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A new piperazine: Spectroscopic and theoretical conformational studies

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ABSTRACT

The reaction of benzylamine with the *N*-tosylaziridine prepared from (*S*)-serine and bearing an amide group at C2 afforded a single open chain compound, in contrast to the lack of regioselectivity for the ring opening of the analogous 2-carbalkoxy derivative. The (*S*)-amide substituted piperazine was prepared by *N*,*N'*-bisalkylation of the corresponding open chain compound. Theoretical calculations for the piperazine and NMR experiments indicated that for all three most stable conformations the amide group is axially positioned.

1. Introduction

Epoxides and aziridines are key reagents for the construction of molecules bearing heteroatoms. In this sense, the N-tosylaziridines **1**, easily prepared from the readily available L-serine, are potential candidates for the ring opening click reaction with amines [1]. Such method would lead to open chain compounds containing a vicinal diamino moiety, many of them of biological importance as, for example, natural anti-cancer agents like mytomycins or anti-HIV chiral substituted piperazines [2]. As for non activated aziridines bearing an ester or an amide group at C2, similar regioselectivity was observed for the ring opening process by amines. The recent report on the synthesis of Lacosamide and its derivatives is representative of such issue [3]. In that case, during the synthetic key step, the ethyl 1-[(*R*)-1-phenylethyl]aziridine-(2*R*)-carboxylate or its benzylamide counterpart were submitted to ring opening at C-2 using several different amines, leading to ca 80 : 2 regioisomeric ratio. We now wish to report that, in contrast to these findings, for the *N*-benzylamine promoted ring opening reaction of N-tosylaziridines **1**, having at the 2-position an ester or an amide group, the latter derivative should be the substrate of choice for attaining good regioselectivity.

Our main interest in investigating the above mentioned model reaction was to develop a simple and efficient method for the preparation of chiral piperazines **3** and **4** (Scheme 1).

2. Experimental procedures

NMR spectra were recorded on a Varian Inova-300 spectrometer, using $CDCl_3$ as solvent, and tetramethylsilane as internal standard. A Finnigan ITD-800 and a MicroToF Bruker Daltonics spectrometers were used for recording low- and high-resolution spectra, respectively. The conformational search protocol was performed using the Spartan16 software [4] which generated a total of 72 conformations for the **3b** structure. In order to determine the most stable conformers, the employed conformational search followed a standard protocol, with small differences depending of the software used. Initially, Molecular Mechanics methodology (MMFF) was applied to perform an exploratory search for conformers, which were then re-optimized using the PM6 Force Field semi-empirical strategy. Then Gaussian09D [5] was used to optimize the 20 most stable conformers using the Hartree-Fock method with the 6-21G basis set [6] for all atoms. The 10 more stable resulting conformers were further studied by Density Functional Theory

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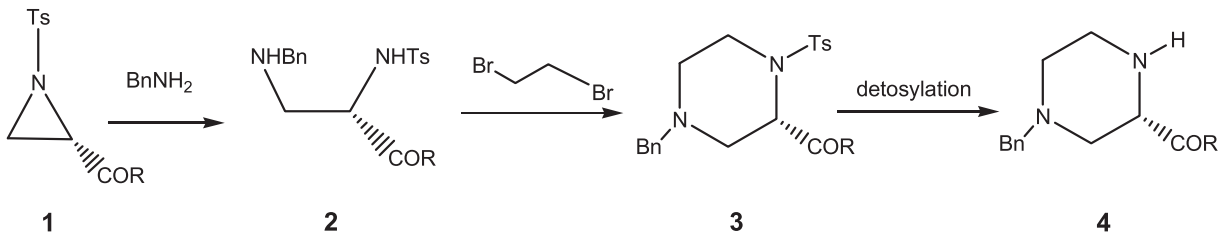


(**a**): R=OCH_3; (**b**): R=NH^tBu

Scheme 1. En route to piperazines **3** and **4**.

