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# Experimental and DFT study of the conversion of ephedrine derivatives into oxazolidinones. Double $S_N2$ mechanism against $S_N1$ mechanism

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ABSTRACT

Sulfonation of the *N*-Boc derivatives of 1,2-aminoalcohols, such as ephedrine, pseudoephedrine, norephedrine, norpseudoephedrine, thiomicamine, and chloramphenicol yields a mixture of the corresponding oxazolidinones with inversion (*erythro* derivatives) and/or retention of configuration (*threo* derivatives)at C5. We suggest a competition between two mechanisms: an intramolecular $S_N2$ process initiated by attack of the carbonyl oxygen of the Boc group to the benzylic carbon and the other one through a double $S_N2$ process. In the *erythro* derivatives the first mechanism is predominant, while in the *threo* derivatives both mechanisms have similar energy. This hypothesis is supported by theoretical calculations and additional experimental assays.



## 1. Introduction

1,2-Aminoalcohol functional groups are often found in many bioactive compounds and their stereoselective synthesis and reactions are of wide interest.[1] Among the numerous aminoalcohols, the aryl aminoalcohols such as ephedrine **1**, pseudoephedrine **2**, norephedrine **3**, norpseudoephedrine **4**, thiomicamine **5**, and chloramphenicol **6**, are of particular interest (Fig. 1).[2] 1,2-Aminoalcohols have an outstanding significance as chiral ligands and as precursors of chiral oxazolines and 1,3-oxazolidin-2-ones. The 1,3-oxazolidin-2-ones are a very interesting class of compounds due to their various pharmacological effects and applications in asymmetric synthesis.[3]

The conventional methods for the synthesis of 1,3-oxazolidin-2-ones involve the reaction of 1,2-aminoalcohols with different reagents, such as phosgene,[4] urea,[5] dialkylcarbonate,[6] isocyanates,[7] etc. Another method uses *N*-*tert*-butyloxycarbonyl (*N*-Boc) derivatives. Using this method, the compounds **1a**–**4a** have been converted into 1,3-oxazolidin-2-ones with different stereochemical results depending on the reaction conditions.[8] It is possible to prepare the corresponding 1,3-oxazolidin-2-ones with retention of configuration at C5 on using a proper base, trough an intramolecular transesterification of the initially formed alkoxide (Scheme 1, Path 1).[9–11] On the other hand, the conversion of the hydroxy group into a suitable leaving group (LG) allows the intramolecular attack of the Boc group leading, through a $S_N2$ process, to an inversion of configuration at C5 (Scheme 1, Path 2).

However, using the last method, there are precedents in the literature describing examples of anomalous stereochemistry control, including examples with either total or partial retention of configuration at C5.[9,10,12] For example, sulfonation of the *N*-Boc derivatives **2a**,[8] **4a**,[8] and **15**[10] yields a mixture of the corresponding oxazolidinones with retention (**7**, **9**, and **16**) and inversion (**8**, **10**, and **17**) of configuration at C5 (Scheme 2). Despite the great importance of this type of compounds there is not reasonable explanation of the causes of this phenomenon, only a $S_N1$ mechanism has been suggested by some researchers.[8,10,12]

Another reaction that can be used to convert the hydroxy group into a good LG is the Mitsunobu reaction[13] ($Ph_3P$, dialkyl azodicarboxylate). Intramolecular attack of the carbonyl group of the carbamate to the phosphonium intermediate would lead to the oxazolidinone with a predictable inversion of configuration at C5 (Scheme 1, Path 2, $R^2$=$Ph_3P^+$). This type of strategy, to the best of our knowledge, it has not been used successfully with ephedrine systems and derivatives. A few examples of using the Mitsunobu reaction or the related $Ph_3P/CCl_4/Et_3N$ system with hydroxyamides for the preparation of oxazolines[14–16] and *N*-arylpiperazinones[17]

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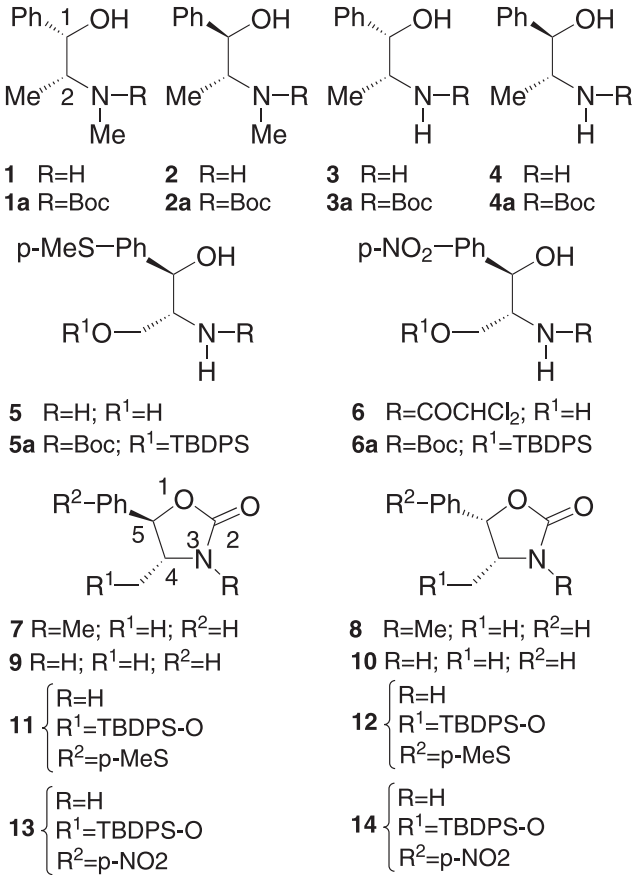
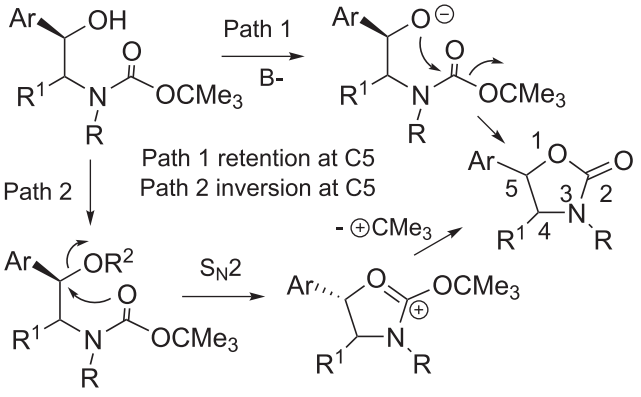
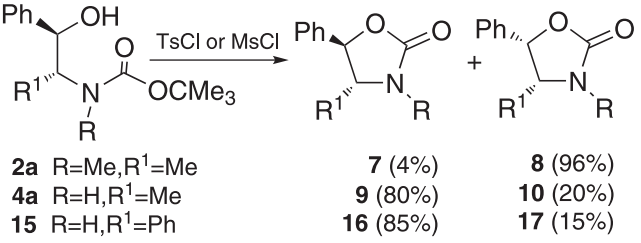



**Figure 1.** Aryl 1,2-Aminoalcohols (**1**–**6**), *N*-Boc derivatives (**1a**–**6a**) and 1,3-oxazolidin-2-ones (**7**–**14**).




**Scheme 1.** Synthesis of oxazolidinones from *N*-Boc derivatives of 1,2-aminoalcohols.




**Scheme 2.** Sulfonation of the *N*-Boc derivatives **2a**, **4a** and **15.**

have been reported. Recently, the $Ph_3P/CCl_4/Et_3N$ system has been used successfully for the conversion of *N*-Boc-β-aminoalcohols into 1,3-oxazolidin-2-ones.[18] One problem of this strategy is the formation of aziridines.[14]

Continuing our research[19] in the chemistry of aminoalcohols, we are interested in the conversion of the chiral *N*-Boc-2-amino-1-aryl-1-propanols (**1a**–**4a**) and *N*-Boc-2-amino-1-aryl-1,3-propanediols (**5a**, **6a**) into 1,3-oxazolidin-2-ones (**7**–**14**). The aim of this paper is the study of the potential influence of the stereochemistry and substituents of the aryl aminoalcohols, as well as the reaction conditions, on the conversion into 1,3-oxazolidin-2-ones. To this end, we have carried out a study of the sulfonation and Mitsunobu reactions of the *N*-Boc derivatives **1a**–**6a**. Moreover, a possible mechanism of reaction is suggested, which is based on DFT calculations and additional experimental evidences.

## 2. Results and discussion

Firstly, we describe the synthesis of starting compounds (**1a**–**6a**) and their transformation into 1,3-oxazolidin-2-ones (**7**–**14**). Secondly, we study the possible mechanisms of reaction and based on theoretical calculations suggest the most likely. Finally, we report additional experiments that support the proposed mechanism.

