ORGANIC LETTERS

2002
Vol. 4, No. 3
363−366

Lewis Acid Promoted Highly Stereoselective Rearrangement of 2,3-Aziridino Alcohols: A New Efficient Approach to β-Amino Carbonyl Compounds

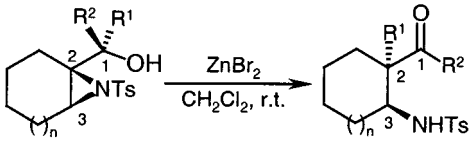
Bao Min Wang, Zhen Lei Song, Chun An Fan, Yong Qiang Tu,* and Yian Shi†

Department of Chemistry and National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

tuyq@lzu.edu.cn

Received November 13, 2001

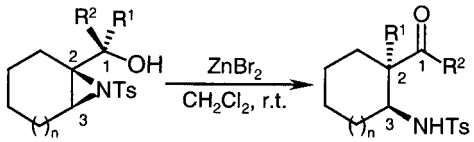
ABSTRACT



A new Lewis acid promoted rearrangement reaction of 2,3-aziridino alcohols was discovered, which involved the highly stereoselective construction of a diastereogenic quaternary carbon center and efficient formation of β-amino carbonyl compounds in excellent yields. A wide variety of Lewis acids were proved to be effective for the reaction, and a possible reaction mechanism was also discussed.

In recent years, the chemistry of aziridines has been attracting much interest of synthetic organic chemists, mainly as a result of their highly regio- and stereoselective ring-opening reactions and their great potential as building blocks for the synthesis of a wide range of biologically significant nitrogen-containing compounds.[1] Many reactions reported involve the C−N bond cleavage of the aziridines, and few reports incorporate carbon−carbon migration. The aza-Payne rearrangement[2] reported by Ibuka merely results in the formation of 2,3-epoxy amines without any carbon skeleton change of the substrates. Although the chemistry of 2,3-epoxy alcohols has been studied extensively,[3] the reactions of 2,3-aziridino alcohols have seldom been investigated. Recently, our independent research has brought about for the first time the discovery of a new rearrangement of 2,3-aziridino alcohols promoted effectively by a variety of Lewis acids, with zinc bromide being the most effective (Scheme 1). The

Scheme 1



synthetic value of this reaction involves the stereoselective derivation of two adjacent stereocenters, with one being the quaternary. The stereoselective construction of quaternary

† Visiting professor from Colorado State University.

(1) For a general review of aziridine chemistry, see: (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 1a. (c) Rayner, C. M. *Synlett* **1997**, 11. (d) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (e) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519.

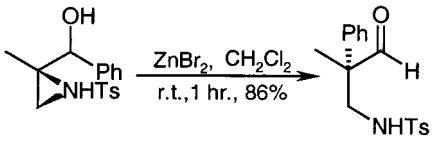
(2) (a) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Otaka, A.; Tamamura, H.; Fuji, N.; Mimura, N.; Miwa, Y.; Taga, T.; Chounan, Y.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 2044. (b) Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145.

10.1021/ol0170410 CCC: $22.00
Published on Web 01/10/2002

carbon centers, still remaining a crucial aspect of several areas in organic synthesis, is of particular importance. Quaternary carbon has long been an important class of structure, although much progress has been achieved in the area.[4] An additional significant value of this reaction is that it provides an alternative efficient method for the preparation of β-amino ketones and aldehydes (Mannich bases), which are particularly versatile synthetic intermediates and find great use in medicinal chemistry.[5] Generally, the β-amino carbonyl compounds were prepared by Mannich reaction and its modern variants[6] and by Michael additions of amines to α,β-unsaturated carbonyl compounds. However, these procedures sometimes showed poor regio- and stereoselectivity.[7] The development of new alternative methods for the synthesis of β-amino carbonyl compounds is therefore of considerable synthetic importance.[8] In contrast, the procedure here reported demonstrated excellent regio- and stereoselectivity in all examples we examined. Herein, we wish to report the experimental results of the Lewis acid promoted rearrangement of 2,3-aziridino alcohols.

The 2,3-aziridino alcohols we investigated were prepared in racemic form (except for entry 3 of Table 2) with moderate yields from the corresponding allylic alcohols via the aziridination method developed by Sharpless.[9] Thus, the 2,3-aziridino alcohols were subjected to the rearrangement reaction to afford β-amino ketone or aldehyde in a single diastereoisomeric form, whose relative configuration was determined by NOSEY spectrum of the product of entry 1 in Table 2 selected as a model and by comparison of ^{1}H NMR chemical shifts with that of approximate compounds in the literature.[7b] All results were tabulated in Tables 1 and 2 and Scheme 2, from which it can be seen that all reactions

Scheme 2



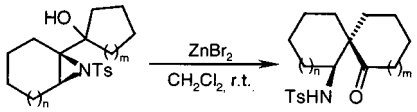
were complete in less than 1 h with the exclusive formation of β-amino ketones and aldehydes stereoselectively in excellent yields, indicating the convenience and synthetic value of this reaction.

