ORGANIC LETTERS

2004
Vol. 6, No. 24
4499−4501

# Synthesis of Enantiopure Imidazolines through a Ritter Reaction of 2-(1-Aminoalkyl)aziridines with Nitriles

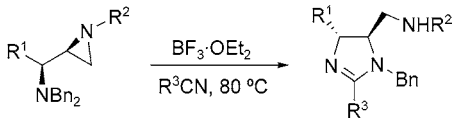
**José M. Concellón,*[†] Estela Riego,[†] José Ramón Suárez,[†] Santiago García-Granda,[‡] and M. Rosario Díaz[‡]**

*Departamento de Química Orgánica e Inorgánica y Departamento de Química Física y Analítica, Facultad de Química Universidad de Oviedo, Julián Clavería, 8, 33071 Oviedo, Spain*

*jmcg@fq.uniovi.es*

**Received September 9, 2004**

## ABSTRACT




**1** **2**

**The Ritter reaction of enantiopure 2-(1-aminoalkyl)aziridines 1 with different nitriles afford enantiopure tetrasubstituted imidazolines 2. The opening of the aziridine ring takes place with total regio- and stereoselectivity. A mechanism to explain the described addition reaction is proposed.**

4,5-Dihydro-1*H*-imidazoles (2-imidazolines) are useful intermediates for the synthesis of molecules with pharmacological activities such as antihypercholesterolemic,[1] antiinflammatory,[2] antidiabetic,[3] antihypertensive,[4] or anticancer.[5] In addition, imidazolines have been used as synthetic intermediates[6] and as auxiliaries[7] or catalysts[8] for asymmetric synthesis. Several syntheses of differently substituted imidazolines as racemic mixtures have been described.[9] Unfortunately, the synthesis of stereodefined imidazolines has been scarcely reported despite their usefulness. Optically active imidazolines are generally obtained from enantiopure 1,2-diamines,[10] although other chiral compounds[11] have occasionally been used. However, these methodologies are limited by the difficult availability of the enantiopure precursors, and for this reason the variety of groups bonded

[†] Departamento de Química Orgánica e Inorgánica.
[‡] Departamento de Química Física y Analítica.

(1) Li, H.-Y.; Drummond, S.; DeLucca, I.; Boswell, G. A. *Tetrahedron* **1996**, *52*, 11153−11162.
(2) (a) Ueno, M.; Imaizumi, K.; Sugita, T.; Takata, I.; Takeshita, M. *Int. J. Immunopharmacol*. **1995**, *17*, 597−603. (b) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 353l-3535.
(3) Rodu, F.; Le Bihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, T.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J. J. *J. Med. Chem.* **1997**, *40*, 3793−3803.
(4) Bousquet, P.; Feldman, J. *Drugs* **1999**, *58*, 799−812.
(5) Chern, J.-W.; Liaw, Y.-C.; Chen, C.-S.; Rong, J.-G.; Huang, C.-L.; Chan, C.-H.; Wang, A. H.-J. *Heterocycles* **1993**, *36*, 1091−1103.
(6) (a) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707−1710. (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1711−1714. (c) Puntener, K.; Hellman, M. D.; Kuester, E.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 8301−8306.
(7) Dalko, P. I.; Langlois, Y. *Chem. Commun*. **1998**, 331−332.
(8) Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783−785.
(9) (a) Mansura, A.; Luu-Duc, C.; Gellon, G. *Synthesis* **1985**, 537−541. (b) Molina, P.; Díaz, I.; Tárraga, A. *Synlett* **1995**, 1031−1032. (c) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969−4972. (d) Hulme, C.; Ma, L.; Romano, J.; Morrissette, M. *Tetrahedron Lett.* **1999**, *40*, 7925−7928. (e) Dghaym, R. A.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228−3230. (f) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 3533−3535. (g) Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, 1433−1440.
(10) (a) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, *370*, 17−31. (b) Dauwe, C.; Buddrus, J. *Synthesis* **1995**, 171−172. (c) Dalko, P. I.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 8107−8117. (d) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Rusell, D. R. *J. Chem. Soc., Perkin Trans.* **2001**, 1500−1503. (e) Dupont, J.; Ebeling, G.; Delgado, M. R.; Consorti, C. S.; Burrow, R.; Farrar, D. H.; Lough, A. *J. Inorg. Chem. Commun.* **2001**, *4*, 471−474. (f) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010−5017. (g) Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993**, *34*, 6329−6332. (h) Gilbert, I. H.; Rees, D. C. *Tetrahedron* **1995**, *51*, 6315−6336. (i) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586−3591.

