Schmidt reaction) after cyclization offers a novel approach to azabicyclic ring systems.[3,4] Acid-mediated inter- and intramolecular Schmidt reaction of azidoalkenes[3] and azidoketones[4] has been extensively studied; however, the synthetic potential of the corresponding epoxide-initiated Schmidt reaction is yet to be explored.

The azabicyclic ring skeleton is an important structural subunit present in numerous biologically active natural products.[5] In this family, indolizidine alkaloids are the most important class of compounds, known for their wide range

† Dedicated with deep respect to Professor E. J. Corey on the occasion of his 75th birthday.

‡ Correspondence regarding X-ray analysis: Regional Sophisticated Instrumentation Center, IIT Madras, Chennai-600036, India.

(1) (a) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 3, p 341. (b) Bartlett, P. A. In *Asymmetric Syntheses*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 341. (c) Johnson, W. S. *Tetrahedron* **1991**, *47* (41), xi.

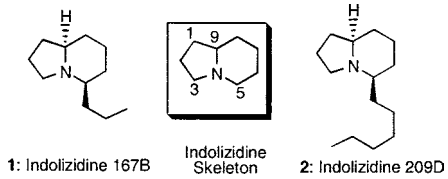
(2) (a) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999. (b) Corey, E. J.; Wood, H. B., Jr. *J. Am Chem. Soc.* **1996**, *118*, 11982. (c) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (d) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005.

(3) (a) Pearson, W. H.; Hutta, D. A.; Fang, W. *J. Org. Chem.* **2000**, *65*, 8326. (b) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183. (c) Pearson, W. H.; Schkeryantz, J. S. *Tetrahedron Lett.* **1992**, *33*, 5291.

(4) (a) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974. (b) Smith, B. T.; Gracias, V.; Aube, J. *J. Org. Chem.* **2000**, *65*, 3771. (c) Forsee, J. E.; Aube, J. *J. Org. Chem.* **1999**, *64*, 4381. (d) Milligan, G. L.; Mossman, C. J.; Aube. J. *J. Am. Chem. Soc.* **1995**, *117*, 10449.

10.1021/ol027563v CCC: $25.00
Published on Web 01/18/2003

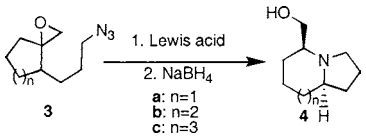
Scheme 1



of pharmaceutical applications (Scheme 1).[6] Herein, for the first time, we report a general and highly diastereoselective approach for the construction of 5-hydroxymethyl azabicyclic compounds and its application in the synthesis of indolizidine alkaloids based on epoxide-initiated electrophilic cyclization of azides. In addition, the hitherto unknown synthetic potential of this cyclization, in tandem cation−olefin−azide cyclization to the novel azepine skeleton, is further exploited.

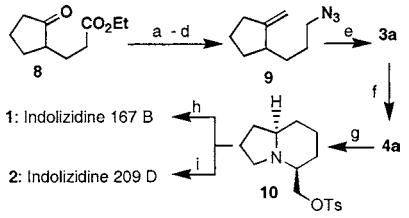
We envisioned that the treatment of an epoxy azide **3** with a Lewis acid would lead to the cyclization followed by intramolecular Schmidt reaction and in situ reduction of the intermediate iminium ion resulting in an azabicyclic alcohol **4** (Scheme 2). To test the viability of the above strategy we

Scheme 2. Epoxide-Initiated Electrophilic Cyclization of Azides



have chosen a five-membered epoxyazide **3a**, which can be readily obtained from cyclopentanone (Scheme 3). Treatment

Scheme 3. Total Synthesis of Indolizidine 167 B and 209 D[a]

