ORGANIC LETTERS

2005
Vol. 7, No. 26
5861−5864

3-Aminopyrrolidines via Ring Rearrangement of 2-Aminomethylazetidines. Synthesis of (–)-Absouline

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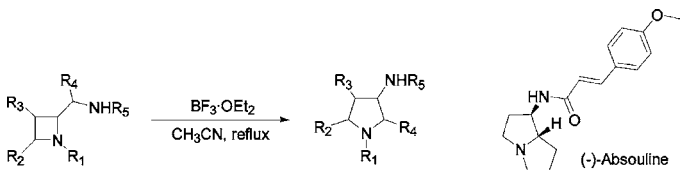
Received October 3, 2005

ABSTRACT



A new entry to enantiopure 3-aminopyrrolidines was developed using a boron trifluoride-mediated rearrangement of 2-aminomethylazetidines. The method is quite general and produces rearranged products in good yield regardless of both substitution pattern and relative stereochemistry of the starting material. A concise stereocontrolled synthesis of (–)-absouline was achieved on the basis of this new method.

3-Aminopyrrolidines are ubiquitous structural motifs that are found in natural products[1] such as absouline **1**[1a] and pharmaceuticals displaying a broad spectrum of biological activities ranging from antidepressant to analgesic, antiviral, antibacterial, or antitumoral. Recent and well-known drugs incorporating this skeleton include Moxifloxacin **2** (antibacterial),[2] Nemonapride **3** (antipsychotic),[3] or the influenza neuraminidase inhibitor A-192558 **4** (Figure 1).[4] Acting as chiral auxiliaries, 3-aminopyrrolidines have been found to be especially efficient for the asymmetric addition of organolithium reagents to aldehydes.[5]

A number of syntheses of 3-aminopyrrolidines have been reported: they rely on, for example, cyclization of asparagine derivatives,[6] reduction of cyclic enamines,[4,7] Mitsunobu reaction of 4-hydroxy-proline derivatives,[8] or asymmetric

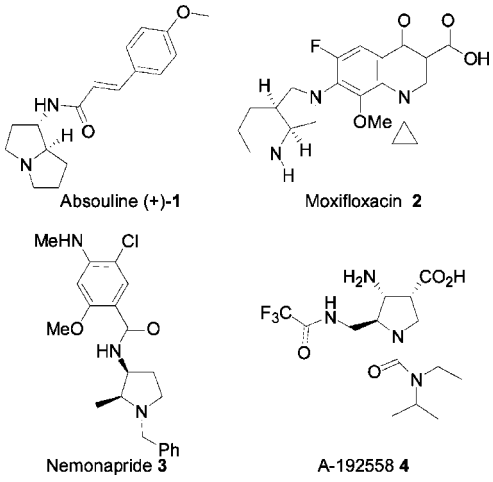


Figure 1. Natural or biologically active 3-aminopyrrolidines.

(1) (a) Ikhiri, K.; Ahond, A.; Poupat, C.; Potier, P.; Pusset, J.; Sévenet, T. *J. Nat. Prod.* **1987**, *50*, 626. (b) Neuner-Jehle, N.; Nesvadba, H.; Spiteller, G. *Monatsh. Chem.* **1965**, *96*, 321.

(2) Barrett, J. F. *Curr. Opin. Invest. Drugs* **2000**, *1*, 45.

(3) Iwanami, S.; Takashima, M.; Hirata, Y.; Hasegawa, O.; Usuda, S. *J. Med. Chem.* **1981**, *24*, 1224.

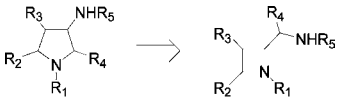
(4) Wang, W. T.; Chen, Y.; Wang, S.; Gentles, R.; Sowin, T.; Kati, W.; Muchmore, S.; Giranda, V.; Stewart, K.; Sham, H.; Kempf, D.; Laver, W. G. *J. Med. Chem.* **2001**, *44*, 1192.

(5) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266.

