Ring cleavage of 1-alkyl-2-aryl-3-(hydroxymethyl)pyrrolidines. A PM3 semiempirical study of molecular mechanism

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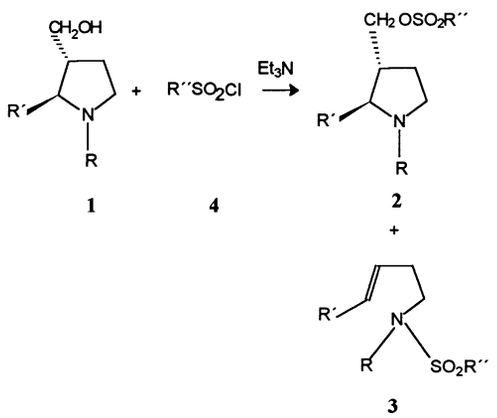
A fragmentation reaction at room temperature takes place when 2-aryl-3-(hydroxymethyl)-1-methylpyrrolidines react with different arenesulfonyl chlorides and triethylamine. A PM3 semiempirical study of the fragmentation reaction of the quaternary benzenesulfonamide salt of 1-methyl-2-phenyl-3-(hydroxymethyl)pyrrolidine shows that the reaction proceeds by a stepwise mechanism through the formation of a benzylic cation.

Introduction

In the course of a synthetic project on 2-aryl-3-pyrrolidine acetic acid derivatives as potential therapeutic agents in neurodegenerative disorders we found[1] that in the reaction of *trans*-3-(hydroxymethyl)-2-(*p*-methoxyphenyl)-1-methylpyrrolidine **1c** (R′ = *p*-CH_3O–C_6H_4) with *p*-toluenesulfonyl chloride and sodium hydroxide in dichloromethane at room temperature, instead of the expected tosylated alcohol **2c**, the sulfonamide **3c** (R′ = *p*-CH_3O–C_6H_4, R″ = *p*-CH_3–C_6H_4) was isolated (Scheme 1). Other pyrrolidine alcohols such as **1a** and **1b** (R′ = C_6H_5 and



Scheme 1

R′ = *p*-CH_3–C_6H_4) afforded mixtures of the tosylated derivatives, along with the elimination products (Table 1).

The formation of the sulfonamides **3** was reported as an unusual Hofmann elimination reaction,[1] however it could be better described as a fragmentation reaction[2] with a sulfonamide as the leaving group and formaldehyde as 'electrofuge'.

In this work we report the scope of this reaction with changes of the substituents in the substrate and reagents. A PM3 semiempirical study supports the mechanism proposed for this fragmentation reaction.

Computing methods and models

The computational study has been carried out using the PM3 semiempirical method[3] implemented in the MOPAC93 program.[4] The molecular geometries of the transition structures (TS) were optimized using optimization routine TS.[5] Stationary points on the potential energy surface (PES) were located by minimizing the gradients of energy to 0.5 kcal mol^{-1} $Å^{-1}$ rad^{-1}.† Examination of the TSs has been achieved by the evaluation of Hessian matrix; the nature of these stationary points was established by analytical calculations and diagonalization of the matrix of energy second derivatives, in order to determine the unique imaginary frequency. Once the stationary points were obtained, the Hessian was recalculated and the zero-order atom dynamics were obtained by calculation of normal modes, obtaining the transition vector (TV) that yields very concisely the essentials of the chemical process under study.[6] These calculations have been carried out using the GAUSSIAN92 program.[7]

The geometry optimization for the stationary structures on PES including solvent effects has been carried out at PM3 semiempirical level using the Conductor-like Screening Model (COSMO) option[8] included in MOPAC93. This COSMO model, proposed by Klamt and Schüürmann,[8] calculates the electrostatic solvation energy by representing the solute charge distribution as a set of point charges and dipoles in the neglect differential diatomic overlap formalism. In this procedure the solvent is assimilated to a continuous medium characterized by the relative permittivity (ε) which surrounds a molecular-shaped cavity in which the solute is placed. We have used the relative permittivity at 298 K, $\varepsilon = 9.08$, for the dichloromethane.