### 2.1. Experimental studies

The aminoalcohols **1**–**4** were subjected to reaction with di-*tert*-butyl dicarbonate and $Et_3N$ to afford the carbamate derivatives **1a**–**4a**.[20] Also, the amide group of chloramphenicol **6** was hydrolyzed with aqueous sodium hydroxide [21] to yield the corresponding derivative with the free amino group. This last compound and thiomicamine **5** reacted with di-*tert*-butyl dicarbonate/$Et_3N$ in a first stage and then with *tert*-butyldiphenylsilyl chloride/pyridine to afford the monosilylated *N*-Boc derivatives **6a** and **5a**, respectively.

With the *N*-Boc derivatives **1a**–**6a** in hand, we have carried out the sulfonation and Mitsunobu reactions. The results of these reactions can be seen in Table 1.

**Table 1**
Sulfonation and Mitsunobu reactions of *N*-Boc derivatives **1a**–**6a**

| Entry | Compound | Reaction products | |
|---|---|---|---|
| | | Sulfonation[a]/Method[b] | Mitsunobu[a] |
| **1** | **1a** | **7** (100)/A | **1a** (50):**7** (50) |
| **2** | **2a** | **2a** (5):**7** (15):**8** (80)[c]/A | **2a** (60):**7** (24):**8** (16) |
| **3** | **3a** | **9** (100)/A | **3a** (50):**9** (50) |
| **4** | **4a** | **9** (80):**10** (20)/A | **4a** (80):**9** (20) |
| **5** | **5a** | **11** (49%)/B | **11** (60%) |
| **6** | **6a** | **13** (40%)/B | **13** (35%) |

[a] Ratio of reaction products from $^1H$ NMR of the crude of reaction (entries 1–4). Yield (%) after column chromatography (entries 5–6).
[b] Method A (TsCl/pyridine). Method B (MsCl/DMAP/TEA/$CH_2Cl_2$).
[c] Literature ratio **7**/**8** (4:96).[8]

The carbamate derivatives **1a**–**4a** were subjected to the sulfonation conditions using *p*-toluenesulfonyl chloride (TsCl/pyridine; method A) affording directly the oxazolidinones **7**–**10**. The crude of reaction was analyzed by $^1H$ NMR spectroscopy. It is worth to note that during the tosylation reactions, we never detected the presence of the tosylate intermediates. This fact indicates that the rate-limiting step for the conversion of aminoalcohols into oxazolidinones is the sulfonation reaction. Once the benzylic alcohol is converted into the corresponding sulfonate, this reacts quickly to give the final products. Although the sulfonate intermediate has sometimes been isolated,[8,22,23] it has always been in cases where

the sulfonates were not benzylic, which are less reactive towards nucleophilic attack through $S_N1$ or $S_N2$ processes.

As can be seen in Table 1, the tosylation of the compounds **1a** and **3a** (entries 1 and 3) afforded the corresponding 1,3-oxazolidin-2-ones **7** and **9** with inversion of configuration at C5. The presence of the possible products of retention of configuration at C5 (**8** and **10**) were not detected in the $^1$H NMR of the crude of reaction. In the tosylation reaction of **2a** and **4a** (entries 2 and 4) mixtures of the oxazolidinones with inverted configuration (**8** and **10**) and retained configuration (**7** and **9**) at C5 were obtained. In the case of **2a**, small amounts of starting material were detected.

The alcohols **5a** and **6a** did not react under the tosylation conditions, probably due to the steric hindrance of the silyl group; therefore they were subjected to mesylation (entries 5 and 6) using methanesulfonyl chloride/DMAP/TEA/dichloromethane (method B). Due to the complexity of the signals in the $^1$H NMR spectra, the crude of reaction was purified by column chromatography and the only product identified was the 1,3-oxazolidin-2-one **11** or **13**, respectively, both with retention of configuration at C5.

Similar stereochemical control was observed in the reaction of **1a**–**6a** under the Mitsunobu conditions. For compounds **1a**–**4a**, important amounts of unreacted starting materials were isolated.[24] It is interesting to note that under the Mitsunobu conditions the amount of retention product is always the same or higher than the amount obtained by sulfonation.

The formation of the inverted 1,3-oxazolidin-2-ones can be easily explained through a $S_N2$ mechanism by intramolecular attack of the Boc group into the LG initially formed (Scheme 1, Path 2). However, the formation of products with retention of configuration at C5 is more difficult to explain. In this context, a $S_N1$ mechanism has been suggested.[8,10,12] The substitution at the N atom (*N*–H or *N*–Me), as reported by other researchers,[8,9] is not decisive for the retention or inversion of configuration at C5 (see entries 2 and 4). The alkyl substituent at the N atom (*N*–Me) only gives a lower proportion of retention product (entry 2). The presence of either electron-donating groups (MeS–, compound **5a**) or electron-withdrawing groups ($NO_2$–, compound **6a**) in the aromatic ring and/or additional substituents (TBDPS–O group) have not effect in the stereochemistry control. In both cases (entries 5 and 6) the retention of configuration at C5 takes place.

According to the obtained results, it can be deduced that the determining factor to produce the retention or inversion of configuration is the relative stereochemistry of the carbons C1 and C2 in the starting aminoalcohols. The *erythro* derivatives **1a** and **3a** (1*S*,2*R* or 1*R*,2*S*) give, under the sulfonation and Mitsunobu conditions, the corresponding 1,3-oxazolidin-2-ones **7** and **9**, with inversion of configuration at C5. However, the *threo* derivatives **2a**, **4a**, **5a**, and **6a** (1*R*,2*R* or 1*S*,2*S*) lead to the corresponding oxazolidinones with either partial or almost total retention of configuration at C5.

The spectroscopic data of the oxazolidinones **7**–**10** were in complete agreement with those reported in the literature.[25] The coupling constants of the oxazolidinones **11** and **13** ($J$=4.9 Hz and $J$=4.0 Hz, respectively) supported the assigned *threo* (trans) configuration.[26] In addition, both compounds **11** and **13** have been synthesized, in an unambiguous manner (Scheme 1, Path 1), by reaction of the *N*-Boc derivatives **5a** and **6a** using NaH in toluene (method D, see Experimental section).

### 2.2. Study of reaction mechanism

To study the reaction mechanism, we have selected the sulfonation of the *N*-Boc derivatives and its transformation into the oxazolidin-2-ones.

An initial mechanism considered to explain the formation of oxazolidinones, with retention of configuration at C5, is the acid–base reaction of the hydroxyl group at C1 in the starting aminoalcohol with the basic medium used in the sulfonation conditions, to afford the corresponding alkoxide. Intramolecular transesterification of this alkoxide with the carbamate group leads to the oxazolidinone with retention of configuration (Scheme 1, Path 1). This possibility was discarded because in the reaction of aminoalcohol **2a** with either pyridine or DMAP/TEA in dichloromethane at 25 °C/7 days (tosylation or mesylation conditions without the sulfonating reagent), we recovered the starting unreacted alcohol. Therefore, the presence of sulfonating reagent is necessary and we can assume that the sulfonate is formed in first place. Once the benzylic alcohol is converted into the corresponding sulfonate, this experiment the anomalous mechanism to give the final products.

In the Scheme 3, we can see the possible mechanistic pathways, which were starting from the *N*-Boc derivatives with the alcohol group converted in a good LG (mesylate or tosilate), can lead to the final 1,3-oxazolidin-2-ones **7**–**14**.

The Path 2 is the normal course, which would give the oxazolidinones with inversion of configuration in the benzylic position C5. It is initiated with a $S_N2$ attack of the carbonyl oxygen of the Boc group to the benzylic carbon, with extrusion of the LG $OR^2$, to give the cationic *O*-alkylated oxazolidin-2-one intermediate **IN1**. Final extrusion of $+CMe_3$ leads to the oxazolidinones **7**–**14**.

The Path 3 involves a mechanism of unimolecular nucleophilic substitution ($S_N1$). The initial extrusion of the $OR^2$ group gives the benzylic carbocation **IN2**, which by attack of the Boc group in both sides of the carbocation leads to a mixture of intermediates **IN1** with both inversion and retention of configuration at the benzylic carbon. This is the suggested mechanism by some researchers to explain the anomalous retention of configuration.[8,10,12]

The Path 4 involves the possibility of initial assistance of the amine group in the extrusion of the LG $OR^2$ to give an aziridinium cation intermediate **IN3**. The subsequent opening of the aziridinium cation by the carbonyl of the Boc group gives again the intermediate **IN1**, in this case, with retention of configuration in the benzylic position as a consequence of the double inversion occurred during the process. This option has been excluded since even with the formation of the possible aziridinium cation intermediate **IN3**,[14,23] the subsequent intramolecular attack of the Boc group to produce a $S_N2$ reaction is geometrically impossible.