10.1021/ol052388e CCC: $30.25
Published on Web 11/19/2005

conjugate additions to chiral bicyclic lactams.[9] However, these methods suffer limitations in terms of optical purity of the products or scope or use not so readily available starting materials. In our continuing efforts to expand the utility of azetidine chemistry,[10] we envisioned that the ring rearrangement of 2-aminomethylazetidines **5** would yield 3-aminopyrrolidines **6** in a concise and especially straightforward fashion (Scheme 1). We therefore report in this

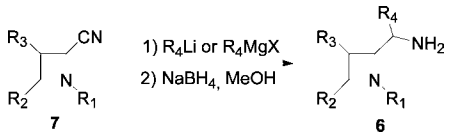
Scheme 1. Preparation of 3-Aminopyrrolidines via Ring Rearrangement of 2-Aminomethylazetidines



communication a highly stereoselective approach to 3-aminopyrrolidines; the utility of this methodology is further demonstrated in a straightforward asymmetric synthesis of pyrrolizidine alkaloid (−)-absouline.

To explore the possibility of this rearrangement, we prepared a series of diamines **6** using our addition/reduction sequence[11] from cyanoazetidines **7** (Scheme 2).[12] Therefore,

Scheme 2. Synthesis of Azetidinic Diamines

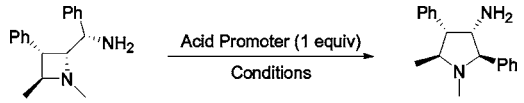


by reacting **7** with either an organolithium or a Grignard reagent followed by in situ reduction of the produced imine, diamines **6**, whose structures are represented in Table 2, were obtained in good yields and excellent selectivities.[13]

With a set of 2-aminomethylazetidines in hand, we next focused on the ring rearrangement. For this crucial step, we anticipated that the strain release during the four- to five-membered ring transformation would be a sufficient driving force for the reaction, as previously documented in ring expansion reactions.[10b,14,15]

In considering methods to promote this rearrangement starting from diamine **6a**, we were initially interested in the use of Brønsted acids. Therefore, diamine **6a** was reacted with 1 equiv of acid in refluxing toluene, but no conversion was obtained (Table 1, entries 1 and 2). We next screened

Table 1. Evaluation of Acid Promoters and Solvents



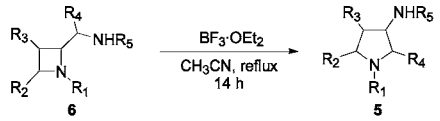
entry	acid promoter	conditions	conversion (%)
1	APTS	toluene, reflux, 14 h	0
2	TfOH	toluene, reflux, 14 h	0
3	$AlMe_3$	CH_2Cl_2, reflux, 14 h	0
4	$Ti(OiPr)_4$	CH_2Cl_2, reflux, 14 h	0
5	$TiCl_4$	CH_2Cl_2, reflux, 14 h	6
6	$BF_3{\cdot}OEt_2$	CH_2Cl_2, reflux, 14 h	11
7	$BF_3{\cdot}OEt_2$	toluene, reflux, 14 h	54
8	$BF_3{\cdot}OEt_2$	CH_3CN, reflux, 14 h	>95

