Molecules **2002**, *7*, 902-906

molecules

ISSN 1420-3049

http://www.mdpi.org

Short and Efficient Synthesis of Optically Active N-Tosyl Aziridines from 2-Amino Alcohols

Lothar W. Bieber* **and Maria C. F. de Araújo**

Departamento de Química Fundamental, Universidade Federal de Pernambuco, 50607-901 Recife – PE, Brazil

*Author to whom correspondence should be addressed; e-mail: bieberlothar@hotmail.com

Received: 3 November 2002; in revised form: 2 December 2002 / Accepted 2 December 2002 / Published 31 December 2002

Abstract: Two alternative and complementary one-pot procedures for the direct transformation of 2-amino alcohols to N-tosyl aziridines are presented. The unsubstituted parent compound and its less hindered homologues can be obtained in high yields by tosylation and in situ cyclisation effected by potassium hydroxide in water/dichloromethane. Higher substituted amino alcohols give better yields using potassium carbonate in acetonitrile. Both procedures use simple inorganic bases and produce only inorganic salts as byproducts.

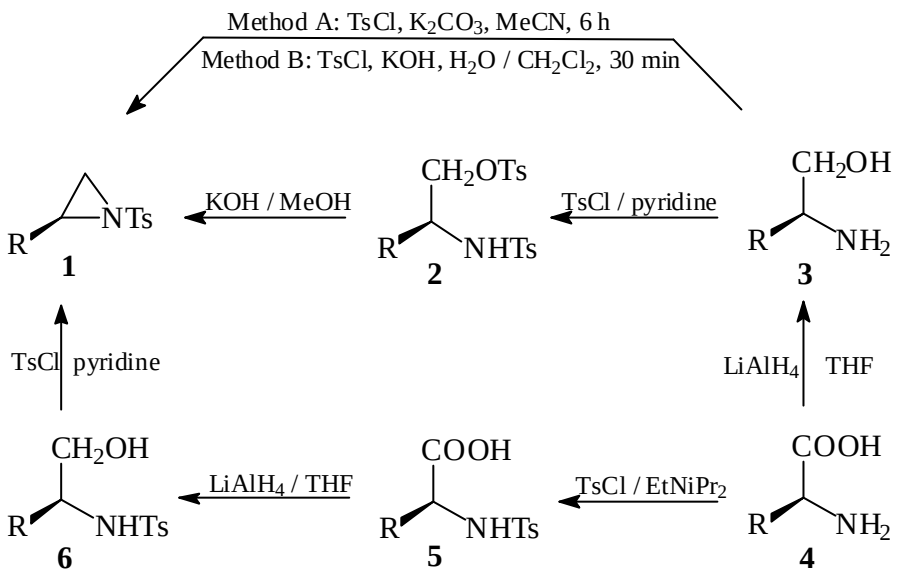
Keywords: Amino alcohols, bis-tosylation, inorganic bases, 1,3-elimination, aqueous solvent.

Introduction

Aziridines are interesting synthetic building blocks for the construction of complex nitrogen containing compounds. When activated by a N-tosyl group, they are especially reactive towards nucleophilic ring opening and provide an easy access to a wide variety of alkaloid structures [1]. Although several methods have been reported for the direct asymmetric transfer of N-tosyl nitrene to

olefinic double bonds in recent years [2], the most obvious precursors for chiral N-tosyl aziridines **1** are 2-amino alcohols **3** derived from natural or unnatural amino acids **4**. Initially, compounds of type **1** have been prepared in moderate yields via the unstable bis-tosylates **2** using traditional acylation and ring closure procedures [1b,3]. Alternatively, N-tosylated amino acids **5** have been reduced to the alcohols **6**, submitted to a second tosylation and cyclised *in situ* to **1** (Scheme 1) [4].

Scheme 1: Synthesis of N-tosylaziridines



Although the latter procedure is high yielding, it requires several steps and anhydrous reaction conditions. The first inconvenient has been avoided in two procedures previously described for special intermediates in alkaloid syntheses: (S)-leucinol (**3**, R = CH_2iPr) has been transformed in a one-pot procedure to the corresponding N-tosylaziridine **1** using excess of tosyl chloride and triethylamine and catalytic amounts of 4-dimethylaminopyridine in dichloromethane [5], similarly, the chiral key intermediate **1** (R = nPr) of our Pumiliotoxin C synthesis has been obtained directly from (S)-norvalinol with sodium hydride as base in anhydrous THF [6]. However, the experimental risks due to the use and destruction of large amounts of hydride and the need for anhydrous reagents and solvents, represented serious limitations for a general application, especially under tropical conditions of extreme humidity, and prompted us to look for less hazardous solvent/base combinations.

Results and Discussion

In previous work, anhydrous potassium carbonate in aprotic, but undried commercial solvents has been useful for the alkylation of 1,3-dicarbonyl compounds [7] and a similar procedure seemed promising for the direct acylation of **3** and subsequent ring closure to **1**. Indeed, first experiments using this base in undried DMF, DMSO or HMPA as solvent at room temperature produced **1** in moderate

yields, but the crude product contained considerable amounts of polymeric material and required chromatographic purification. Use of a weaker base like potassium bicarbonate or fluoride stopped the reaction partially at the level of compounds **2** and did not avoid polymerization. Finally, when K_2CO_3 was used in commercial undried acetonitrile, a smooth and clean reaction was accomplished in 6 h at room temperature and high yields of several substituted (S)-aziridines **1** were obtained after separation of insoluble salts and evaporation of the solvent (Table 1, entries 4-9, method A).