(DFT) calculations with the functional ωB97XD [7] using the 6-31G(d,p) basis set [8]. After DFT optimization, 3 pairs of conformers presented the same coordinates and energy, and the remaining 7 conformers are presented as supplementary data. The solvent effects in chloroform were considered by employing the Solvation Model based on the density solvation model [9]. Each optimized geometry was confirmed as minimum by absence of imaginary frequencies. The cartesian coordinates and potential energies for the seven more stable conformations can be found as a part of the supplementary data.

Aziridine ring opening-method A: A mixture of aziridine **1b** (0.23 g; 0.76 mmol), benzylamine (0.082 g; 0.76 mmol) and triethylamine (20 μL; 0.15 mmol), in 1.0 mL of THF was stirred, at room temperature, for 24 h. The solvent was removed under vacuum and the residue submitted to column chromatography separation in aluminum oxide, using hexane/acetone (7:3). Compound **2b** was obtained as colorless oil (0.25 g; 80%). ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.26 (s; 9H; Hb), 2.38 (s; 3H; He), 2,41 (dd; $J_1 = 12.3$ Hz; $J_2 = 6.6$ Hz; 1H; H3), 3.10 (dd; $J_1 = 12.3$ Hz; J2 = 4.4 Hz; 1H; H3'), 3.56 (d; $J = 13.1$ Hz; 1H; Hc), 3.69 (d; $J = 13.1$ Hz; 1H; Hc'), 3.75 (dd; $J_1 = 6.6$ Hz; $J_2 = 4.4$ Hz; 1H; H2), 7.21–7.36 (7H; H-Ar), 7.70 (d; $J = 7.8$ Hz; 2H; Hd). ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.50 ($(\underline{C}H_3)_3C$); 28.57 ($\underline{C}H_3$—C_6H_5), 49.76 (C3), 51.32 ($\underline{C}(CH_3)$), 53.18 (C5), 55.39 (C2), 127.3, 127.4, 128.2, 128.6, 129.8 (C-Harom), 136.0, 139.1, 143.8 (Cquat-arom), 168.7 (C=O). HRMS (ESI) Calcd. for $C_{21}H_{30}N_3O_3S^+$: 404.2008, Found: 404.1998.

*Piperazine **3b***. A mixture of **2b** (1.1 mmol), potassium carbonate (1.7 mmol), 1,2-dibromoethane (2.2 mmol), benzyl triethylammonium chloride (25 mg), in acetonitrile (5 mL), was refluxed for 2 h. After removal of the solid by filtration, the organic phase was concentrated under vacuum and submitted to column chromatography separation on silica gel using $CHCl_3/CH_3OH$ (10:0.5). Compound **3b** was obtained as yellow oil (46% yield). ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.28 (s; 9H; Hb), 1.86 (td; $J_1 = 11.8$ Hz; $J_2 = 11.8$ Hz; $J_3 = 3.4$ Hz; 1H; H5-axial), 1.97 (dd; $J_1 = 11.6$ Hz; $J_2 = 4.2$ Hz; 1H; H3-axial), 2.40 (s; He; 3H), 2.58 (dd; $J_1 = 11.6$ Hz; $J_2 = 1.7$ Hz; 1H; H5-equatorial), 3.21 (ddd; $J_1 = 13.5$ Hz; $J_2 = 12.1$ Hz; $J_3 = 3.3$ Hz; 1H; H6-axial), 3.32 (d; 1H; $J = 12.9$ Hz; Hc), 3.34 (dt; $J_1 = 11.6$ Hz; $J_2 = 1.7$ Hz; $J_3 = 1.7$ Hz; 1H; H3-equatorial), 3.47 (d; 1H; $J = 12.9$ Hz; Hc'), 3.78 (bd; $J_1 = 13.5$ Hz; $J_2 = 3.4$ Hz; 1H; H6-equatorial), 4.30 (bs; 1H; H2), 6.66 (bs; 1H; Ha), 7.21–7.35 (m; 7H; H-Ar), 7.70 (d; $J = 7.8$ Hz; 2H; Hd and Hd'). ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.56 ($(\underline{C}H_3)_3C$), 28.64 ($\underline{C}H_3C_6H_5$), 43.13, 50.97, 52.46, 62.51 (C6, C3, C5 and $\underline{C}H_2C_6H_5$), 51.17 ($(CH_3)_3\underline{C}$), 57.3 (C2), 127.3, 127.5, 128.3, 129.0, 129.8 (CHarom), 137.0, 137.1, 143.8 (Cquat-arom), 167.3 (C=O). HRMS (ESI) Calcd. for $C_{23}H_{32}N_3O_3S^+$: 430.2164, Found: 430.2161.