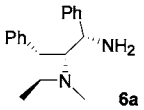
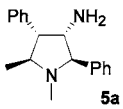
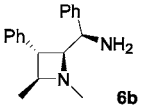
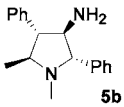
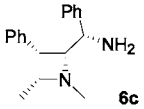
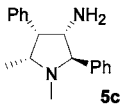
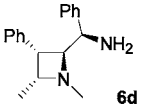
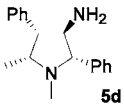
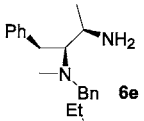
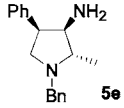
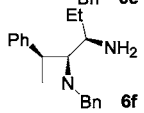
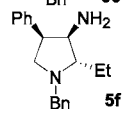
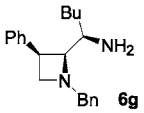
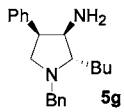
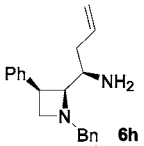
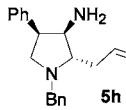
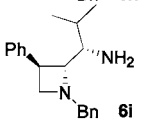
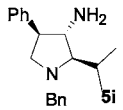
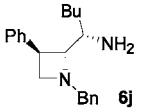
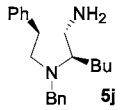
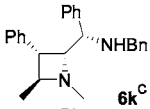
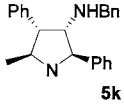
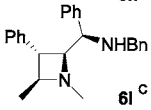
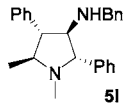
various Lewis acids in refluxing dichloromethane (Table 1, entries 3−6). These studies established the requirement for a strong Lewis acid to promote the reaction ($TiCl_4$ or $BF_3{\cdot}OEt_2$).[16] Further improvement was found in replacing the solvent with acetonitrile, which was found to be especially suitable since it leads to a clean and complete reaction (Table 1, entry 8).

With a viable rearrangement procedure in hand, attention was turned to the generality of the process and the reactivity of a range of structurally diverse azetidinic diamines **6a**−**6l** was studied employing $BF_3{\cdot}OEt_2$ as an acid promoter in refluxing acetonitrile. Results from those experiments are represented in Table 2 and clearly show that polysubstituted 3-aminopyrrolidines are obtained as single diastereoisomers in good to excellent yields in all cases. Interestingly, the reaction is not substrate-dependent since neither the size of the substituents (compare entries 5−9) nor the substitution of the exocyclic amine (compare entries 2 and 12) have a marked effect on reaction time or yield. An interesting feature of this rearrangement, which is in contrast with most of the ring rearrangement reactions involving nitrogen heterocycles,

(6) Maddaluno, J.; Corruble, A.; Leroux, V.; Plé, G.; Duhamel, P. *Tetrahedron: Asymmetry* **1992**, *3*, 1239.
(7) Lee, H.-S.; LePlae, P. R.; Porter, E. A.; Gellman, S. H. *J. Org. Chem.* **2001**, *66*, 3597.
(8) Rosen, T.; Chu, D. T. W.; Lice, I. M.; Fernandes, P. B.; Shen, L.; Borodkin, S.; Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1586.
(9) Andres, C. J.; Lee, P. H.; Nguyen, T. H.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 3189.
(10) (a) Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem.* **2004**, *1*, 133. (b) Couty, F.; Durrat, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2004**, *45*, 7525. (c) Couty, F.; Durrat, F.; Evano, G. *Synlett* **2005**, 1666.
(11) Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Eur. J. Org. Chem.* **2004**, 3893.
(12) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297.
(13) See Supporting Information for more details.
(14) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, Germany, 1991.
(15) For recent examples of ring rearrangement starting from azetidines, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Salgado, N. R. *J. Org. Chem.* **1999**, *64*, 9596. (b) Outurquin, F.; Pannecoucke, X.; Berthe, B.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 1007. (c) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209. (d) Yoneda, R.; Sakamoto, Y.; Oketo, Y.; Harusawa, S.; Kurihara, T. *Tetrahedron* **1996**, *52*, 14563. (e) O'Neil, I. A.; Potter, A. J. *Chem. Commun.* **1998**, 1487. (f) Martorell, A.; Inman, G. A.; Alper, H. *J. Mol. Catal. A: Chem.* **2003**, *204*, 91.
(16) $BF_3{\cdot}OEt_2$ is commonly used in Lewis acid-catalyzed ring openings of aziridines. See: (a) Bodenan, J.; Chanet-Ray, J.; Vessiere, R. *Synthesis* **1992**, 288. (b) Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1997**, *62*, 4277. (c) Cantrill, A. A.; Osborn, H. M. I.; Sweeney, J. *Tetrahedron* **1998**, *54*, 2181. (d) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (e) Xiong, C.; Wang, W.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002**, *67*, 1399. (f) Concellón, J. M.; Riego, E. *J. Org. Chem.* **2003**, *68*, 6407. (g) Concellón, J. M.; Riego, E.; Suárez, R. *J. Org. Chem.* **2003**, *68*, 9242.