Table 1. Direct synthesis of (S)-N-tosyl aziridines **1** from (S)-amino alcohols **2**.

Entry	R =	Method A Yield %	Method B Yield %
1	H	46	74
2	CH_3	53	78
3	C_2H_5	62	86
4	$(CH_3)_2CH$	75	70
5	$CH_3\ CH_2CH_2$	82	73
6	$(CH_3)_2CHCH_2$	76	52
7	$C_6H_5\ CH_2$	92	64
8	$CH_3SCH_2CH_2$	85	67
9	4-HO-$C_6H_4CH_2$ [a]	87	58

[a] Bis-tosylate was obtained using 3.2 (Method A) and 3.5 (Method B) eq. of tosyl chloride, respectively.

However, when the same method was applied to unsubstituted aminoethanol **3** (R = H, entry 1) and the lower amino alcohols (entries 2 and 3), the yields and purities of the compounds **1** obtained were unsatisfactory. As unsubstituted tosyl aziridine has been obtained before in excellent yield by cyclisation of bis-tosylate **2** (R = H) using aqueous potassium hydroxide [8], we tried to combine tosylation and 1,3-elimination in the same solvent/base system. In fact, when tosyl chloride was added to a vigorously stirred mixture of 2-aminoethanol, concentrated aqueous potassium hydroxide and methylene chloride, good yields of the desired tosyl aziridine **1** (R = H) were obtained in a few minutes (Table 1, entry 1, method B). The same procedure proved to be superior or equivalent to method A in the case of small and medium size substituents (entries 2-5), but was less efficient for the higher substituted amino alcohols, probably because in these cases one of the tosylation steps is complicated by steric hindrance. On the other hand, in method A the long reaction time leads to partial polymerization of aziridines bearing smaller substituents.

Conclusions

In conclusion, both methods described herein are short, simple and safe experimental procedures; they are complementary alternatives depending on the steric hindrance of the starting amino alcohol. Both methods make use of inexpensive and easily neutralized inorganic bases and the organic solvents used can be recovered by distillation. The use of moisture sensitive and hazardous reagents and formation of organic waste is avoided. Combined with known methods of sodium borohydride reduction of amino acids **4** [9] they allow one to carry out the whole sequence from **4** to **1** (Scheme 1) using inexpensive reagents and environmentally friendly solvents.

Acknowledgements

This work was supported by grants from CNPq (Brasilia). We thank M. Ricardo O. da Silva for GC-MS analyses.

Experimental

General

All reagents and solvents from commercial suppliers were used without further purification. All products obtained had physical and spectroscopic properties identical to those reported in the literature [3,4,6].

Typical Synthetic Procedures

Method A: Tosyl chloride (2.2 mmol) was added portionwise at r.t. to a stirred mixture of **3** (1.0 mmol), K_2CO_3 (4.0 mmol) and acetonitrile (2.0 mL). After 6 h, toluene (5 mL) was added, the solid was filtered off and the solvents evaporated.

Method B: Tosyl chloride (2.5 mmol) was added portionwise at r.t. under vigorous stirring to a mixture of KOH (2.0 g), **3** (1.0 mmol), water (2.0 mL) and CH_2Cl_2 (2.0 mL). After 30 min, ice and water were added, the organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated.

The crude products were purified by crystallization, short-path distillation or column chromatography. The optical purities of all products were proven to be identical with those of the starting materials. The pure aziridines polymerize at r.t. within a few days, but can be stored at –30º for months.

References

1. (a) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599-619; (b) Osborn, H.M.I.; Sweeney, J. *Tetrahedron Asymmetry* **1997**, *8*, 1693-1715.
2. (a) Halfen, J.A.; Hallman, J.K.; Schultz, J.A.; Emerson, J.P. *Organometallics* **1999**, *18*, 5435-5437; (b) Albone, D.P.; Aujla, P.S.; Taylor, P.C.; Challenger, S.; Derrick, A.M. *J. Org. Chem.* **1998**, *63*, 9569-9571.
3. Daub, G.W.; Heerding, D.A.; Overman, L.E. *Tetrahedron* **1988**, *44*, 3919-3930.
4. Berry, M.B.; Craig, D. *Synlett* **1992**, 41-45.
5. (a) Craven, A.P.; Dyke, H.J.; Thomas, E.J. *Tetrahedron* **1989**, *45*, 2417-2429; (b) Wang, J.Q.; Zhong, M.; Lin, G.Q. *Chin. J. Chem.* **1998**, *16*, 65-77.
6. Oppolzer, W.; Flaskamp, E.; Bieber, L.W. *Helv. Chim. Acta* **2001**, *84*, 141-145.
7. Araújo, A.C.V.; Almeida, F.V., Bieber, L.W. *Química Nova* **1996**,*19*, 79-81.
8. Martin, A.E.; Ford, T.M.; Bulkowski, J.E. *J. Org. Chem.* **1982**,*47*, 412-415.
9. (a) McKennon, M.J.; Meyers, A.I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568-3571; (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517.

Sample Availability: Not available.