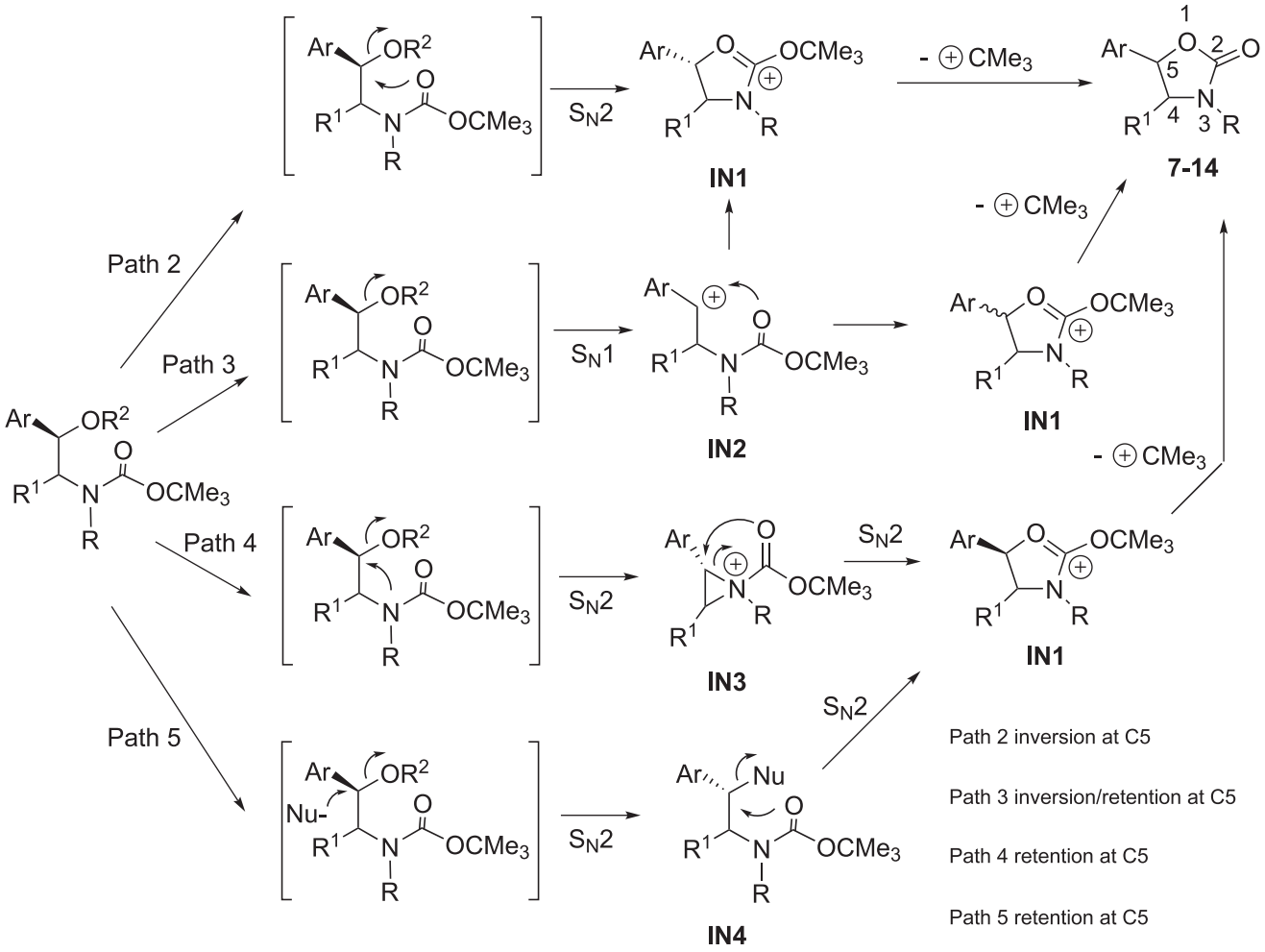
Finally, the Path 5 involves the retention of configuration at C5 through a double nucleophilic substitution. Firstly, an intermolecular $S_N2$ reaction occurs by a nucleophilic attack on the benzylic carbon by a nucleophile present in the reaction to give the intermediate **IN4**, and then an intramolecular $S_N2$ reaction similar to the one of Path 2 would give the intermediate **IN1** with retention of configuration.

Therefore, to explain the formation of mixtures of products with retention and inversion of configuration at C5, there are two possibilities.

(a) Mechanism of unimolecular nucleophilic substitution ($S_N1$, Path 3) competitive with or without simultaneous $S_N2$ (Path 2).
(b) Competition between $S_N2$ (Path 2) and double $S_N2$ (Path 5).

This is a dilemma that has dragged on for many years and always arises in nucleophilic substitution reactions (not only in ephedrine derivatives) with partial retention of configuration.[27] It is generally postulated 'pure' $S_N1$ mechanisms or 'borderline' mechanisms. Only a few cases of double $S_N2$ have been suggested.

To help distinguish between the two possibilities (a) the $S_N1$ mechanism (and its variants) competitive with or without simultaneous $S_N2$ and (b) competition between $S_N2$ and double $S_N2$ mechanism, we have carried out a series of theoretical calculations.




**Scheme 3.** Mechanistic pathways for the conversion of *N*-Boc derivatives, with the alcohol group converted in a good LG, into oxazolidinones **7**-**14.**

## 2.3. Theoretical studies

Firstly, we will discuss the $S_N1$ mechanism competing with $S_N2$ mechanism, and later we will study the second alternative, $S_N2$ competing with a double $S_N2$.

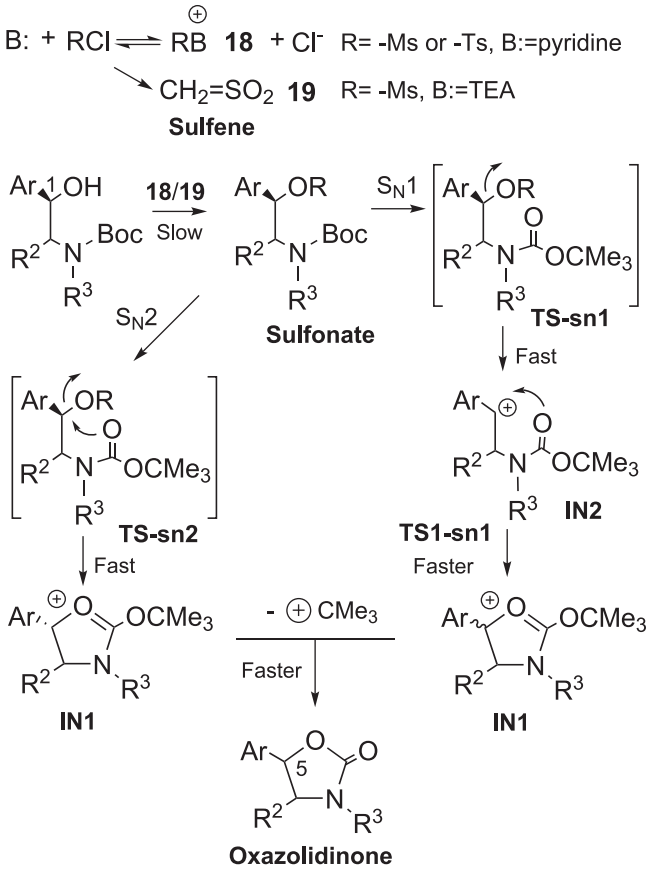
*2.3.1. Computational methods.* All calculations were carried out with the Gaussian 03 suite of programs.[28] Density functional theory[29] calculations (DFT) have carried out using the B3LYP[30] exchange-correlation functionals, together with the standard 6-31G** basis set.[31] Since the mechanism involves ionic species the inclusion of solvent effects have been considered by using a relatively simple self-consistent reaction field (SCRF) method[32] based on the polarizable continuum model (PCM) of Tomasi's group.[33] Geometries have been fully optimized with PCM. As solvent we have used $CH_2Cl_2$ (method B in experimental). Some experiments (method A) are using pyridine as solvent, but pyridine is not included in the Gaussian 03 program. However pyridine and $CH_2Cl_2$ have similar dielectric constants (12.97 and 8.93, respectively), so we would not expect major changes. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[34]

*2.3.2. $S_N1$ versus $S_N2$.* The complete mechanism for the conversion of *N*-Boc derivatives into oxazolidinones through sulfonation is presented in Scheme 4. There is a pre-equilibrium between the sulfonyl chloride and the unstable quaternary compound **18**, which is formed by attack of the corresponding base (pyridine) to the sulfonyl chloride, however with MsCl and TEA, the reaction might proceed via the sulfene **19**.[35] Compound **18** or **19** reacts later with the alcohol to give the corresponding sulfonate, with retention of configuration at C1. Once the benzylic alcohol is converted into the corresponding sulfonate, this reacts quickly trough a $S_N2$ or a $S_N1$ mechanism to give the final products.

