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Access to Optically Active 3-Azido- and 3-Aminopiperidine Derivatives by Enantioselective Ring Expansion of Prolinols

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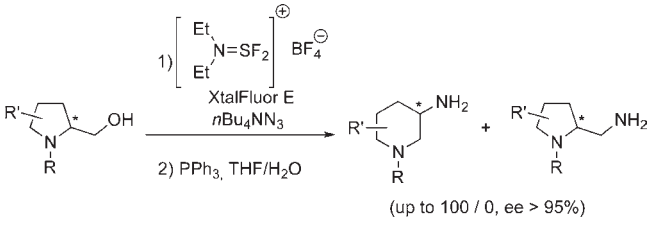
ABSTRACT



The activation of *N*-alkyl prolinols by XtalFluor E allowed the formation of an aziridinium intermediate that can react with tetrabutylammonium azide (nBu$_4$NN$_3$) to produce 3-azidopiperidines and/or 2-(azidomethyl)pyrrolidines, in a ratio up to 100/0. These 3-azidopiperidines can be reduced to the corresponding 3-aminopiperidines.

A great number of patents related to 3-aminopiperidine derivatives have been taken out due to the potential biological activities of these products. For example, 3-aminopiperidine derivatives can present antitumoral,[1] antibacterial,[2] anti-inflammatory,[3] analgesic,[4] antiviral,[5] antidepressive,[6] and anti-ischemic[7] properties. They can also be receptor ligands of the CNS[8] and can find applications as psychotropic agents[9] as well as in the treatment of hormone deficiency[10] and neurological disorders related to β-amyloid production.[11] Thus, efficient and selective methods to obtain optically active 3-aminopiperidine derivatives of type **A** are of interest (Figure 1).

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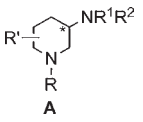
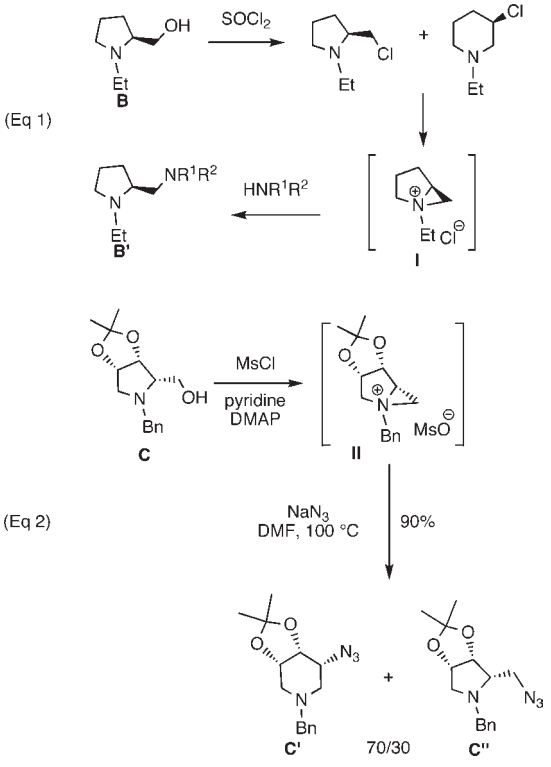


Figure 1. 3-Aminopiperidine derivatives of type **A**.

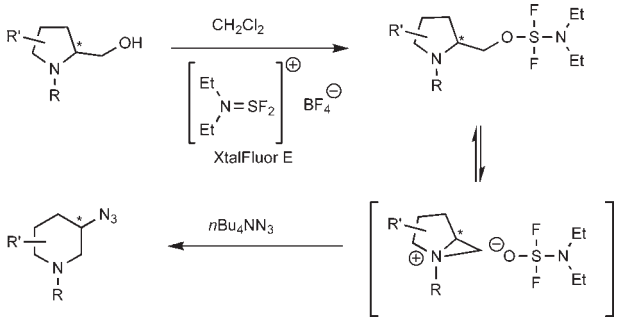
Contrary to the formation of 3-hydroxypiperidines from *N*-alkyl prolinols *via* an aziridinium intermediate,[12] the synthesis of 3-azido- or 3-aminopiperidines by ring enlargement of prolinols using an azide anion or amines is either very lengthy or problematic.[13] When, after activation of *N*-alkyl prolinol **B** by $SOCl_2$, the resulting reactive aziridinium intermediate **I** was treated with an amine, 2-(methyl)aminopyrrolidine **B′** was exclusively formed and no traces of the corresponding 3-aminopiperidine was detected.[14] In the particular case of *N*-alkyl prolinol **C**, when activated with mesyl chloride and treated with sodium azide at 100 °C in DMF, a mixture of 3-azidopiperidine **C′** and 2-(azidomethyl)pyrrolidine **C″** was formed in a ratio of 70/30 with a global yield of 90% (Scheme 1, eq 2).[15] This is one of the few examples reported in the literature for the transformation of an *N*-alkyl prolinol to a mixture of the corresponding 3-azidopiperidine and 2-(azidomethyl)pyrrolidine.[16]