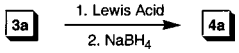


[a] Reagents: (a) Zn, CH_2Br_2, $TiCl_4$ (1 M), CH_2Cl_2, 20 °C, 1 h, 71%. (b) $LiAlH_4$, THF, 0 °C, 2 h, 95%. (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 100%. (d) NaN_3, DMF, 55 °C, 4 h, 98%. (e) mCPBA, CH_2Cl_2, 0.5 M $NaHCO_3$, 0 °C, 2.5 h, 68%. (f) $EtAlCl_2$, CH_2Cl_2, −78 °C, 45 min, $NaBH_4$ in 15% aq NaOH, 1 h, 63%. (g) TsCl, Et_3N, DMAP (cat.), 25 °C, 2 h, 94%. (h) EtMgBr, CuCN, Et_2O, − 78 °C, 62%. (i) $C_5H_{11}MgBr$, CuCN, Et_2O, −78 °C, 67%.

of epoxy azide **3a** with 1.1 equiv of TfOH in CH_2Cl_2 medium at −40 °C followed by the addition of a solution of sodium borohydride gave hydroxymethyl indolizidine **4a** in 25% yield as a single detectable diastereomer as judged by the ^1H and ^{13}C NMR data.

To explore a suitable Lewis acid for this useful transformation, an extensive investigation was carried out with different Lewis acids (Table 1). Among all the Lewis acids

Table 1. Epoxide-Initiated Electrophilic Cyclization of Azide with Different Lewis Acids



entry	Lewis acid	temp, °C	% yield[a]
1	TfOH	−40	25
2	TMSOTf	−78	21
3	$BF_3{\cdot}OEt_2$	−78	50
4	$TiCl_4$	−25	43
5	$InCl_3$	0	25
6	$EtAlCl_2$	−78	63

[a] Isolated yields.

studied, $EtAlCl_2$ was found to be the ideal choice. In all cases, isolation of the single diastereomer emphasizes the structural[7] and stereochemical control[8] of this reaction. The relative stereochemistry at C5 and C9 was unambiguously established by the single-crystal X-ray analysis of the corresponding hydrochloride salt of *p*-bromobenzoate ester **7** (Figure 1).

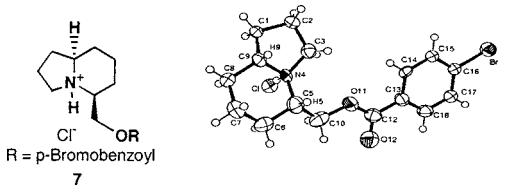


Figure 1. Single-crystal X-ray structure.

The generality of this transformation was further tested with different ring sizes. The results are summarized in Table 2. The epoxy azides **3b** and **3c** were prepared by similar strategy as shown in Scheme 3, starting from cyclohexanone and cycloheptanone, respectively.

Interestingly, the hydroxymethyl indolizidine **4a** has a similar relative stereochemistry at C5 and C9 of indolizidine alkaloids such as indolizidine 167B and 209D. Hence, we anticipated that an efficient entry to this class of alkaloids

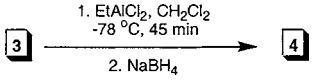
(5) For a review on these natural products, see: Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162.

(6) (a) Daly, J. W.; Sande, T. F. In *Alkaloids: Chemical and Biological Prospectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1. (b) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227.

(7) The proton-initiated intramolecular Schmidt reaction of the azidoalkene, leading to a mixture of regioisomeric azabicyclic products, has been reported (ref 3b). However, under our cyclization conditions, we do not observe any other regioisomers.

(8) (a) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (b) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, 55, 4688.

Table 2. Epoxide-Initiated Electrophilic Cyclization of Azides with Different Ring Sizes



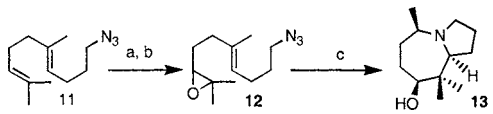
n	substrate	product[a]	% yield
1	**3a**	**4a**	63
2	**3b**[b]	**4b**	42
3	**3c**[b]	**4c**	47

[a] Single diastereomer. [b] Mixture of diastereomers.