3. Results and discussion

Having in hands both N-tosylaziridines **1a**,**b**, prepared from natural L-serine as described elsewhere [10] and in order to investigate the regioselectivity for the ring opening reaction of both substrates, we elected two protocols, *i.e.* using benzylamine and 20 mol% of triethylamine or, alternatively, using excess of benzylamine in the absence of any added base. Although very similar yields of the resulting **2a,b** compounds were observed for both 2-substituted aziridines, complete regioselectivity could be achieved only for **1b** (Table 1). It should be mentioned that, for 2-carboalkoxy substituted aziridines, poor regioselectivity results were previously reported [11].

As for the major regioisomer resulting from the ring opening of aziridine **1a**, the comparison with ^{1}HNMR data of the analogous compound **5** and its regioisomer **6** [12] supports structure **2a** (Table 2). In fact, the selected chemical shifts for **2a** and **5** are quite similar, but very different from those for compound **6**.

The ring opening reaction of **1b** with benzylamine could be easily followed by recording, at selected time intervals, the ^{1}H NMR spectra of a $CDCl_3$ solution of reagents, base and employing dibenzyl ether as internal standard. After 15 h, ca. 80% of **1b** was converted into the corresponding **2b** [13].

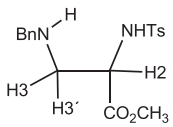
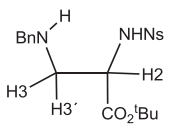
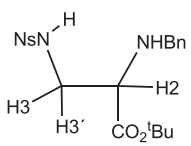
The identities of regioisomers resulting from the ring opening at C-3 of **1a** or **1b** were also confirmed by mass spectrometry analysis, as the expected fragment $m/z = 120$ could be detected for the major isomers of **2a** (rel. intensity = 31%) or **2b** (rel. intensity = 100%). In both cases, the fragment $m/z = 184$ (that would be expected for ring opening at C2) was absent (Scheme 2, R = OMe or NH^tBu).

Table 1
Results for reactions of **1a**,**b** with benzylamine.

Aziridine	Benzylamine equiv.	Method[a]	Time (h)	Yield[b] (%)	Isomer from ring opening at C-3
1a	1	A	10	33[d]	2a (major)
1a	10	B	7	40[d]	2a (major)
1b	1	A	6	55 (80)[c]	only
1b	10	B	6	40	only

[a] Method A: 0.2 equiv. Et_3N/THF, r.t.; Method B: CH_2Cl_2, r.t.
[b] By column chromatography on silica gel.
[c] By column chromatography on Al_2O_3.
[d] In admixture with side products.

Table 2
Selected ^{1}HNMR chemical shifts for compounds **2a**, **5** and **6.**

Compound	δ H2 (ppm)	δ H3/H3' (ppm)
 **2a**	4.03	2.89
 **5**	4.19	2.99
 **6**	3.13−3.07	3.39−3.27

