Pergamon

Tetrahedron Letters 39 (1998) 5373–5374

TETRAHEDRON
LETTERS

Synthesis of Enantiopure Substituted Aziridines by Diastereoselective *N*-Bromocyclization and Nucleophile-Mediated Regioselective Opening

Claude Agami, Franck Amiot, François Couty* and Luc Dechoux*

Laboratoire de Synthèse symétrique associé au CNRS, Université P. et M. Curie, 4 place Jussieu, 75005 Paris, France

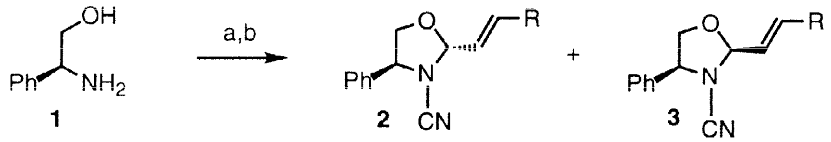
Received 8 April 1998; accepted 25 May 1998

Abstract: Enantiopure β-substituted aziridines were prepared from (*S*)-phenylglycinol through a key *N*-bromocyclization of an unsaturated iminoether. A total control of the regioselectivity was observed during the opening of these aziridines by various nucleophiles (N_3^-, H_2O, EtOH, Me_2CuLi).

Current interest in enantiopure aziridines[1] stems from their ability to undergo highly regio and stereoselective ring opening reactions.[2] This property has resulted in the synthesis of complex molecules.[3] Moreover, number of potent biologically active compounds bear an aziridine moiety.[4]

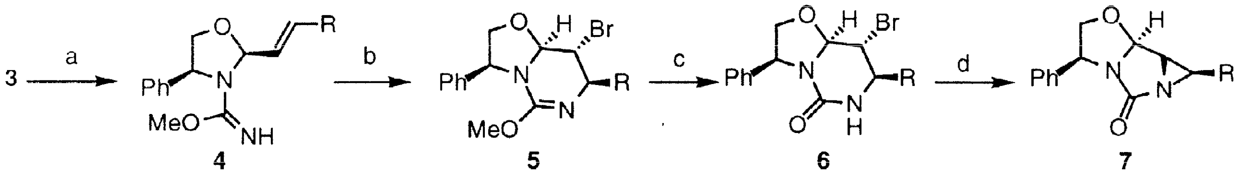
Herein, we present a method that allows the synthesis of enantiopure aziridines **7** (see Scheme 2) from (*S*)-phenylglycinol and α,β-unsaturated aldehydes. The key reaction of this process is the formation of a *N,N*-disubstituted urea via a cyclofunctionnalization initiated by bromination of the unsaturated oxazolidines **4**. In addition, we present our preliminary results on the regio and stereoselective opening of these highly strained aziridines **7** by various nucleophiles.

The *N*-cyano oxazolidines **2** and **3** were prepared from (*S*)-phenylglycinol **1** in a one-pot reaction. This cyclization involved this β-aminoalcohol, an α,β-unsaturated aldehyde and cyanogen bromide eventually leading to oxazolidines **2** and **3** (5:95 respective ratio). The diastereomeric oxazolidines **2** and **3** were separated by column chromatography, and their structures were established unambiguously by ^1H NOE experiments.



Scheme 1: (a) (*E*) O=CH-CH=CH-R, CH_2Cl_2, rt; (b) BrCN, CH_2Cl_2, $NaHCO_3$, H_2O (R=Ph: 51% two steps, R=*n*-Pr: 60% two steps).

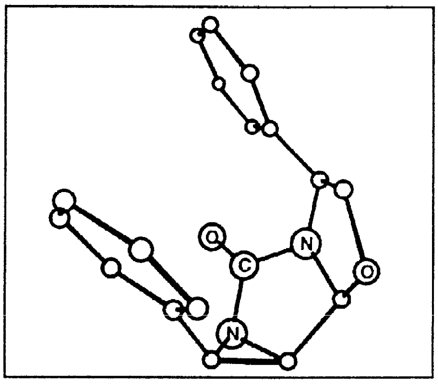
Iminoethers **4** prepared from the major diastereomers **3** were submitted to bromocyclization and afforded quantitatively bicyclic products **5** (R=Ph and *n*-Pr); these cyclizations were completely stereoselective (de>98%). Bicyclic bromides **5** were then transformed into aziridines **7** following a two-step sequence: (i) acidic hydrolysis of the iminoether moiety, leading to ureide **6**, and (ii) deprotonation of the urea by NaH followed by an intramolecular alkylation.[5,6]



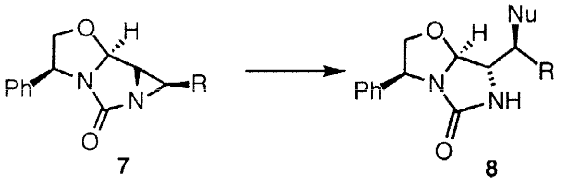
Scheme 2: (a) MeONa, MeOH, rt; (b) NBS, CH_2Cl_2, 0°C; (c) HCl 20%, CH_2Cl_2, rt, (R=Ph: 82% three steps, R=*n*-Pr: 74% three steps); (d) NaH, THF, rt, (R=Ph: 92%, R=n-Pr: 95%).

