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Synthesis of enantiopure azetidines: a route to new β-amino alcohols

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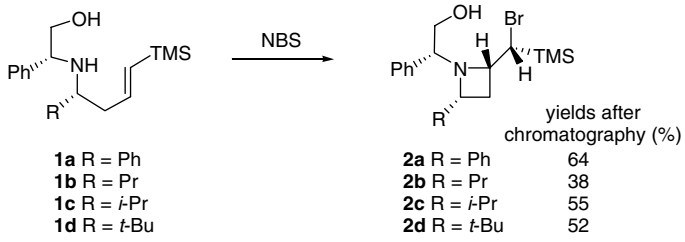
Abstract—β-Amino alcohols possessing an *E* vinylsilane moiety were cyclized in the presence of *N*-bromosuccinimide to afford diastereoisomerically pure polyfunctional azetidines. These azetidines were then transformed into enantiopure β-amino alcohols with a *Z* vinylic bromide moiety.

Azetidines have received much synthetic attention during the last decade[1,2] because of their utilization as ligands,[3] their detection as natural products[4] and their biological and pharmaceutical activities.[5] Electrophile-induced intramolecular cyclization of unsaturated amines appeared as an efficient method to produce these nitrogen heterocyclic compounds.[6]

In the course of studies of the enantioselective synthesis of pipecolic acid[7a] and proline derivatives[7b] from unsaturated and silylated β-amino alcohols **1**,[8] we were interested by the synthesis of other azaheterocyclic compounds. Thus, this letter describes a novel synthetic application allowing a rapid access to diastereoisomerically pure azetidine derivatives and their subsequent transformation into new β-amino alcohols.

When treated with NBS, amino alcohols **1a–d** were cyclized in a totally regio and diastereoselective manner to afford azetidines **2**, with some recovered unreacted starting material **1** (Scheme 1).

As shown in Table 1, which collects the experimental data of the cyclization performed on the amino alcohol **1d**, the best conditions in order to increase the **2d/1d** ratio was the use of 1.05 equiv of *N*-bromosuccinimide, at 0 °C in acetonitrile (entry 7). Whereas the temperature and the time had no significant influence on this



Scheme 1.

Keywords: Azetidines; β-Amino alcohols; *N*-Bromosuccinimide; Vinylsilane; Vinylbromide.
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Table 1.

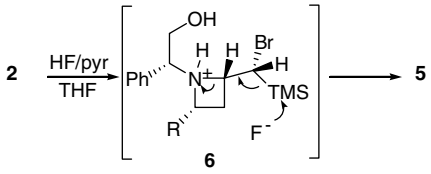
Entry	Solvent	NBS (equiv)	Temp, time	Ratio **2d/1d**
1	CH_2Cl_2	2	0 °C→rt; 20 h	67/33[a]
2	CH_2Cl_2	1.05	0 °C→rt; 20 h	73/27[a]
3	CH_2Cl_2	1.05	0 °C→rt; 30 min	77/23[b]
4	CH_2Cl_2	1.05	rt; 72 h	77/23[b]
5	THF	1.05	0 °C→rt; 72 h	—
6	CH_3CN	1.05	0 °C→rt; 72 h	87/13[b]
7	CH_3CN	1.05	0 °C→rt; 1 h 30 min	89/11[b]

[a] Determined after chromatography on silica gel.
[b] Determined by ^1H NMR analysis of the crude reaction.

cyclization, the reaction was governed by a solvent effect: acetonitrile giving the best results. This solvent was already reported as the more efficient solvent for a 4-*exo*-*trig* cyclization process.[9,6b]

The absolute configuration of **2d** was determined by an X-ray analysis.[10] The stereoselectivity displayed by this bromocyclization could be explained by the formation of the intermediate bromonium **3**, which was followed by the intramolecular attack of the nitrogen atom, according to a 4-*exo*-*tet* cyclization.[11] The spatial layout of the atoms involved in this reaction; that is, nitrogen, carbon and bromine correspond to a minimization of the steric interactions. The bromonium ion was formed on the face of the double bond allowing the attack of the doublet of the nitrogen atom in an *anti* position relative to the C–Br bond, in a likely concerted process (Scheme 2). The regioselectivity was due to a dissymmetry of the bromonium ion as a consequence of the β-effect of the silicium.[12,13]

In order to specify the synthetic utility of these azetidines, we attempted the cleavage of the silicon–carbon bond. Compound **2d** was first treated by tetrabutylammonium fluoride, and was thus transformed into bicyclic product **4**. Formation of compound **4** results from a desilylation followed by a cyclization. The stereochemistry of this unexpected compound has not been determined. On the other hand, when azetidines **2a**–**d** were treated with fluorohydric acid in pyridine, amino alcohols **5**, with a *Z*-vinylic bromide moiety, were isolated in very high yields (Scheme 3). This reaction was very clean and no purification of the products was necessary.[14]



Scheme 4.

This reaction is stereospecific and took place in the following way: (i) protonation of the nitrogen atom to give the ammonium intermediate **6** and (ii) *anti*-elimination of the trimethylsilyl group by the attack of the fluoride ion with departure of ammonium (Scheme 4).[15]

In conclusion, we have synthesized in two totally stereoselective steps a new class of enantiopure amino alcohols with a *Z*-vinylic bromide moiety from amino alcohols with an *E*-vinylsilane terminator, via the diastereoselective synthesis of highly substituted azetidines. Works are in progress to develop the chemistry of these new compounds: azetidines **2** and β-amino alcohols **5**.

Acknowledgements

We thank Dr. Carine Guyard-Duhayon for X-ray analysis of compound **2d**. Dr. Louis Hamon is acknowledged for helpful discussions.

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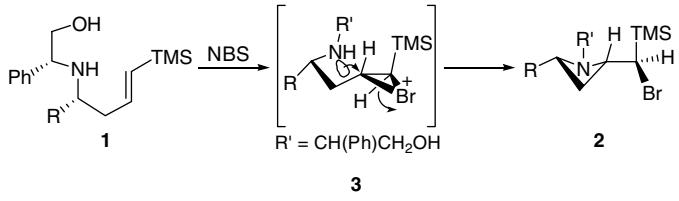
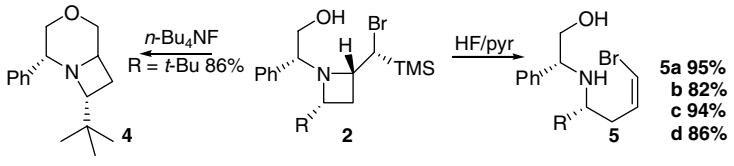


Scheme 2.



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