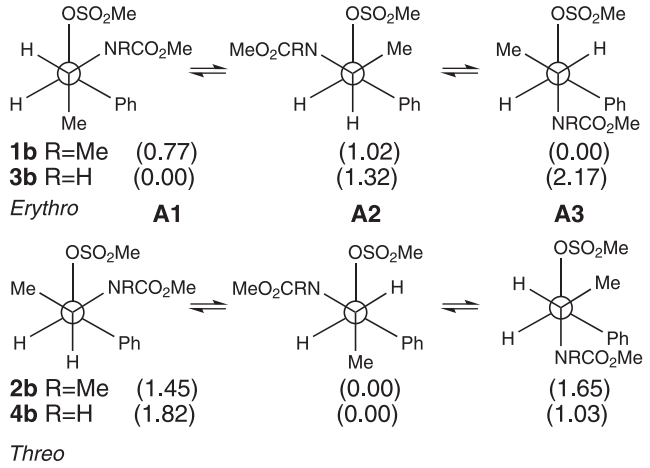
The two paths share a common intermediate **IN1**. The formation of this intermediate determines the stereochemistry of the final product, and the subsequent extrusion of $+CMe_3$ gives the final oxazolidinone. Previous calculations, with inclusion of the entropy to the free energies, indicate that the formation of the intermediate **IN1** is ca. 4 kcal/mol higher than the subsequent extrusion of the *tert*-butyl group.[19e] As usual in a $S_N1$ mechanism, we assume that the second step (**TS1**-**sn1**) is faster than the formation of the cationic intermediate **IN2** (**TS**-**sn1**). Therefore, the kinetics of the process, from sulfonate, through a $S_N2$ mechanism or a $S_N1$ mechanism is controlled by the **TS**-**sn2** or **TS**-**sn1**, respectively.

For the theoretical calculations, we have selected as LG the mesylate group, and the $CMe_3$ in the Boc group has been simplified as Me (compounds **1b**, **2b**, **3b**, and **4b** in Scheme 5). This simplification seems reasonable since the *tert*-butyl moiety is not involved in the **TS**-**sn2** or in the **TS**-**sn1**.

We have carried out, initially, a theoretical study of the thermodynamic stability of mesylates **1b**–**4b** (Scheme 5, Fig. S1, Table S1). The mesylates **1b**–**4b** can adopt three staggered conformations resulting from rotation of the C1–C2 bond. The conformation A1 displays the *N*–$CO_2$Me group *gauche* to the phenyl and mesylate




**Scheme 4.** Mechanistic pathways for the conversion of *N*-Boc derivatives into oxazolidinones trough a $S_N2$ or $S_N1$ process.




**Scheme 5.** Different conformations and relative energies, to the more stable conformer, ($\Delta E$, kcal/mol, in $Cl_2CH_2$) for compounds **1b**–**4b**.

groups. The conformation A2 displays the *N*–$CO_2$Me group *gauche* to the mesylate group while the conformation A3 displays the *N*–$CO_2$Me group *anti* to the mesylate group. It is worth noting that the carbonyl of the carbamate group and the C1–H adopt a preferential *syn-periplanar* arrangement (Fig. S1). The energetic results show that in the *threo* derivatives **2b** and **4b** the most stable conformation is the A2, while the *erythro* derivatives **1b** and **3b** prefer the conformation A3 and A1, respectively (Table S1).

For the kinetic study of the possible mechanisms of reaction, we started with the $S_N2$ mechanism. Figure 2 shows the geometries of transition states involved in the mechanism and the energies of the relevant species are in Table 2.

In all transition states (**TS-sn2**) the aromatic ring adopts a planar arrangement with respect to the benzyl carbon. This allows a greater delocalization of the negative charge that is being transferred from the carbonyl oxygen to the mesylate group. The lengths of the O–C forming bond are between 2.116 and 2.252 Å. The lengths of the C–O breaking bond are between 2.193 and 2.425 Å

The conversion of the mesylates **1b**, **2b**, **3b**, and **4b** into the corresponding intermediates **IN1** (Scheme 4) have an energy barrier of 20.2 kcal/mol (**TS-sn2-1b**), 25.4 kcal/mol (**TS-sn2-2b**), 24.7 kcal/mol (**TS-sn2-3b**), and 27.0 kcal/mol (**TS-sn2-4b**), respectively (Table 2). According to these results, the conversion of the *erythro* derivatives **1b** and **3b** into the **IN1** trough a $S_N2$ process

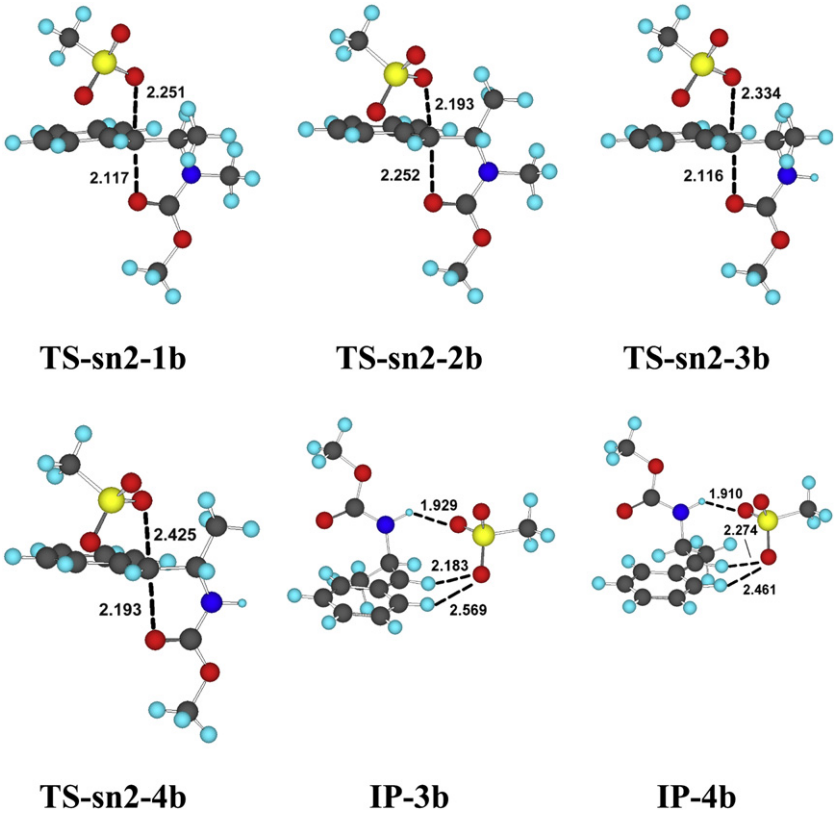



**Figure 2.** Transition structures corresponding to the conversion of the mesylates **1b**–**4b**, trough a $S_N2$ mechanism, into intermediates **IN1**. Ion-pairs corresponding to the reaction of the mesylates **3b** and **4b**, trough a $S_N1$ mechanism. The values of the lengths are given in angstroms.

**Table 2**
Relative energies to the more stable conformer ($\Delta E$, kcal/mol in $Cl_2CH_2$), of some species involved in the conversion of mesylates **1b**–**4b** into oxazolidinones trough a $S_N2$ or $S_N1$ process

| | $\Delta E$ | | $\Delta E$ |
|---|---|---|---|
| **1b-A3** | 0.00 | **TS-sn2-3b** | 24.7 |
| **TS-sn2-1b** | 20.2 | **IP-3b** | 31.8 |
| **2b-A2** | 0.00 | **4b-A2** | 0.00 |
| **TS-sn2-2b** | 25.4 | **TS-sn2-4b** | 27.0 |
| **3b-A1** | 0.00 | **IP-4b** | 23.8 |

are favored in 5.2 kcal/mol and 2.3 kcal/mol, with respect to the corresponding *threo* derivatives **2b** and **4b**. These different energy results can be explained if we look at the geometry of the transition states (Fig. 2). The transition states **TS-sn2-1b** and **TS-sn2-3b** have an *anti* disposition between the methyl and phenyl groups, which is more favorable, than a *gauche* disposition observed in the transition states **TS-sn2-2b** and **TS-sn2-4b**. In addition, the transition states **TS-sn2-2b** and **TS-sn2-4b** present an additional *gauche* interaction between the methyl group and the leaving mesylate group. It is interesting to note that the transition states **TS-sn2-1b** and **TS-sn2-2b** (with *N*-methyl) have a lower energy than transition states **TS-sn2-3b** and **TS-sn2-4b** (with *N*-H). This energy difference varies between 1.6 and 3.3 kcal/mol. The electron-releasing character of the methyl group present on the nitrogen atom causes a larger stabilization of the positive charge that is being formed in transition states **TS-sn2-1b** and **TS-sn2-2b**. In consequence, these transition states are being more stabilized than its nor-analogues. This fact has been observed experimentally[8,9] and previously calculated at theoretical level.[19e]

To study the $S_N1$ mechanism, we have chosen the *threo* mesylate **4b** initially, as it presents experimentally the highest percentage of retention of configuration at C5 in the final product.