could be achieved readily by further functional group manipulation of the hydroxy group in the side chain. Modified methylenation of the known ketoester **8**[9] with the $CH_2Br_2/Zn/TiCl_4$ reagent system[10] gave olefin ester in 71% yield, which was converted to the corresponding azido-alkene **9**[3b] in three steps as shown in Scheme 3. Azido-alkene **9** upon exposure to mCPBA yielded the epoxyazide **3a** as a mixture of cis and trans isomers in a 1:3 ratio. Treatment of the major diastereomer[11] with $EtAlCl_2$ at −78 °C followed by reduction with sodium borohydride afforded azabicyclic alcohol **4a** in 63% yield. The alcohol was converted to the corresponding tosylate **10** in 93% yield. Treatment of the tosylate **10** with $Et_2CuCNMgBr$ in Et_2O medium at − 78 °C afforded indolizidine 167B in 62% yield. Under similar reaction conditions tosylate **10** was converted to indolizidine 209D in 67% yield upon treatment with $(C_5H_{11})_2CuCNMgBr$. The spectroscopic data of these two compounds are in complete agreement with the reported data.[8b]

The scope of this methodology was further extended to the novel tandem cation−olefin−azide cyclization, wherein

Scheme 4. Cation-Induced Tandem Cyclization of Epoxy[a] Azides

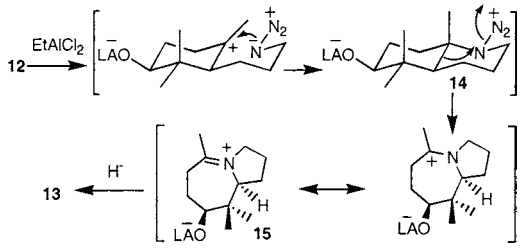


[a] Reagents: (a) NBS, aq THF, 0 °C. (b) K_2CO_3, MeOH, rt, 54% (overall). (c) $EtAlCl_2$, CH_2Cl_2, −78 °C, 45 min, $NaBH_4$ in 15% aq NaOH, 1 h, 36%.

the epoxyazide **12** under similar cyclization conditions afforded the substituted azepine **13** in 36% yield as a single diastereomer. The azidoalkene **11** used for this study was prepared from geraniol.[12] Regioselective epoxidation of the azidoalkene **11** was achieved in two steps via bromohydrin.[13]

The remarkable stereochemical outcome of this reaction was rationalized by invoking the similar stereoselective reduction of the intermediate iminium ion reported in the literature.[3a,8] A plausible mechanism is shown in Scheme 5.

Scheme 5. A Plausible Mechanism for Tandem Epoxide Initiated Electrophilic Cyclization



NOE and 2D NMR studies on the corresponding acetate of **13** confirmed the relative stereochemistry at C5, C8, and C9.

In conclusion, for the first time, a novel and general method for the stereoselective construction of 5-hydroxymethyl azabicyclic ring skeletons based on epoxide-initiated electrophilic cyclization of azides has been developed and applied in the synthesis of (±)-indolizidine 167B and 209D with an overall yield of 16.5% and 17.8% respectively, starting from a known ketoester **8**. The efficiency of this methodology is further exemplified in tandem cation−olefin−azide cyclization to the novel azepine skeleton. Application of this methodology in asymmetric synthesis of indolizidine alkaloids (alkyl and polyhydroxy indolizidines) will be reported in due course.

Acknowledgment. We thank the Department of Science and Technology, New Delhi for financial support and P.G.R. thanks CSIR, New Delhi for a research fellowship. We are grateful to RSIC, IIT Madras, for spectral data.

Note Added after ASAP Posting. The equation in Table 1 contained errors in the version posted January 18, 2003. The corrected version was posted February 3, 2003.

Supporting Information Available: Characterization data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027563V

(9) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc*. **1963**, *85*, 207.

(10) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1978**, *19*, 2417.

(11) Surprisingly the minor diastereomer under similar cyclization conditions failed to give the cyclized product.

(12) Azido olefin **11** was prepared from the known compound (4*E*,8*E*)-ethyl 5,9-dimethyldeca-4,8-dienoate (Robinson, J. A.; Dyer, U. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 53) in three steps by reduction, mesylation, and nucleophilic displacement with sodium azide.

(13) (a) Hanzlik, R. P. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 560. (b) vanTamelen, E. E.; Sharpless, K. B. *Tetrahedron Lett*. **1967**, 2655.