(3) (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (b) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944. (c) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem.* **1999**, *64*, 629. (d) Tu, Y. Q.; Fan, C. A.; Ren, S. K.; Chan, A. S. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3791. (e) Fan, C. A.; Wang, B. M.; Tu, Y. Q.; Song, Z. L. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3877.

(4) For recent reviews on stereoselective construction of a quaternary carbon center, see: (a) Fuji, K.*Chem. Rev.* **1993**, *93*, 2037. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (c) Corey, E. J.; Angel, G.-P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.

(5) (a) Dimmock, J. R.; Sidhu, K. K.; Chen, M.; Reid, R. S.; Allen, T. M.; Kao, G. Y.; Truitt, G. A. *Eur. J. Med. Chem.* **1993**, *28*, 313. (b) Traxler, P.; Trinks, U.; Buchdunger, E.; Mett, H.; Meyer, T.; Müller, M.; Regenass, U.; Rösel, N.; Lydon, N. *J. Med. Chem.* **1995**, *38*, 2441.

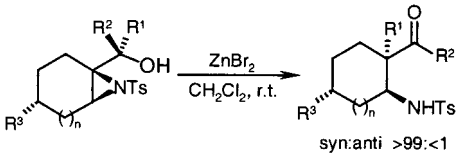
Table 1. Rearrangement of 2,3-Aziridino Alcohols Promoted by $ZnBr_2$ Leading to Spirocyclic β-Amino Ketones



entry	n	m	yield (%)	time (min)
1	1	0	98	10
2	1	1	95	30
3	1	2	90	30
4	1	3	92	30
5	0	2	91	30
6	0	3	93	30

In Table 1, six spirocyclic β-amino ketones were designed as the target molecules. Although this kind of spiro compound could be prepared via an intramolecular Mannich-type reaction of benzylic azides with ketones,[7b] the stereoselectivity was very poor and an unremovable phenyl group was attached to the nitrogen atom instead of a *p*-toluenesulfonyl group. Notably, this kind of chiral spirocyclic β-amino ketones may have some synthetic utility not only because they can be easily transformed into 1,3-amino alcohols but also because spiro compounds have been investigated recently as possible chiral ligands for catalytic asymmetric reactions.[10] Although the migration of the methyl group is difficult in many cases,[3b−d] in entries 1−4 and 6 of Table 2, however, it seems very easy. Interestingly, in entry

Table 2. Rearrangement of 2,3-Aziridino Alcohols Promoted by $ZnBr_2$ Leading to β-Amino Ketones and Aldehydes



entry	*n*	R^1	R^2	R^3	yield (%)	time (min)
1	1	Me	Me	H	88	30
2	0	Me	Me	H	85	30
3	1	Me	Me	Me	78	60
4	1	Me	Et	H	90	30
5	1	Et	Me	H	89	30
6	0	Me	Ph	H	85	30
7	1	Ph	H	H	85	40
8	0	Ph	H	H	83	40
9	0	H	*o*-ClC_6H_4	H	85	40

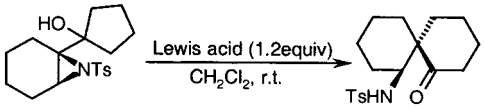
3[11] the methyl substituent in the cyclohexane ring has no significant effect on the rearrangement ability of the substrate. Of particular interest is that secondary 2,3-aziridino alcohols (entries 7 and 8 in Table 2 and the substrate in Scheme 2) could also undergo this rearrangement reaction to afford

β-amino aldehydes, which can be easily converted into α,α geminally disubstituted β-amino acids,[12] vital compounds for the synthesis of β-peptide, via oxidation. Notably, in entries 4 and 5 of Table 2, a pair of separable diastereoisomeric 2,3-aziridino alcohols afforded methyl and ethyl migration products, respectively, which was verified by the ^{1}H NMR spectra of the products. This unusual fact indicates that the migration priority of two different groups of R^1 and R^2 (Scheme 1) depends seriously on the configuration of the carbon bearing a hydroxyl group but not on the migration ability. Further study led to the discovery that methyl migrates prior to phenyl in entry 6 (Table 2) and hydride prior to *o*-chlorophenyl in entry 9 (Table 2), which further verified our presumption. This phenomenon is of great interest and has seldom been reported.

To expand the scope of this rearrangement reaction, we examined the acyclic substrate (Scheme 2), which was prepared from 2-bromopropene via a Grignard reaction with benzaldehyde followed by aziridination of the allylic alcohol thus formed. The rearrangement of this acyclic 2,3-aziridino alcohol proceeded smoothly to afford the corresponding β-amino aldehyde when exposed to the standard condition, indicating the broad scope of the substrates.