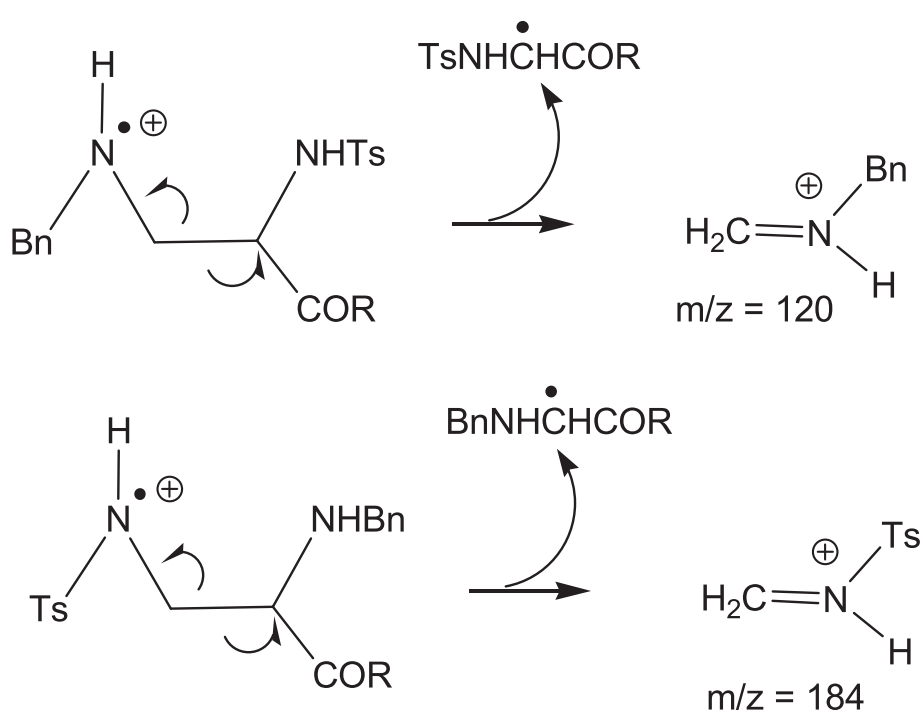
En route to the expected piperazine **3b**, compound **2b** was submitted to the reaction with 1,2-dibromoethane, under solid/liquid phase-transfer condition, in analogy to the previously described procedure for the *N*-alkylation of α-aminoesters sulfonamides [14]. Although two isomeric compounds **3b** and **7** (Scheme 3) could result upon alkylation of **2b**, the ^{1}H and ^{13}C NMR spectra of the crude product indicated the formation of only one compound.

The structure of the product was determined by NMR spectroscopy [15], as follows: i) DEPT-135 experiment indicated that two new methylene carbons were incorporated to the product molecular structure; ii) broad singlets at 4.30 and 6.66 ppm could be assigned to H2 and Ha, respectively, for each isomers; iii) NOE effect was observed between Ha and Hb, thus supporting structure **3b** instead of **7**, for which no such effect would be expected. iv) the Ha broad singlet is consistent with structure **3b** [16] but not with **7** for which coupling with Hc/Hc' and Hd/Hd' would lead to a multiplet.