Initial attempts to locate the transition state **TS-sn1** in a possible mechanism $S_N1$, all gave disappointing results. For example, when we have fixed the distance C1–OMs at 3.5 Å to trap the possible carbocation **IN2** (see Scheme 4); the final energy was approximately 30 kcal/mol higher than that of compound **4b**. When the bond C1–OMs was freed, the calculations converged to give the starting mesylate **4b** without passing through any transition state.

We performed a more careful study, based on the most stable conformation **4b-A2** of the mesylate **4b** (Scheme 5), setting the distance C1–OMs in steps of 0.1 Å. The results are shown in the Figure 3 (black dashed line). As can be seen in the energy profile, the energy increases overcoming the energy of **TS-sn2-4b** (27 kcal/mol) corresponding to a $S_N2$ mechanism.

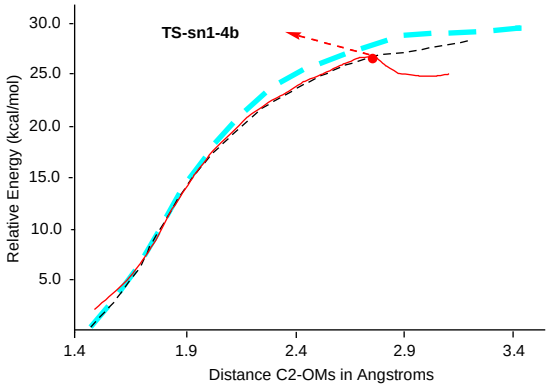



**Figure 3.** B3LYP/6-31G** Energy profiles, in $Cl_2CH_2$, for the transformation of **4b-A2** (black dashed line), **4b-A1** (red plain line) and **2b-A2** (blue bold dashed line) into the corresponding ion-pair trough a $S_N1$ mechanism. The energies are relative to the more stable conformer.

When we conducted a similar study based on the most unstable conformer **4b-A1**, we found a different energy result (red plain line in Fig. 3). The energy profile rises to a maximum (about a distance C1–OMs of 2.7 Å), and then descends gently. When the distance C1–OMs is left free to 2.9 Å, the energy decreases and stabilizes at 23.8 kcal/mol above the most stable conformer **4b-A2**, and corresponds to the ion-pair **IP-4b** (Fig. 2). In this ion-pair the negative charge on the mesylate group and the positive charge of the carbocation, is stabilized by a triple hydrogen bond between two of the oxygens of the mesylate and the proton of the N–H group, the benzylic hydrogen and the aromatic hydrogen. The formation of the ion-pair **IP-4b** from conformer **4b-A1**, is facilitated by the initial geometry of this conformer. As can be seen in Figure S1, in this conformer there is a hydrogen bond (length 2.576 Å) between the mesylate oxygen and the hydrogen of the *N*–H group. The maximum in the energy profile corresponds to the **TS-sn1-4b** (Fig. 3) and has an energy barrier of 26 kcal/mol, 1 kcal/mol more stable than **TS-sn2-4b**. This small energy difference between **TS-sn2-4b** and **TS-sn1-4b** would allow a competence between both mechanisms, $S_N2$ and $S_N1$.

For the *erythro* derivative **3b**, we have not made the complete energy profile. The corresponding ion-pair **IP-3b** (Fig. 2) has a similar geometry to that of the ion pair **IP-4b.** The ion pair **IP-3b** has an energy barrier of 31.8 kcal/mol (Table 2) respect to the most stable conformer **3b-A1.** This energy is 7.1 kcal/mol higher than the energy of the transition state **TS-sn2-3b** for the $S_N2$ mechanism. According to these results the *erythro* derivative **3b** prefers the $S_N2$ mechanism leading preferentially to the oxazolidinone **9** with inversion of configuration at C5.

Finally, we conducted a similar study with the compound **2b** since experimentally leads to a 15% of retention product at C5. All attempts to trap the corresponding ion-pair were unsuccessful. This is not surprising since, as we saw earlier, the ion-pair is stabilized by a hydrogen bond between one of the oxygens of the mesylate and the proton of the *N*–H group. Since in this case the presence of *N*–Me prevent this option, all attempts to trap the ion-pair gives back the initial product. Moreover, as can be seen in the energy profile (Fig. 3), the energy increases continuously overcoming the energy of **TS-sn2-2b** (25.4 kcal/mol) corresponding to a $S_N2$ mechanism. These results indicate that it is unlikely that the presence of retention product at C5 is due to action of a $S_N1$ mechanism.

In conclusion, we can explain the presence of the retention product **9** in the sulfonation of the *threo N*–H derivative **4a**, through a 'borderline' mechanism with simultaneous operation of both the $S_N1$ (ion-pair mechanism) and $S_N2$ mechanisms. But this possibility can hardly explain the presence of the retention product **7** in the sulfonation of the *threo N*–Me derivative **2a**.

*2.3.3. $S_N2$ versus double $S_N2$.* For the theoretical study we have selected the compounds **3b** and **4b**. The double $S_N2$ mechanism requires the presence of a nucleophile (Scheme 3, Path 5). The nucleophile used is the chloride ion ($Cl^-$) present in the medium of reaction, and it has been included in all calculations.

The suggested mechanism is presented in Scheme 6; the energies of the relevant species are in Table 3 and Figure 4. Finally, Figure 5 and Figure 6 show the geometries of transition states involved in the mechanism.

For the conversion of **3b** into **9** or **10** we have investigated two possible reactions pathways (Path 2-I and Path 5-I in Scheme 6). In the first pathway (Path 2-I), mesylate **3b** is converted into oxazolidin-2-one **9** through **TS1-I**. **TS1-I** arises from the intramolecular attack of the carbonyl group of the carbamate to the benzylic carbon with simultaneous extrusion of mesylate group. Final loss of +Me in the cationic *O*-alkylated oxazolidin-2-one intermediate **IN1-I** leads to the oxazolidinone **9** with inverted configuration at C5. It should be noted that the first stage is the formation of the five-membered intermediate **IN1-I**, which is the rate-limiting step of the process being more energetic than the posterior extrusion of the methyl framework.[19e] In the second reaction pathway (Path 5-I), **3b** is converted into oxazolidinone **10** through **TS2-I** and **TS3-I**. **TS2-I** corresponds to an intermolecular attack of the chloride to the benzylic carbon with extrusion of mesylate group. The chloride intermediate **IN4-I** trough **TS3-I** experiments an intramolecular attack similar to the **TS1-I** leading to intermediate **IN1-II**. Extrusion of +Me yields the oxazolidinone **10** with retention at C5.

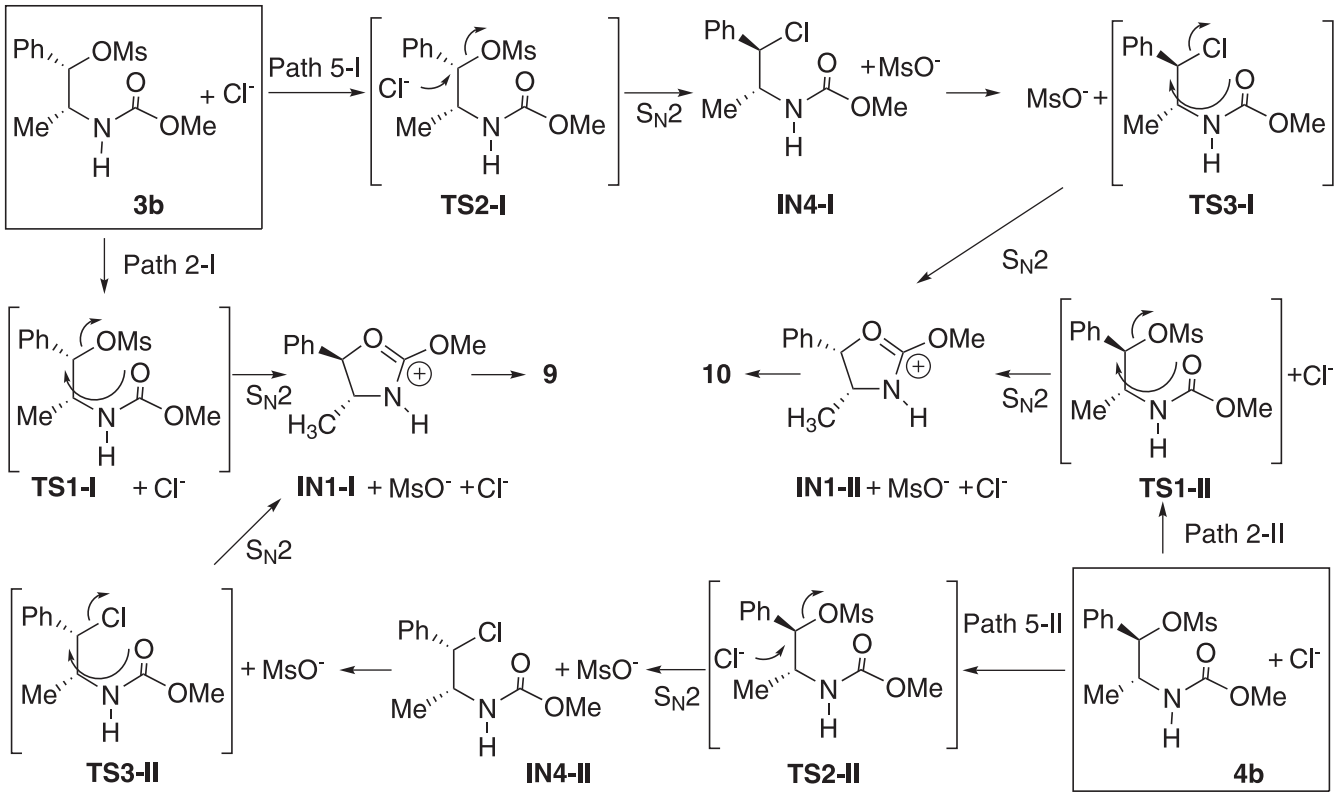
Conversion of mesylate **4b** into oxazolidinones **9** or **10** is similar to the conversion of **3b** into **10** or **9.** In this case **4b** is converted into **10** through **TS1-II** (Path 2-II) and into **9** through **TS2-II** and **TS3-II** (Path 5-II).