10.1021/ol048176j CCC: $27.50 
**Published on Web 10/27/2004**

at C-4 or C-5 of the ring is quite limited. Most of the enantiopure imidazolines described are only 4-substituted[10a,f,g,11d] or 4,5-disubstituted with the same group (generally phenyl).[10a−e,11a] Only a few examples of syntheses of 4,5-disubstituted enantiopure imidazolidines (containing a range of groups) have been reported.[11b−d] Moreover, in some cases, where enantiopure imidazolidines are obtained, they are formed in low enantiomeric excess.[11c] For these reasons, an efficient synthesis of enantiopure 2,4,5-trisubstituted imidazolines, which could be manipulated to include a variety of substituent groups from easily available enantiopure precursors, would be very interesting.

In addition, the Ritter reaction of nitriles with different compounds constitutes an important methodology to obtain amides or heterocyclic compounds.[12] However, to the best of our knowledge few papers have described the use of the Ritter reaction to prepare enantiopure compounds in general[13] or optically active imidazolines in particular.[11b,14]

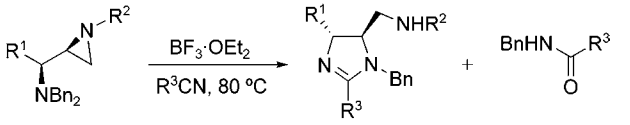
Previously, we described the synthesis of enantiopure 2-(1-aminoalkyl)aziridines[15] and the aziridirine ring opening by different nucleophiles with total regio- and stereoselectivity.[16] Very recently, we reported the synthesis of aziridine-borane complexes, their lithiation, and their selective reaction with different electrophiles.[17]

To extend the scope of synthetic applications of 2-(1-aminoalkyl)aziridines, we report herein the Ritter reaction of **1** with a range of nitriles. The opening of the aziridine ring takes place with total regio- and stereoselectivity, affording enantiopure 2,4,5-trisubstituted imidazolines.

Treatment of amino aziridines **1** with various nitriles was carried out in the presence of $BF_3{\cdot}OEt_2$ to activate the aziridine ring because this Lewis acid had previously been used successfully to activate compounds **1**.[16] Thus, a solution of amino aziridines **1**, in the corresponding nitrile, was treated with 1 equiv of $BF_3{\cdot}OEt_2$ and heated at reflux for 6 h.[18] A mixture of imidazolines **2** and *N*-benzylamides **3** was obtained in moderate or high yields after hydrolysis of the mixture reaction (Scheme 1, Table 1). The chain $R^3$ of the obtained *N*-benzylamides and the starting nitriles was the same.

The results of the synthesis of imidazolines via Ritter reaction of aminoaziridines are listed in Table 1. This process

**Scheme 1.** Synthesis of Imidazolines **2**




1 2 3

appears to be general; thus the reaction can be performed with a variety of amino aziridines (derived from leucine, phenylalanine, and serine)[15] and nitriles (aromatic, aliphatic, and alkoxy-functionalized). Consequently, the substituents of the imidazolines can also be widely varied.