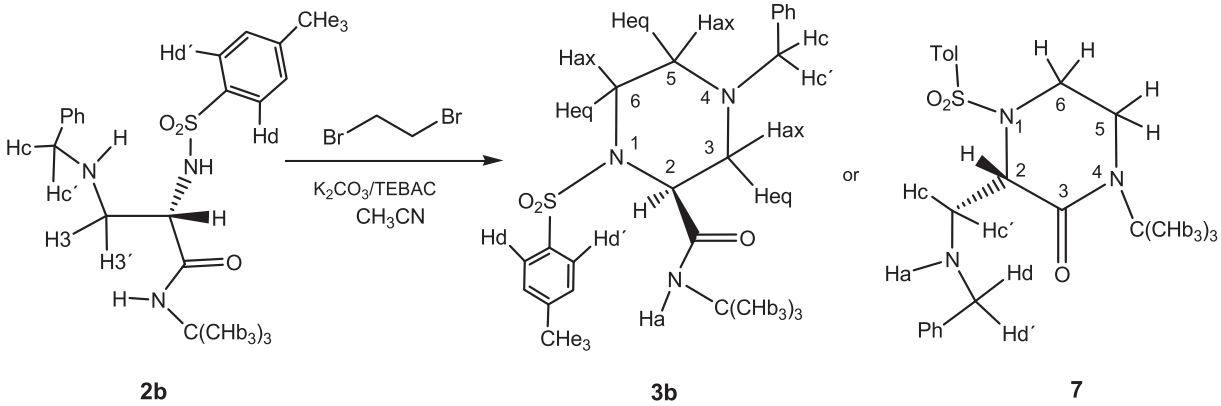
As a next step, further refinements concerning the conformation of **3b** were gathered from the following evidences: i) HETCOR correlates protons signals at 1.86(td)/2.58(bd), 3.21(ddd)/3.78(bd), and 1.97(dd)/3.34(dt) to the three cyclic methylene carbons (at 50.97, 43.13, and 52.46 ppm, respectively), and, at 3.32(d)/3.47(d) ppm, to the benzyl carbon (at 62.51 ppm) [17]; ii) the NOE effect between Hd or Hd' (at 7.70 ppm) and hydrogen resonating at 3.78 ppm indicates that the latter is attached to C6; iii) mutual strong NOE effects are observed for protons at 1.86/2.58 and at 3.21/3.78 ppm that should be attached to C5 and C6 atoms, respectively; iv) signals at 1.86 (td; $J_1 = 11.8$ Hz; $J_2 = 11.8$; Hz $J_3 = 3.4$ Hz) and 3.21 ppm (ddd; $J_1 = 13.5$ Hz; $J_2 = 12.1$; Hz; $J_3 = 3.3$ Hz) can be assigned to axial H5 and H6, respectively and, therefore, signals at 2.58 (bd; $J_1 = 11.6$ Hz; $J_2 = 1.7$ Hz) and 3.78 ppm (bd; $J_1 = 13.5$ Hz; $J_2 = 3.4$ Hz) are assigned to the equatorial H5 and H6, respectively; v) the observed NOE effect between Ha and axial H6 and the lack of a strong coupling between H2 and any of the hydrogens at C3 clearly indicates that the carboxamide group occupies an axial position. Consequently, the preferential conformation for **3b** (Fig. 1) can be advanced.

Conformational searches for **3b** were performed, and the resulting three most stable conformations are presented according to their energy content (Fig. 2). The two most stable structures **3b-I** and **3b-II**, both having very similar free energy content, can be considered equally probable in the conformational equilibrium. Calculations also pointed to the third conformation **3b-III**, but of slightly higher energy.

The main structural feature for distinguishing among the three mentioned conformations refers to the relative position of the



Scheme 2. Comparison of the expected mass fragmentations for the regioisomeric open chain compounds **2a**,**b**.



Scheme 3. Possible isomeric piperazines resulting from *N,N′*-bisalkylation of **2b**.

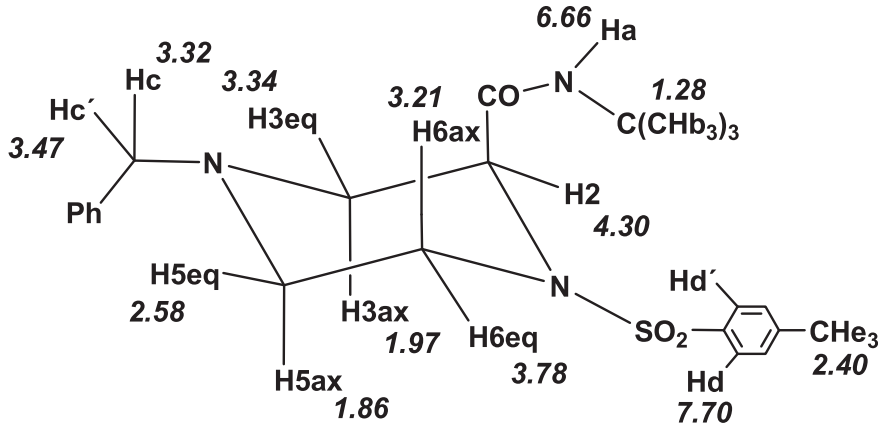


Fig. 1. ^{1}H NMR chemical shifts (δ, in ppm) for the favored conformation of compound **3b**.