A wide variety of other Lewis acids were also examined for this reaction, with the 2,3-aziridino alcohol in entry 2 of Table 1 to be a model substrate, and it was found that many of them could act as promoter to give good to excellent product yields in short time (Table 3). Of all the efficient

Table 3. Effective Lewis Acids for the Rearrangement of 2,3-Aziridino Alcohol

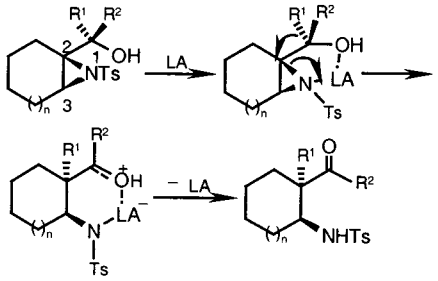


entry	Lewis acid	yield (%)	time (min)
1	$AlCl_3$	40	30
2	$ZnCl_2$	74	60
3	$Sn(OTf)_2$	80	60
4	$BF_3{\cdot}Et_2O$	82	10
5	$SnCl_4$	86	10
6	SmI_2	93	40
7	ZnI_2	82	60
8	$TiCl_4$	55	10
9	$Sc(OTf)_3$	74	60
10	$ZrCl_4$	76	20

Lewis acids investigated, SmI_2 gave the best result, while $AlCl_3$ was found to be too reactive to afford high yield.

On the basis of the abnormal migration mentioned above and on the relative configurations of the products, a possible reaction mechanism of this rearrangement of 2,3-aziridino alcohols was proposed (Scheme 3), in which the Lewis acid first coordinates to the aziridine nitrogen and the hydroxyl oxygen, and the cleavage of the activated C−N bond of the aziridine then occurs concomitantly with 1,2-migration of

Scheme 3



the migrating group in a transition state geometry resembling that of ordinary nucleophilic substitution proceeding with inversion of configuration. The five-membered ring structure resulting from coordination of the Lewis acid to nitrogen and oxygen prevents the free rotation of the C1−C2 bond, and thus the group R^1 that is anti to the C−N bond migrates. The rearrangement reaction here reported is therefore highly stereoselective. The mechanism above interprets very well why entry 4 in Table 2 gave the methyl migration product while in entry 5 ethyl migrated. On the basis of this mechanism and the relative configurations of the products, the stereochemistry of the diastereomerically pure substrates in entries 4−9 of Table 2 was assigned as illustrated. There are no existing methods to determine the relative configurations of such compounds, and the search for experimental evidence toward this objective is ongoing.

In summary, we have discovered a new stereoselective rearrangement reaction of 2,3-aziridino alcohols, which proceeds under fairly mild conditions with the highly efficient formation of β-amino carbonyl compounds containing a quaternary carbon center at the α-position. Although reactions of 2,3-aziridino alcohols with Olah's reagent have been reported by Laurent,[13] to the best of our knowledge this type of rearrangement reaction of 2,3-aziridino alcohols has not

(6) For a general review on Mannich reaction and its modern variants, see: (a) Blicke, F. F. *Org. React. (NY)* **1942**, *1*, 303. (b) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791. (c) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 893. (d) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 953. (e) Overmann, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1007. (f) Tramontini, M.; Angiolini, L. *Mannich-Bases, Chemistry and Uses*; CRC: Boca Raton, FL, 1994. (g) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1044. (h) Miura, K.; Tamaki, K.; Nakagawa, T.; Hosomi, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1958.

(7) (a) Saidi, M. R.; Heydari, A.; Ipaktschi, J. *Chem. Ber.* **1994**, *127*, 1761. (b) Wrobleski, A.; Aubé, J. *J. Org. Chem.* **2001**, *66*, 886.

(8) Matthew, J.; Jonathan, B. S. *Org. Lett.* **2001**, *3*, 25.

(9) Jeong, J. K.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

(10) (a) Srivastava, N.; Mital, A.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1992**, 493. (b) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc.* **1997**, *119*, 9570. (c) Arai, M. A.; Arai, T.; Sasai, H. *Org. Lett.* **1999**, *1*, 1795.

(11) This chiral 2,3-aziridino alcohol was prepared from *R*-(+)-pulegone. For the preparation of the allylic alcohol, see: (a) Neichinasi, E. H. *J. Org. Chem.* **1970**, *35*, 2010. (b) Neidigk, D. D.; Morrison, H. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

(12) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1 and references therein.

been reported previously. The use of chiral Lewis acids for the rearrangement and the applications of this synthetically valuable reaction to other aspects of organic synthesis, such as synthesis of natural products and preparation of chiral ligands[14] for catalytic asymmetric reactions, are currently under investigations.

Acknowledgment. This work was supported by NSFC (29972019, 29925205 and QT program), FUKTME of China, the Young Teachers' Fund of Ministry of Education and the Fund of Ministry of Education (99209). We thank Ms. Wang Kai Qiu and Mr. Qi Xiu Zhu for their assistance in NMR and MS studies.

Supporting Information Available: Typical experimental procedure of the rearrangement reaction and spectra data of the rearrangement products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0170410

(13) Alvernhe, G.; Lacombe, S.; Laurent, A.; Rousset, C. *J. Chem. Res., Synop.* **1983**, 246.

(14) (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (b) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *19*, 382.