Fax: (33) 1 44 27 26 20; E-mail: dechoux@ccr.jussieu.fr

0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)01109-5



The stereochemical outcome of this cyclization is in accordance with our previous work in this field[7] about halocarbamation of *N*-Boc-alkenyl oxazolidines. As shown in the following Table, aziridines **7** were treated with different nucleophiles. The opening of the three membered ring was entirely regioselective and yielded 2-imidazolidinones **8**: a nucleophilic attack on the aziridine carbon adjacent to the oxazolidine moiety would have resulted in the formation of a 6-membered ring which was not detected in the crude mixtures by ^{1}H NMR.[5,8] AM1 Calculations[9] give the optimized geometry (see the opposite Figure) of tricyclic compound **7** (R = Ph) which clearly indicates that this regioselectivity was not dictated by steric constraints. Most likely, the electroattracting effect of the oxazolidine moiety deactivates the proximal aziridine carbon towards nucleophilic attacks. Similar results have already been reported in the case of epoxides and bridged bromonium ions linked to oxazolidines.[7]



7 **8**

R	reagents and conditions	Nu	yield %
Ph	Me_2CuLi, THF, 0°	Me	62
Ph	EtOH, NH_4Cl, reflux	OEt	98
Ph	NaN_3, EtOH, NH_4Cl, reflux	N_3	90
Ph	H_2O/THF:1/1, NH_4Cl, reflux	OH	63
n-Pr	NaN_3, EtOH, NH_4Cl, reflux	N_3	94

In conclusion, this methodology allows the stereocontrolled formation of three contiguous chiral centers on an imidazolidinone core fused to an oxazolidine moiety. Since imidazolidinones as well as oxazolidines have been widely used as chiral auxiliaries,[7,10] our attention is now focused on the use of the new chiral heterocycles reported here in asymmetric synthesis.

References and Notes

1. For a recent review, see: Osborn, H.M.I.; Sweeney J. *Tetrahedron Asym.* **1997**, *8*, 1693-1715.
2. Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599-619.
3. Fort, S.; McCort, I.; Dureault, A.; Depezay, J.C. *Synlett.* **1997**, 1235-1236. and references cited herein.
4. For a review see Kasai, M.; Kono, M. *Synlett.* **1992**, 778-790.
5. Stereochemistry of **6** was determined by ^{1}H NOE experiments; stereochemistry of **7** and **8**, which result from stereospecific reactions from **6**, were then deduced. ^{1}H and ^{13}C NMR data showed that the formation of products **7** as well as the formation of products **8** were totally stereoselective.
6. Selected data for **7** (R=Ph), IR (KBr): 1720, 1674, 699; $[\alpha]_D^{20}$ -188 (*c* 0.5, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 250 MHz): 3.25 (d, 1H, J=3.4 Hz), 3.36 (d, 1H, J=3.4), 4.18 (dd, 1H, J=3.3-8.9), 4.22 (dd, 1H, J=7-8.9), 4.55 (dd, 1H, J=3.4-6.9), 5.33 (s, 1H), 7.15-7.26 (m, 10H). ^{13}C NMR: ($CDCl_3$, 62.5 MHz): 47.7, 49.7, 61.3, 76.2, 92.3, 126.4, 128.1, 128.6, 128.8, 135.6, 136.7, 166.7.
7. Agami, C.; Couty, F.; Hamon, L.; Venier, O. *J. Org. Chem.* **1997**, *62*, 2106-2112.
8. Selected data for **8** (R=Ph, Nu=Me), $[\alpha]_D^{20}$ -82 (*c* 2.25, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 250 MHz): 1.30 (d, 3H, J=6.9 Hz), 2.70-2.85 (m, 1H), 3.83 (dd, 1H, J=3.1 and 9.8 Hz), 4.10 (dd, 1H, J=2.3 and 8.8 Hz), 4.20 (dd, 1H, J=6.5 and 8.8 Hz), 4.53 (dd, 1H, J=2.3 and 6.5 Hz), 4.56 (bs, 1H), 5.03 (d, 1H, J=3.1 Hz), 7.15-7.28 (m, 10H). ^{13}C NMR: ($CDCl_3$, 62.5 MHz): 17.1, 43.8, 60.5, 62.0, 75.7, 94.8, 127.2, 127.4, 127.9, 128.5, 128.9, 138.8, 142.0, 159.4.
9. We thank Dr. Louis Hamon who performed these calculations.
10. See for instance: (a) Palomio, C.; Oiarbide, M.; Gonzalez, A.; Garcia, J.M.; Berree, F.; Linden, A. *Tetrahedron Lett.* **1996**, *37*, 6931-6934. (b) O'Brien, P.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 3051-3054.