Very recently, Charette et al. reported a ring expansion of dihydropyrrole producing tetrahydropyridine *via* an activated aziridinium intermediate.[17] Due to these results, we would like to report here a direct ring expansion of *N*-alkyl prolinols induced by XtalFluor E[18] which allowed the formation of an aziridinium intermediate that can react with tetrabutylammonium azide (nBu_4NN_3) to produce the corresponding 3-azidopiperidines with good to excellent regio-, diastereo-, and enantioselectivity (Scheme 2). We have to point out that these two methods are complementary and can produce 3-aminopiperidines differently substituted.

Scheme 1. Addition of Amines or Azide Anion on an Aziridinium Intermediate

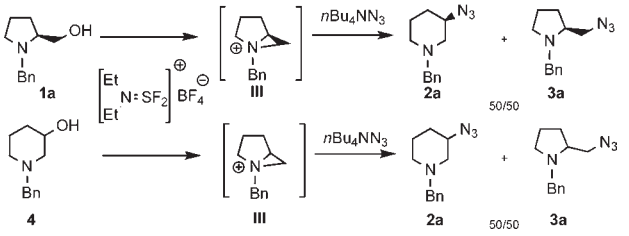


Scheme 2. Ring Expansion of Prolinols Induced by XtalFluor E



At first, prolinol **1a** was treated with nBu_4NN_3 (1.1 equiv) in CH_2Cl_2 at 0 °C followed by the addition of XtalFluor E. After 10 min, two products were formed, 3-azidopiperidine **2a** and 2-(azidomethyl)pyrrolidine **3a** in 70% yield, in a 1/1 ratio. As **2a** and **3a** were obtained with the same ratio when the 3-hydroxypiperidine **4** was treated with XtalFluor E and nBu_4NN_3, we can conclude that the aziridinium intermediate **III** was completely formed (Scheme 3).

Scheme 3. Ring Expansion of Prolinol **1a** and Ring Contraction of 3-Hydroxypiperidine **4**



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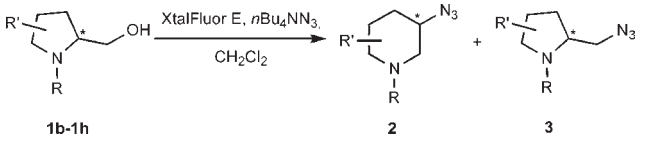
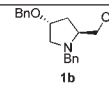
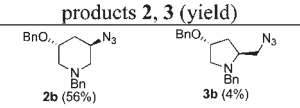
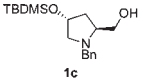
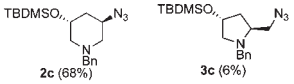
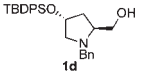
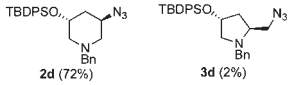
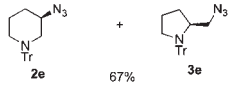
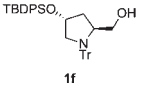
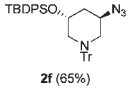
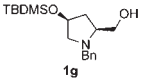
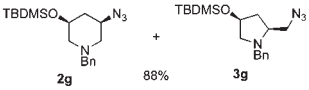
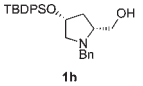
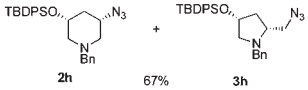
As the ring expansion of *N*-alkyl prolinols, *via* an aziridinium intermediate, is favored under kinetic control when steric hindered substituents are present at N1 and C4,[19] compounds **1b**–**1h** were prepared[20] and treated with XtalFluor E in the presence of nBu_4NN_3. The results are reported in Table 1.