Table 2. 3-Aminopyrrolidines via Ring Rearrangement of 2-Aminomethylazetidines: Scope and Limitations



entry	azetidinic diamine	3-aminopyrrolidine	yield,[a] dr[b]
1	 **6a**	 **5a**	77%, >95%
2	 **6b**	 **5b**	67%, >95%
3	 **6c**	 **5c**	67%, >95%
4	 **6d**	 **5d**	68%, >95%
5	 **6e**	 **5e**	69%, >95%
6	 **6f**	 **5f**	78%, >95%
7	 **6g**	 **5g**	82%, >95%
8	 **6h**	 **5h**	67%, >95%
9	 **6i**	 **5i**	50%, >95%
10	 **6j**	 **5j**	82%, >95%
11	 **6k**[c]	 **5k**	88%, >95%
12	 **6l**[c]	 **5l**	75%, >95%

[a] Yield of isolated, pure product. [b] Determined by ^{1}H NMR analysis of crude reaction mixtures. [c] Prepared by benzylation of the corresponding primary amines **6a** and **6b**. See Supporting Information for details.

is that the relative stereochemistry of the substrate does not have a pronounced influence on the efficiency of the reaction since diastereoisomers **6a**, **6b**, **6c**, and **6d** all rearrange in comparable yields (entries 1−4). More importantly, the rearrangement proceeds in a complete stereospecific way, and no epimerization at the reacting centers is observed.

Relative stereochemistry of the obtained 3-aminopyrrolidines was elucidated on the basis of NOE experiments. Moreover, an X-ray structure of the *N*-Boc derivative of pyrrolidine **5l** confirmed the anti relationship of the substituents at positions 4 and 5 of the pyrrolidine ring (Figure 2).

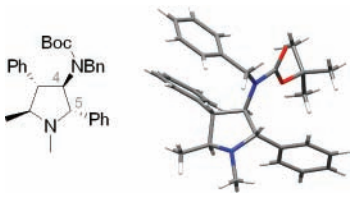
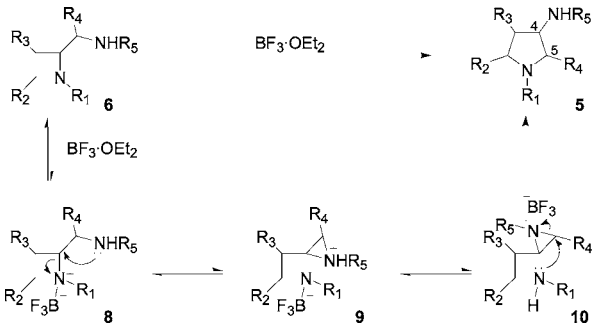


Figure 2. X-ray structure of *N*-Boc derivative of **5l**. The structure was obtained by reaction of **5l** with Boc_2O in AcOEt.

To explain both the rearrangement itself and its stereochemical outcome, we propose the mechanism depicted in Scheme 3 inspired by related ring transformations.[16f,g] After

Scheme 3. Proposed Mechanism for the Rearrangement



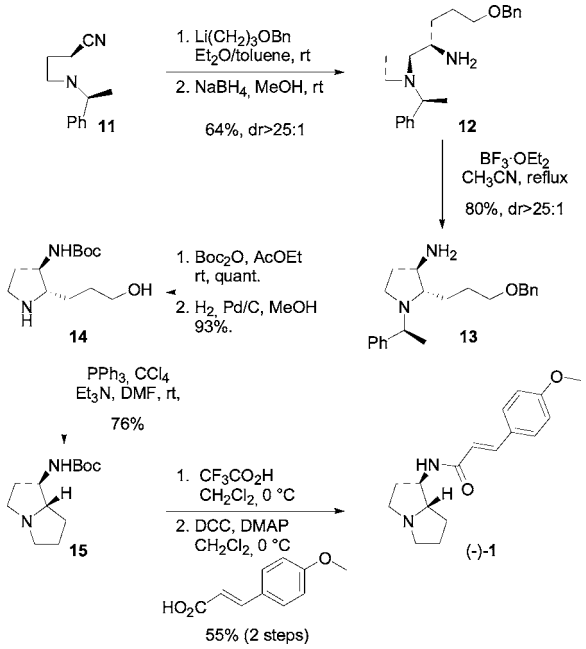
coordination of the azetidine nitrogen to the Lewis acid, which results in an activation of the azetidine ring toward nucleophiles, an intramolecular ring opening by nucleophilic attack of the exocyclic amine with inversion of configuration would afford the aziridinium salt **9**. Migration of boron trifluoride to the more basic cyclic amine followed by a