The conversion of the mesylate **3b** (actually, the molecular complex between **3b** and $Cl^-$) into the oxazolidinones **9** has an energy barrier of 14.76 kcal/mol (**TS1-I**), while the energy barrier to be transformed into oxazolidinone **10** is of 24.84 kcal/mol (**TS2-I**). In the latter case, the initial intermolecular attack of the chloride ion (**TS2-I**) is the rate determining step of the process, being more energetic than the posterior intramolecular attack of the carbamate (19.51 kcal/mol, **TS3-I**). The transition state **TS1-I** is 10.08 kcal/mol more stable than **TS2-I**. According to these results the *erythro* derivative **3b** prefers the pathway 2-I (through **TS1-I** and a $S_N2$ mechanism) leading preferentially to the oxazolidinone **9** with inversion of configuration at C5.

The conversion of the mesylate **4b** into the oxazolidinones **9** and **10** goes through the transition states **TS2-II** and **TS3-II** or **TS1-II**, respectively. The energy barriers with reference to the molecular complex of **4b** with $Cl^-$ are 20.43 kcal/mol (**TS2-II**), 19.15 kcal/mol (**TS3-II**) and, 22.37 kcal/mol (**TS1-II**) (It should be noted that in Table 3, the relative energies are with reference to the molecular complex of **3b** with $Cl^-$). In this case, the pathway 5-II is favored from the kinetic point of view, being the transition state **TS2-II** 1.94 kcal/mol more stable than **TS1-II**. This fact indicates that the *threo* derivative **4a**, through the pathway 5-II (double $S_N2$ mechanism), will give preferentially the oxazolidinone **9** with retention of configuration at C5 together with the oxazolidinone **10** with inversion of configuration at C5 (Path 2-II, single $S_N2$ mechanism) as minor compound. This small energy difference between both pathways (Path 5-II and Path 2-II) allows a competence between both mechanisms, and small changes in the substituents of the aryl aminoalcohols, as well as the reaction conditions, can lead to different results depending on the followed pathway.

For example, the *N*-methyl derivative **2a** (see Table 1, entry 2) gives only 15% of the oxazolidinone **7** with retention at C5 together with a 80% of the oxazolidinone **8** with inversion at C5. This fact indicates a small preference of the Path 2-II versus Path 5-II, that is to say, a higher stability of the transition state **TS1-II** than **TS2-II**. If we see the transition state **TS2-II** (Fig. 6), the presence of the *N*-methyl group almost does not affect such transition state neither by steric interaction nor electronic factors, since the carbamate group is not involved directly in the process. However, as mentioned above, the electron-releasing character of the methyl group present on the nitrogen atom causes a larger stabilization of the positive charge that is being formed in transition state **TS1-II**. In consequence, this **TS1-II** is being more stabilized than its nor-analogue without the *N*-methyl substituent. This *N*-methyl effect, as previously calculated, is between 1.6 and 3.3 kcal/mol. With this effect, the transition state **TS1-II** would be similar or even more stable than **TS2-II**, being favored the formation of the oxazolidinone **8** with inversion of configuration at C5.

Because we are comparing intermolecular reactions (**TS2-II**) with intramolecular reactions (**TS1-II**), entropic effects may be important. As shown in Table 3, the inclusion of these effects (see $\Delta G$) increases the free activation energy by about 1 kcal/mol, but




**Scheme 6.** Mechanism of the mesylation reaction of the *N*-$CO_2$Me derivatives **3b** and **4b**.

**Table 3**
Relative energies ($\Delta E$, kcal/mol in $Cl_2CH_2$) and relative free energies ($\Delta G$, kcal/mol, 25 °C, 1 atm) of the stationary points for the transformation of **3b** and **4b** into **9** and **10**

| | $\Delta E$ ($\Delta G$) | | $\Delta E$ ($\Delta G$) |
|---|---|---|---|
| **3b** | 0.00 (0.00) | **4b** | −3.61 |
| **TS1-I** | 14.76 | **TS1-II** | 18.76 (19.90) |
| **IN1-I** | 1.29 | **TS2-II** | 16.82 (18.48) |
| **TS2-I** | 24.84 | **IN4-II** | −3.66 |
| **IN4-I** | 0.10 | **TS3-II** | 15.54 (16.67) |
| **TS3-I** | 19.51 | | |
| **IN1-II** | 2.45 | | |

[a]Energies of **3b**, **4b**, **TS1-I**, and **TS1-II** correspond to the energies of the molecular complex between these species with $Cl^-$. Energies of **IN4-I**, **IN4-II**, **TS3-I**, and **TS3-II** correspond to the energies of the molecular complex between these species with $MsO^-$. Energies of **IN1-I** and **IN1-II** correspond to the energies of the molecular complex between these species with $Cl^-$ and $MsO^-$.

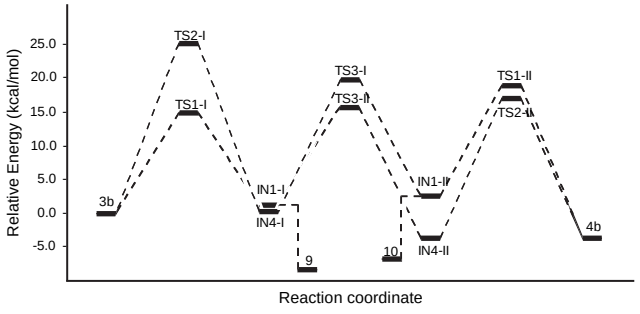



**Figure 4.** B3LYP/6-31G** Energy profiles for the transformation of **3b** and **4b** into **9** and **10** in $Cl_2CH_2$. **9** and **10** are off the scale.

does not substantially change the energy difference between **TS2-II** and **TS1-II**.

These theoretical results are in agreement with the experimental results explaining the anomalous results observed in the

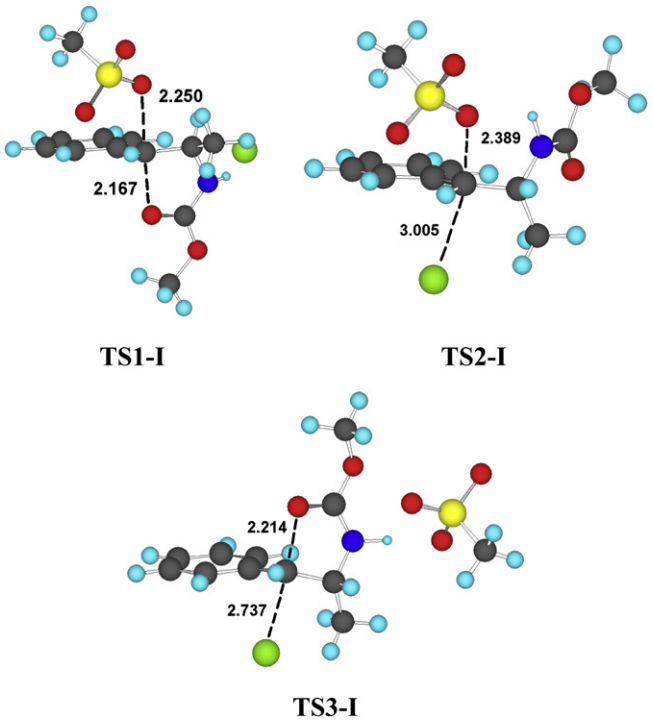



**Figure 5.** Transition structures corresponding to the conversion of **3b** into **9** (**TS1-I**) and **10** (**TS2-I**, **TS3-I**). The values of the lengths of the bonds involved obtained in $Cl_2CH_2$ are given in angstroms.