Table 1. Ring Expansion of 4-Hydroxyprolinol Derivatives



entry	1	products **2**, **3** (yield)	**2**/**3**
1[c]			94/6[a]
2[c]			92/8[a]
3[c]			97/3[a]
4[d]			88/12[b]
5[e]			100/0
6[f]			60/40[b]
7[c]			60/40[b]

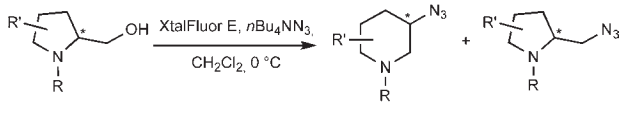
[a] Separable by chromatography on silica gel. [b] Inseparable. [c] The reaction was carried out at −78 °C for 4.5 h. [d] The reaction was carried out at −78 °C for 20 min. [e] The reaction was carried out at 0 °C for 30 min. [f] The reaction was carried out at 0 °C for 2.5 h.

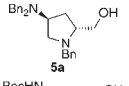
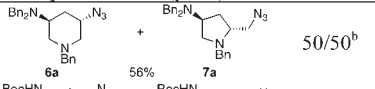
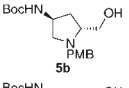
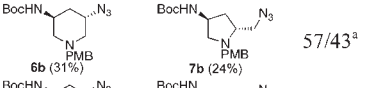
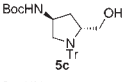
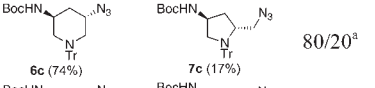
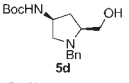
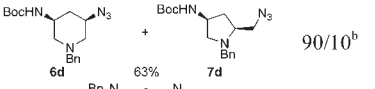
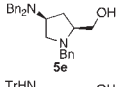
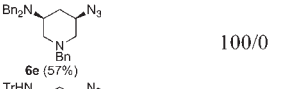
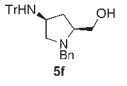
By increasing the steric hindrance at C4 in *N*-benzylprolinols **1b**–**d**, the ratio of 3-azidopiperidine **2**/2-(azidomethyl)pyrrolidine **3** was increased and the ratio **2**/**3** was superior to 92/8 (Table 1, entries 1–3). The steric hindrance of the *N*-alkyl group, such as a trityl group, could also increase the proportion of 3-azidopiperidine but was not as effective as the substituent at C4, as the ratio **2e**/**3e** was 88/12 (Table 1, entry 4). However, by combining the steric hindrance of N1 and C4 in prolinol **1f**, **2f** was exclusively formed in 65% yield (Table 1, entry 5). It is worth mentioning that even if 3-azidopiperidines **2g** and **2h** were the major compounds, the piperidine/pyrrolidine ratio was not as good as that for the *trans*-2,4-disubstituted prolinols **1b**–**d** and **1f**.

We have to point out that for piperidines **2b**–**d** and **2f**, the diastereoselectivity was greater than 95/5, and for compound **2e**, the enantioselectivity exceeded 95/5.

Amines and carbamates were tolerated under the conditions developed for the ring expansion of *N*-alkyl prolinols to the corresponding 3-azidopiperidines (nBu_4NN_3, XtalFluor E). The results are reported in Table 2.

Table 2. Ring Expansion of 4-Aminoprolinol Derivatives



entry	5	products **6**, **7** (yield)	**6**/**7**
1[c]			50/50[b]
2[c]			57/43[a]
3[d]			80/20[a]
4[c]			90/10[b]
5[c]			100/0
6[c]			100/0

[a] Separable by chromatography on silica gel. [b] Inseparable. [c] The reaction was carried out for 4.5 h. [d] The reaction was carried out for 2.5 h. [e] The reaction was carried out for 15 min.

Contrary to the C4-hydroxylated prolinols, the *cis*-amino substituted prolinols were transformed exclusively to the corresponding 3-azidopiperidines (Table 2, entries 5–6) and the *trans*-amino substituted prolinols led to a mixture of piperidines/pyrrolidines in a ratio which was increased in favor of the piperidine when the steric hindrance was increased at N1 (Table 2, entries 1–3).

As fluorine atoms can have a big impact on the biological activity of compounds, the ring expansion of 4-fluoropyrrolidines has been considered. The results are reported in Table 3.