**Table 1.** Synthesis of Imidazolines **2**

| entry | **2** | $R^1$ | $R^2$ | $R^3$ | yield[a] *(%)* |
|---|---|---|---|---|---|
| 1 | **2a** | *i*-Bu | Bn | Me | 45 |
| 2 | **2b** | *i*-Bu | Bn | Et | 52 |
| 3 | **2c** | *i*-Bu | Bn | *i*-Pr | 46 |
| 4 | **2d** | *i*-Bu | allyl | Me | 48 |
| 5 | **2e** | *i*-Bu | allyl | $MeOCH_2$ | 58 |
| 6 | **2f** | Bn | Cy | $MeOCH_2$ | 49 |
| 7 | **2g** | Bn | Bn | Me | 42 |
| 8 | **2h** | Bn | Bn | *i*-Pr | 61 |
| 9 | **2i** | Bn | Bn | Ph | 50 |
| 10 | **2j** | $BnOCH_2$ | Bn | $MeOCH_2$ | 53 |
| 11 | **2k** | $BnOCH_2$ | Bn | Ph | 55 |

[a] Isolated yield after column chromatography based on the starting amino aziridine **1**.

In all cases the ring-opening reaction of amino aziridines **1** was highly regio- and stereoselective and other isomeric forms of imidazolines were not observed in the crude reaction products by $^1H$ and $^{13}C$ NMR (300 MHz), within the limits of NMR analysis. Synthesis of imidazolines **2** proceeded with no detectable racemization. The enantiomeric purity of **2h** was determined by chiral HPLC analysis, showing an enantiomeric excess (ee) >99%. To exclude the possibility of coelution of both enantiomers, a racemic mixture of **2h** was prerared and analyzed by HPLC.[19]

The structure and absolute configuration of compound **2h** was established by single-crystal X-ray analysis,[20] and the

(11) (a) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999−1002. (b) Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Rec. Trav. Chim. Pays-Bas* **1992**, *111*, 59−68. (c) Zhou, X. T.; Lin, Y. R.; Sun, J.; Xia, L. J.; Tang, M. H. *J. Org. Chem.* **1999**, *64*, 1331−1334. (d) Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Smyth, M. P. *J. Org. Chem.* **2002**, *67*, 3919−3922.

(12) (a) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213−325. (b) Bookes-Milburn, K. I.; Guly, D. J.; Lox, B.; Procopin, P. A. *Org. Lett.* **2003**, *5*, 3313−3315.

(13) Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Tetrahedron* **1994**, *50*, 8997−9008.

(14) (a) Bucciarelli, M.; Formi, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2073−2080. (b) Katagin, T.; Takahashi, M.; Fujiwara, Y.; Ihara, M.; Uneyama, K. *J. Org. Chem.* **1999**, *64*, 7323−7329.

(15) Concellón, J. M.; Bernad, P. L.; Riego, E.; García-Granda, S.; Forcén-Acebal, A. *J. Org. Chem.* **2001**, *66*, 2764−2768.

(16) (a) Concellón, J. M.; Riego, E. *J. Org. Chem.* **2003**, 6*8*, 6407−6410. (b) Concellón, J. M.; Riego, E.; Suárez, J. R. *J. Org. Chem.* **2003**, 6*8*, 9242−9246.

(17) Concellón, J. M.; Suárez, J. R.; García-Granda, S.; Díaz, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4333−4336.

(18) **Representative Experimental Procedure.** To a stirred solution of the corresponding amino aziridine **1** (0.2 mmol) in the corresponding nitrile (1 mL) was added $BF_3{\cdot}OEt_2$ (0.025 mL, 0.2 mmol) at room temperature. After stirring at 80 °C for 6 h, an aqueous saturated solution of sodium bicarbonate (5 mL) was added, and the mixture was stirred at room temperature for 5 min. Then, the aqueous phase was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography on silica gel ($CH_2Cl_2$/MeOH/$NH_3$, 90:5:1) provided pure compounds **2**.

(19) Chiracel OD, UV detector 210 nm, 0.9 mL/min, 70:30 hexane/propan-2-ol, rt: **2h** 9.560; rt: enantiomer of **2h** 6.453.

(20) CCDC-244660 (**2h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or the Cambridge Data Centre, 12, Union Road, Cambridge CB21EZ, U.K., fax (+44)1223-336.033; or deposit@ccdc.cam.ac.uk).

structure and absolute configuration of the other imidazolines **2,** as depicted in Scheme 1, was assigned by analogy. NOESY experiment in compound **2c** was according to the proposed structure of compounds **2**.