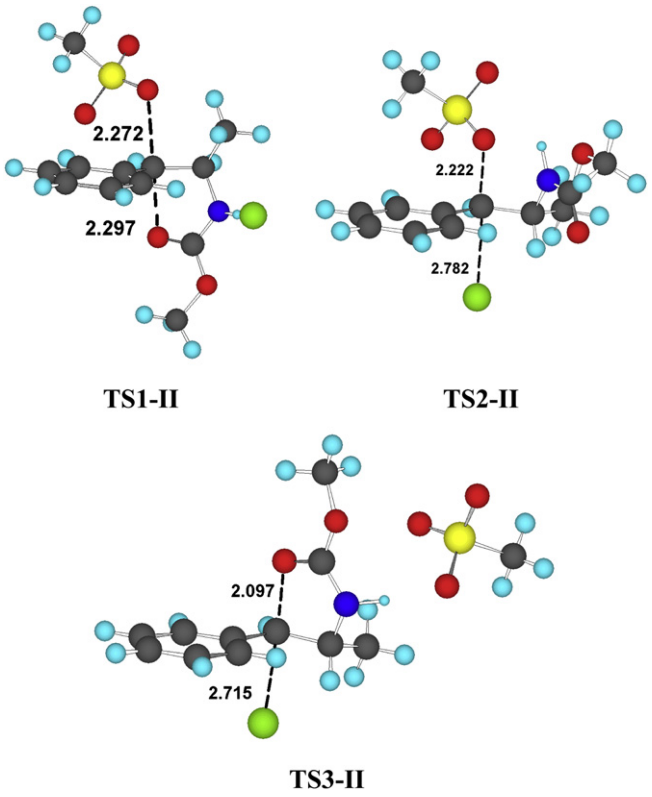



**Figure 6.** Transition structures corresponding to the conversion of **4b** into **10** (**TS1-II**) and **9** (**TS2-II**, **TS3-II**). The values of the lengths of the bonds involved obtained in $Cl_2CH_2$ are given in angstroms.

reactions of sulfonation of the *N*-Boc derivatives of the benzylic aminoalcohols. Without dismissing the possibility of a $S_N1$ mechanism, we suggested the double $S_N2$ mechanism to explain the appearance of oxazolidinones with retention of configuration at C5.

The Mitsunobu reaction between optically active alcohols and carboxylic acids has been studied theoretically at DFT level.[36] It has been postulated the presence of pentavalent phosphorus intermediate to explain the emergence of products with inversion or retention of configuration at the carbon bearing the alcohol functionality. Without discarding the possibility that such mechanism could be adapted to the conversion of *N*-Boc derivatives of 1-aryl-2-amino-1-ols into oxazolidinones, and in view of the similar stereochemical results obtained with the Mitsunobu and sulfonation reactions, we suggested the possibility of a similar mechanism in both cases. In the Mitsunobu reaction, the LG would be the phosphine oxide and the nucleophile could be one of the nucleophiles present in the complex medium of reaction that could act in the second phase as a LG.[13,36,37]

The Figures 5 and 6 show the geometries and the values of the lengths of the bonds of transition states involved in the mechanism. A balanced measure of the extent of bond formation or bond breaking along a reaction pathway is provided by the concept of bond order (BO). This theoretical tool has been used to study the molecular mechanism of chemical reactions. To follow the nature of this process, the Wiberg Bond indices[38] have been computed using the natural bond orbital analysis (Table S4).

The transition structures **TS1-I** and **TS1-II** correspond to an intramolecular nucleophilic attack of the oxygen atom of the carbonyl group of carbamate to the benzylic carbon with simultaneous extrusion of mesylate group. The lengths of the C5—O1 bond being formed are 2.167 and 2.297 Å, whereas the distance between C5 and OMs are 2.250 and 2.272 Å, respectively. Both the shorter C5—O1 bond length and the higher BO value (0.33) in **TS1-I** indicate that the bond formation is more advanced in **TS1-I** than **TS1-II**. The $CH_3$—C4—C5—Ph dihedral angles are 171° and −61°, respectively. This indicates for the transition state **TS1-I** an *anti* disposition between the methyl and phenyl groups, which is more favorable, from the energetic point of view, than a *gauche* disposition observed in the transition state **TS1-II**. In addition, the transition state **TS1-II** presents an additional *gauche* interaction between the methyl group and the leaving mesylate group. This implies that the transition state **TS1-I** is 4 kcal/mol more stable than the transition state **TS1-II** (see Table 3).

The transition structures **TS2-I** and **TS2-II** correspond to an intermolecular nucleophilic attack of the chloride to the benzylic carbon with simultaneous extrusion of mesylate group. The lengths of the C5—Cl bond being formed are 3.005 and 2.782 Å, whereas the distance between C5 and OMs are 2.389 and 2.222 Å, respectively. Both the shorter C5—Cl bond length and the higher BO value (0.40) in **TS2-II** indicated that the bond formation is more advanced in **TS2-II** than **TS2-I**. The $CH_3$—C4—C5—Ph dihedral angles in **TS2-I** and **TS2-II** are −76° and 178°, respectively. In this case, the transition state **TS2-II** presents an *anti* disposition between the methyl and phenyl groups, while in the transition state **TS2-I** such disposition is *gauche*. These facts, together with the additional *gauche* interaction between the methyl group and the leaving mesylate group in the transition state **TS2-I**, implies that the transition state **TS2-II** is 8 kcal/mol more stable than the transition state **TS2-I** (see Table 3).

Geometries of **TS3-I** and **TS3-II**, which correspond to the intramolecular attack of carbamate group to the benzylic carbon with extrusion of chloride, are similar to the geometries of **TS1-II** and **TS1-I**, respectively (chloride instead of mesylate). The shorter C5—O1 bond length (2.097 Å) and the higher BO value (0.42) in the transition state **TS3-II** with respect to the corresponding values in the transition state **TS3-I** (2.214 Å and 0.36) indicate a more advanced process in the former. The $CH_3$—C4—C5—Ph dihedral angles in **TS3-I** and **TS3-II** are −56° and 171°, respectively. The transition state **TS3-I** presents a *gauche* interaction between the methyl and the phenyl and chloride groups, moreover the transition state **TS3-II** presents only a more favorable *anti* disposition between the methyl and the phenyl groups. Therefore, the transition state **TS3-II** is 4 kcal/mol more stable than the transition state **TS3-I**.

It can be observed than the transition states **TS1-I** and **TS1-II** are approximately 0.8 kcal/mol more stable than the analogous transition states **TS3-II** and **TS3-I**, respectively, which indicates that the substitution of the mesylate group is more favorable than the substitution of the chloride.

### 2.4. Additional experimental

With the aim of supporting the suggested double $S_N2$ mechanism, we have carried out additional experimental assays. We have chosen compound **2a**, which presents both processes, inversion and retention, in order to observe the changes in the amount of products. To this end, we have changed the conditions in the sulfonation reaction including the addition of an excess of additional nucleophile (chloride and iodide). The results are shown in Table 4.

As we can see in Table 4, the tosylation reaction of **2a** (method A), without the additional nucleophile (entry 1), leads mostly to the oxazolidinone **8** with inversion of configuration at C5. The ratio between the oxazolidinone **7**, with retention of configuration at C5, and the oxazolidinone **8** is 0.19:1. When we added 3 equiv of NaCl, such ratio increases to 0.54:1 (entry 2). The replacement of chloride by a more powerful nucleophile as iodide (entry 3) leads preferentially to the oxazolidinone **7**, with the ratio between **7** and **8** of 8.25:1. These experimental data support the suggested double $S_N2$ mechanism, since the addition of a nucleophile to the reaction

**Table 4**
Sulfonation of the *N*-Boc pseudoephedrine **2a** with and without an additional nucleophile

| Entry | Method[a] | $Nu^-$ | Products[b] | **7**/**8** ratio |
|---|---|---|---|---|
| **1** | A | | **2a** (5):**7** (15):**8** (80) | 0.19:1 |
| **2** | A | 3 equiv NaCl | **2a** (80):**7** (7): **8** (13) | 0.54:1 |
| **3** | A | 3 equiv NaI | **2a** (63):**7** (33):**8** (4) | 8.25:1 |
| **4** | B | | **2a** (0):**7** (<1):**8** (99) | < 0.01:1 |
| **5** | B | 3 equiv NaI | **2a** (5):**7** (5):**8** (90) | 0.06:1 |
| **6** | C | 3 equiv NaI | **2a** (57):**7** (11):**8** (32) | 0.34:1 |

[a] A: 3 equiv tosyl chloride/pyridine. B: 3 equiv mesyl chloride/DMAP/TEA/dichloromethane. C: 3 equiv mesyl chloride/pyridine.
[b] Ratio from $^1$H NMR of the crude of reaction.

medium favors the transition state **TS2-II** of the Path 5-II versus the transition state **TS1-II** of the Path 2-II (Scheme 6).