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(16) For related reactions, see: (a) Setoi, H.; Takeno, H.; Hashimoto, M. *Heterocycles* **1986**, *24*, 1261–1264. (b) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1995**, *51*, 12611–12630. (c) Lonkar, P. S.; Kumar, V. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2147–2149. (d) Fukuhara, M.; Nishi, T.; Fujii, Y. WO 2007/108209; *Chem. Abstr.* **2007**, *147*, 412648. (e) Pluvinage, B.; Ghinet, M. G.; Brzezinski, R.; Boraston, A. B.; Stubbs, K. A. *Org. Biomol. Chem.* **2009**, *7*, 4169–4172.

(17) Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, doi: 10.1021/ol201349k.

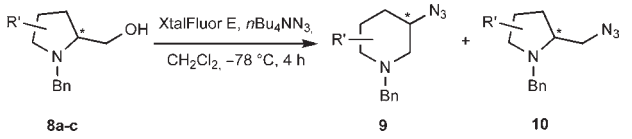
(18) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401–3411.

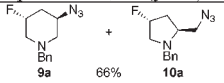
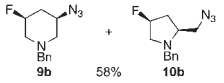
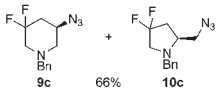
(19) (a) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Synlett* **2007**, 263–267. (b) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2007**, 4224–4234.

(20) The requisite substrates **1a**–**h**, **4**, **5a**–**f**, and **8a**–**c** were prepared from the corresponding proline; see the Supporting Information.

When treated with nBu$_4$NN$_3$ and XtalFluor E, the *trans*-4-fluoroprolinol **8a** was transformed to piperidine **9a** and pyrrolidine **10a** in a ratio of 93/7 in favor of **9a** with a global yield of 66% (Table 3, entry 1). For the *cis*-4-fluoroprolinol **8b**, the ratio of piperidine/pyrrolidine was 1 to 1 (Table 3, entry 2), and this ratio was excellent when two fluorine atoms were present at C4 (**9c**/**10c** = 91/9, Table 3, entry 3).

Table 3. Ring Expansion of 4-Fluoroprolinol Derivatives



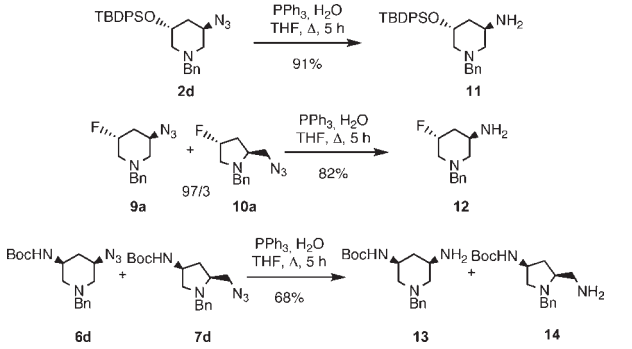
entry	8	products 9, 10 (yield)	9/10
1		 66%	93/7[a]
2		 58%	50/50[a]
3		 66%	91/9[a]

[a] Inseparable.

Substituted 3-aminopiperidines of type **A** can be synthesized easily in good yield from the 3-azidopiperidine products *via* Staudinger reduction[21] of the azido group (Scheme 4). Further selective functionalization of the different nitrogen atom present in the obtained piperidines can be achieved easily as each nitrogen is orthogonally protected (Scheme 4).

(21) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646.

Scheme 4. Staudinger Reduction of the Azido Group



In conclusion, we have shown that *N*-alkyl prolinols can be transformed to an aziridinium intermediate by using XtalFluor E and that this intermediate was able to react with nBu$_4$NN$_3$ to produce 3-azidopiperidines in good yield and excellent diastereo- and enantioselectivity. The ratio of the 3-azidopiperidines and 2-(azidomethyl)-pyrrolidines depends on the steric hindrance at N1 and C4 as well as on the nature and relative stereochemistry of the substituents present in the *N*-alkylprolinols at C2 and C4. In order to understand the influence of the substituents at C4, theoretical calculations are under investigation and will be reported in due course.

Supporting Information Available. Experimental procedure and characterization data of compounds **1g**–**h**, **2a**–**h**, **3a**–**h**, **5a**–**f**, **6a**–**f**, **7a**–**f**, **8a**–**c**, **9a**–**c**, **10a**–**c**, and **11**–**14**. This material is available free of charge via the Internet at http://pubs.acs.org.