second intramolecular nucleophilic substitution within aziridinium **10** would give, after hydrolysis, the 3-aminopyrrolidine product **5**. All steps involved in this mechanism being equilibrated, the driving force of the reaction is the formation of the most stable pyrrolidine product which possesses a ring strain by far smaller than the one of the azetidine starting material or aziridine intermediates. Importantly, this mechanism can account for the stereochemistry of the product, which can be rationalized by the inversion of configuration occurring at each ring-opening/ring-closing step.

As an application of this methodology and to further demonstrate its usefulness, a concise enantioselective route to pyrrolizidine alkaloids absouline was developed. Absouline (+)-**1** as well as its *Z* stereoisomer (+)-isoabsouline and their *N*-oxide derivatives were isolated in 1987 from New Caledonian plants *Hugonia oreogena* and *Hugonia penicillanthemum* and were shown to possess modest antiviral activity.[1a] To date, one racemic[17] and one asymmetric[18] syntheses of absouline have been reported, the major drawback of the latter being the low diastereoselectivity of its key step.

Our synthesis started with cyanoazetidine **11**, whose preparation from (*S*)-α-methylbenzylamine was recently reported.[19] Addition of 3-benzyloxy-propyl lithium to **11** provided diamine **12** in gram quantities and high diastereoisomeric purity (Scheme 4). This set the stage for the key rearrangement step: reaction of **12** with 1 equiv of boron trifluoride in refluxing acetonitrile gave, in excellent yield and selectivity, the desired 3-aminopyrrolidine possessing all the carbon atoms necessary for elaboration of the pyrrolizidine skeleton and the required stereochemistry. Conversion of pyrrolidine **13** to absouline entailed formation of the second ring system and installation of the side chain. Therefore, the exocyclic amine in **13** was protected as a carbamate, and both *N*- and *O*-benzyl-protecting groups were cleaved by hydrogenolysis. Formation of the 1-aminopyrrolizidine skeleton was best effected using Appel's hydroxyl activation protocol, which gave the pyrrolizidine core **15** in 76% yield.[20] Finally, *N*-Boc deprotection followed by DCC/DMAP-mediated coupling of the resulting amine with (*E*)-*para*-methoxycinnamic gave (−)-absouline **1** as a colorless solid whose spectroscopic data were identical to those reported for the natural product.[1a]

Scheme 4. Synthesis of (−)-Absouline



In conclusion, we have developed a new rearrangement that leads to the assembly of functionalized, enantiopure 3-aminopyrrolidines with high efficiency. The methodology has been used as a key step in a stereocontrolled synthesis of pyrrolizidine alkaloid absouline. Further development and application of this ring expansion will be reported in due course.

Acknowledgment. We gratefully acknowledge financial support from CNRS. M.V.S. thanks CONACYT for a graduate fellowship. We thank Dr. Christiane Poupat for a gift of a sample of natural absouline and Prof. Huang Pei-Qiang for sending us copies of ^{1}H and ^{13}C NMR spectra of synthetic absouline and helpful comments. We are indebted to Prof. James S. Panek for HRMS analyses.

Supporting Information Available: Spectroscopic data and experimental procedures for all new compounds; copies of ^{1}H and ^{13}C NMR spectra for synthetic absouline. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052388E

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