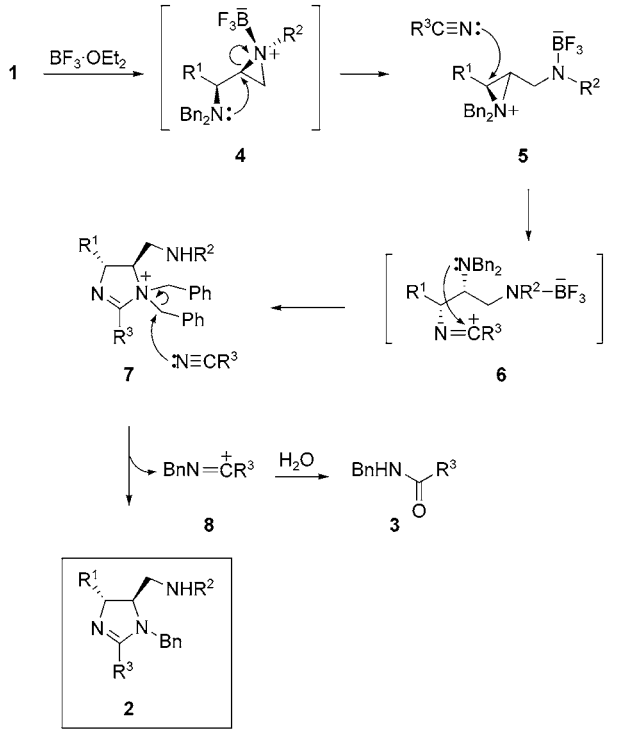
This transformation and the observed stereochemistry of the products **2** may be explained by assuming the selective coordination of the aziridine nitrogen to the Lewis acid. Support for this is provided by the isolation of the amine−borane complexes, obtained by treatment of the amino aminoaziridines **2** with $BF_3{\cdot}Et_2O$ and further treatment with $LiAlH_4$.[17]

An intramolecular ring-opening reaction at C-2 of the activated aziridine, with the consequent inversion of its configuration would occur by means of the nucleophilic attack of the dibenzylamino group, affording a reactive aziridinium salt **5**. It is reasoned that the nitrile would then attack the intermediate compound **5** at C-3,[21] which would suffer an inversion of its configuration affording a cationic intermediate **6**. N-Cyclization of **6** by attack of the dibenzylamino group to the cationic carbon would afford other cationic cyclic intermediate **7**. Debenzylation of **7** by reaction promoted by a second molecule of nitrile would produce the corresponding 2-imidazoline **2** and intermediate **8**, which after hydrolysis yield the corresponding *N*-benzylamide **3**.

In conclusion, we have described a new synthesis of enantiopure trisubstituted imidazolines, with total selectivity by the Ritter reaction of enantiopure 2-(1-aminoalkyl)-aziridines **1** with different nitriles. The opening of the aziridine ring takes place with total regio- and stereoselectivity and provides a wide range of aryl and alkyl imidazolines. A mechanism to explain the described addition reaction is proposed.

(21) The C-3 (versus the C-2) attack of nitrile to **5** may be explained by assuming that this regiochemistry involves a minor electrostatic repulsion between the lone pair of nitrile and the negative charge of the borane atom. The previosly observed opposite regiochemistry of the attack of $H_2O$ or alcohols to intermediate **5** can be consequence of the formation of a hydrogen bond between water or alcohols and a fluorine atom or the $NR^2$ group; see ref 16.

**Scheme 2.** Proposed Mechanism




**Acknowledgment.** We thank Ministerio de Ciencia y Tecnología (BQU2001-3807) for financial support and J. S. Hartman for his revision of the English. J.M.C. thanks Carmen Fernández-Flórez for her time.

**Supporting Information Available:** General methods, spectroscopic data of **2**, $^{13}C$ NMR spectra of **2**, and NOESY of **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048176J