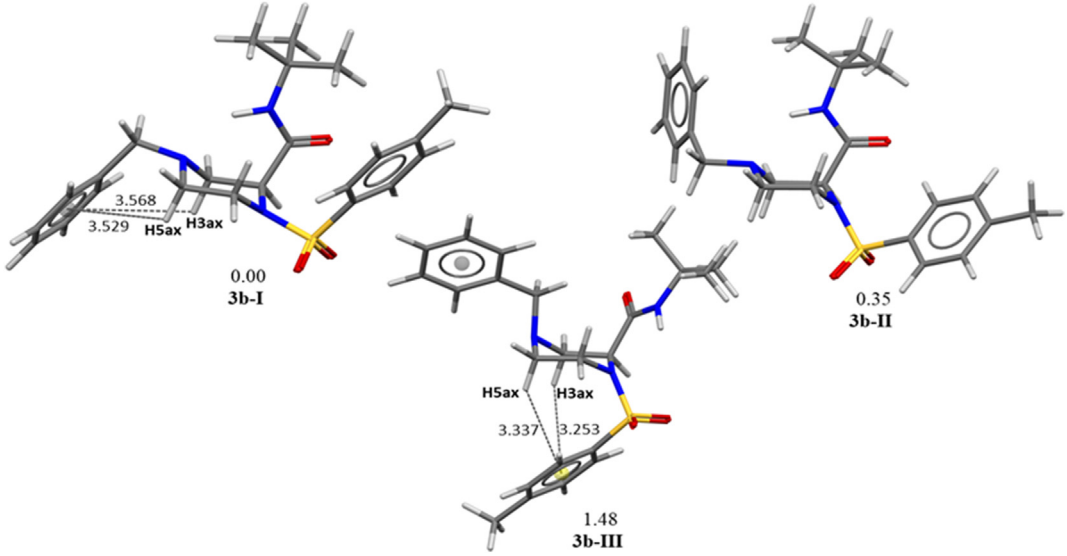


Fig. 2. Calculated conformations of **3b,** relative free energies (in kcal.mol^{-1}), and selected distances (in angstroms).

aromatic tosyl and benzyl rings, as follows: equatorial/equatorial for **3b-I**; axial/equatorial for **3b-II**, and axial/axial for **3b-III**, respectively. It should be mentioned that, for conformations **3b-I** and **3b-III**, the aromatic rings are directed towards the axial H3 and H5 protons of the piperazine moiety. For these two conformations a strong ^{1}H NMR shielding effect should be observed for the axial H3 and H5 protons. In fact the observed chemical shifts for H3ax and H5ax are consistent with this expectation. Although this structural

feature is absent for conformation **3b-II**, the small energy gaps for the three conformations might allow for the coexistence of all of them.

4. Conclusions

In conclusion, comparative studies of the regiochemical pathway for the ring opening of N-tosylaziridines **1a,b,** bearing an amide or an ester group attached to C2, highlight the exclusive attack of benzylamine at C3 for the amide derivative **1b**, probably due to steric effects. The resulting open chain compound **2b** proved to be useful intermediate for the preparation of a new stereo-defined piperazine **3b**. The preferential conformation of this compound, having the CONH^{t}Bu group in axial position, could be accessed by NMR experiments and theoretical calculations.

Author contributions

The following are the authors contributions:L. Marzorati, C. Di Vitta, R. G. Moura, and M. A. Bueno Filho did the synthetic work. A. A. C. Braga and M. P. Franco performed the theoretical calculations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molstruc.2019.127420.

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