It is interesting to note that the inclusion of an additional nucleophile slows the overall rate of reaction and even with increased reaction times it was recovered between 63% and 80% of unreacted starting material (entries 2 and 3). As we have already mentioned, the rate-limiting step is the formation of the tosylate, being the last steps faster. Consequently, the presence of an excess of additional nucleophile slows the formation of tosylate. This fact can be explained bearing in mind that during the sulfonation reaction of the alcohol, there is a pre-equilibrium between the tosyl chloride and the unstable quaternary compound **18**, which is formed by attack of the corresponding base (pyridine) to the tosyl chloride[35] (see Scheme 4). Compound **18** reacts later with the alcohol to give the corresponding sulfonate. During the initial pre-equilibrium the ion chloride is liberated. The presence of an additional chloride (or iodide) displaces the equilibrium to the left decreasing the amount of **18** and therefore the tosylation rate.

When we used methanesulfonyl chloride with DMAP/TEA/dichloromethane (method B) the reaction rate is increased and we observed only a 5% of unreacted starting material on using 3 equiv of NaI (entry 5).This indicates that sulfene formation (see Scheme 4) is little affected by the presence of additional nucleophile. However, the amount of oxazolidinone **7** decreases and only a 5% was obtained. In the absence of additional nucleophile (entry 4) almost there is not product of retention of configuration at C5. The use of these reaction conditions favors the mechanism of reaction through an intramolecular $S_N2$ reaction versus the intermolecular attack of the nucleophile.

If we use the methanesulfonyl chloride in pyridine (method C), we can observe again the slowness of the reaction rate (entry 6), recovering 57% of unreacted starting material. This indicates that in the control of the reaction rate is more important the base/solvent used than the sulfonating agent (entries 3, 5, and 6). The proportion between the oxazolidinones **7** and **8** is of 0.34:1 (entry 6) in comparison with the ratio 8.24:1 observed with the method A (entry 3). Thus, the tosylation reaction favors the retention product at C5 more than the corresponding mesylate.

## 3. Conclusion

The conversion of *N*-Boc derivatives of 1-aryl-2-amino-1-ols in the corresponding 1,3-oxazolidine-2-ones, can be done under sulfonation or Mitsunobu reaction of the hydroxyl group. The determining factor to produce the retention or inversion of configuration at C5 in the oxazolidinones, is the relative stereochemistry of the carbons C1 and C2 in the starting aminoalcohols. The *erythro* derivatives (1*S*,2*R* or 1*R*,2*S*) give the corresponding 1,3-oxazolidin-2-ones, with inversion of configuration at C5. However, the *threo* derivatives (1*R*,2*R* or 1*S*,2*S*) lead to the corresponding oxazolidinones with either partial or almost total retention of configuration at C5.

In the *erythro* derivatives an intramolecular nucleophilic substitution ($S_N2$) initiated by attack of the carbonyl oxygen of the Boc group to the benzylic carbon, with extrusion of the LG, is proposed. For the *threo* derivatives, we suggested a competition between the previous mechanism and other through a double nucleophilic substitution. For the latter, firstly an intermolecular $S_N2$ reaction occurs by attack to the benzylic carbon by a nucleophile present in the reaction to give an intermediate, which undergoes an intramolecular $S_N2$ reaction similar to the one proposed in the mechanism for *erythro* derivatives. The result of this last mechanism is the retention of configuration at C5. This hypothesis is supported by theoretical calculations and additional experimental assays.

These results can be adapted to other reactions associated with ephedrine derivatives or in general to analog benzylic alcohols where, depending on the stereoisomer used, different results are observed. In the *erythro* derivatives, attack by external nucleophiles at the benzylic position is difficult and prefer other processes, such as intramolecular attack. With the *threo* derivatives, the nucleophilic intermolecular reaction is favored and competes with or surpasses other processes.

This work also adds new data to the eternal debate between $S_N1$ or $S_N2$ mechanisms, mixed $S_N1$ and $S_N2$ (or 'borderline' mechanism) and ion-pair mechanism to explain the presence of products with, retention, inversion or both in some nucleophilic substitution reactions.[27]

## 4. Experimental section

### 4.1. General

*N*-Boc derivatives **1a** (98%),[20a] **2a** (97%),[20a] **3a** (95%),[20b] and **4a** (95%)[20c] have been prepared as reported in the literature.

### 4.2. Synthesis of *N*-Boc derivatives of 5 and 6

*4.2.1. Synthesis of (1S,2S)-2-[N-(tert-butoxycarbonyl)amino]-1-(4-methyltiophenyl)-1,3-propanodiol.* To a solution of (1*S*, 2*S*)-(+)-thiomicamine (**5**) (2.34 mmol) in $CH_2Cl_2$: $NEt_3$ (1:1) (8 mL) was added di-*tert*-butyl dicarbonate 0.51 g (2.34 mmol). After 24 h of stirring at room temperature the solvent was concentrated to dryness and purified by silica gel column chromatography afforded the *N*-Boc derivative of **5**. Eluent hexane/ethyl acetate 1:4. Yield 80%.

### 4.3. Synthesis of ((1*R*, 2*R*)-2-[*N*-(*tert*-butoxycarbonyl)amino]-1-(4-nitrophenyl)-1,3-propanodiol)

By the same procedure the (1*R*, 2*R*)-(−)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (obtained by alkaline hydrolysis of (+)-chloramphenicol [21]) afforded the corresponding *N*-Boc derivative of **6**.

### 4.4. Synthesis of silyl derivatives 5a and 6a

To a solution of the *N*-Boc derivatives of the aminodiols **5** and **6** (2.3 mmol), was added a solution of *tert*-butyldiphenylsilyl chloride (2.6 mmol) in dichloromethane:pyridine 3:1 (9 ml) and stirred at room temperature for 48 h. The reaction mixture was washed with water, dried ($Na_2SO_4$), and evaporated. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate mixtures to afford titled compounds **5a** (70%) and **6a** (80%), respectively.

### 4.5. General method A and method C for the synthesis of oxazolidinones

To a solution of the appropriate *N*-Boc derivative aminodiol **1a**–**6a** (1.6 mmol) in pyridine (10 ml) cooled at 0 °C, was added the *p*-toluensulfonyl chloride (method A, 4.8 mmol) or methanesulfonyl

chloride (method C, 4.8 mmol). The mixture was stirred to room temperature for 3 days (method A) or 6 days (method C), water (10 ml) was added and extracted with diethyl ether. The organic extracts were washed with a saturated aqueous solution of NaCl, dried over $Na_2SO_4$, concentrated under reduced pressure and then analyzed by $^1H$ NMR spectroscopy and/or purified by silica gel column chromatography eluting with hexane/ethyl acetate mixtures.

### 4.6. General method B for the synthesis of oxazolidinones

To a solution of the appropriate *N*-Boc derivative aminodiol **1a**–**6a** (1.2 mmol) in dichloromethane (8 mL) were added $Et_3N$ (0.08 ml, 0.57 mmol) and 4-DMPA (4 mg). The mixture was cooled at 0 °C and then methanesulfonyl chloride (3.6 mmol) in diclorometane (8 ml) was added. The ice was removed after 5 min and the solution was heated at room temperature and stirred for 3 days. After this time, the mixture of reaction was processed as before.

### 4.7. General method D for the synthesis of oxazolidinones

The Boc-protected aminoalcohol **2a**, **3a**, **5a** or **6a** (1.6 mmol) in toluene (6 mL) was added at room temperature to a stirred suspension of NaH (5 equiv) in toluene (2 mL). After 72 h, the solvent was removed under reduced pressure and the obtained residue was purified by silica gel column chromatography affording cyclic compounds **7**, **10**, **11** or **13**, respectively.

### 4.8. Mitsunobu reaction[25]

A stirred mixture of the appropriate *N*-Boc-protected aminodiol **1a**–**6a** (0.8 mmol), triphenylphosphine (0.8 mmol) and diethyl azodicarboxylate (0.8 mmol) in dichlorometane (10 mL) was stirred at room temperature for 72 h. After elimination of the solvent under reduced pressure, the crude was analyzed by $^1H$ NMR spectroscopy and/or purified by silica gel column chromatography eluting with hexane/ethyl acetate mixtures.

## Acknowledgements

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## Supplementary data

General Experimental. Analytical and spectroscopic data. $^1H$ NMR and $^{13}C$ NMR spectra of *N*-Boc thiomicamine, **5a**, **6a**, **11**, and **13**. Figure S1. Tables S1–S4. Cartesian coordinates for transition states: **TS-sn2-1b**, **TS-sn2-2b**, **TS-sn2-3b**, **TS-sn2-4b**, **TS1-I**, **TS2-I**, **TS3-I**, **TS1-II**, **TS2-II**, and **TS3-II**.. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.097. These data include MOL files and InChiKeys of the most important compounds described in this article.

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