The benzenesulfonamide salt of *trans*-3-(hydroxymethyl)-2-phenyl-1-methylpyrrolidine **Int1** has been taken as a model for the computational study of ring cleavage of 1-alkyl-2-aryl-3-(hydroxymethyl)pyrrolidines and the trimethylamine as a base.

Results and discussion

Experimental results

Different (R,R′) substituted pyrrolidines (Table 1, entries **a**–**c**, **j**, **k**) have been prepared and their reactivity towards *p*-toluenesulfonyl chloride using triethylamine as a base has been studied. The results show the effect of these substituents on the course of the reaction. When the 1-benzyl-substituted pyrrolidines (entries **j**, **k**) reacted with *p*-toluenesulfonyl chloride, the tosylated alcohols **2** were obtained with no traces of the sulfonamides **3**. Steric factors appear to inhibit the attack of the sulfonyl chloride at the pyrrolidine nitrogen atom.

The reaction of *trans*-3-(hydroxymethyl)-2-(*p*-methoxy-

† 1 cal = 4.184 J.

Table 1 Yield of sulfonated alcohols **2** and sulfonamides **3** obtained by reaction of *trans* 2-aryl-3-(hydroxymethyl)-1-alkylpyrrolidines **1**, with arene or methanesulfonyl chlorides

				Yield (%)	
Entry	R	R′	R″	**2**	**3**
a	CH_3	C_6H_5	*p*-CH_3–C_6H_4	48	3
b	CH_3	*p*-CH_3–C_6H_4	*p*-CH_3–C_6H_4	26	19
c	CH_3	*p*-CH_3O–C_6H_4	*p*-CH_3–C_6H_4	—	32
d	CH_3	*p*-CH_3O–C_6H_4	*p*-CH_3O–C_6H_4	—	26
e	CH_3	*p*-CH_3O–C_6H_4	C_6H_5	48	19
f	CH_3	*p*-CH_3O–C_6H_4	*p*-Br–C_6H_4	32	21
g	CH_3	*p*-CH_3O–C_6H_4	*p*-O_2N–C_6H_4	36	9
h	CH_3	*p*-CH_3O–C_6H_4	CH_3	70	—
i	CH_3	*p*-CH_3–C_6H_4	CH_3	83	—
j	Ph–CH_2	*p*-CH_3O–C_6H_4	*p*-CH_3–C_6H_4	85	—
k	Ph–CH_2	C_6H_5	*p*-CH_3–C_6H_4	92	—

Table 2 Imaginary frequency (cm^{-1}), eigenvalue, selected geometric parameters (*G*), the corresponding eigenvector (*C*) and force constants *F* (au) associated with the unique negative eigenvalue for **TS1** and **TS2**

TS1				**TS2**			
Imaginary frequency: 230.71*i* Eigenvalue: −0.025 52				Imaginary frequency: 234.82*i* Eigenvalue: −0.019 67			
	G	*C*	*F*		*G*	*C*	*F*
N1–C2	2.326	−0.889	0.042	C2–C3	1.379	−0.115	0.971
C2–N1–C5	92.2	0.116	4.800	C3–C9	2.047	0.818	0.102
C3–C2–C6–C7	166.9	−0.155	0.259	C9–O10	1.291	−0.138	0.751
C3–C2–C6–C8	−11.1	−0.144	0.219	H11–N12	1.700	−0.170	0.101
N1–C3–C2–H13	−87.1	−0.248	0.113	C3–C9–H17	98.9	−0.219	0.150
C3–C4–C5–H15	−154.1	0.128	0.171	C3–C9–H18	90.4	−0.280	0.153
C3–C4–C5–H16	88.8	0.104	0.163	N1–C2–C3–H14	−93.7	−0.208	0.163

phenyl)-1-methylpyrrolidine **1** was also studied with different sulfonyl chlorides (entries **d**–**h**). The yields of the sulfonated alcohols **2**, sulfonamides **3** or mixtures of the two compounds obtained in these reactions are shown in Table 1. The reaction of pyrrolidines **1** with methanesulfonyl chloride afforded exclusively the sulfonated alcohols **2** (entries **h**–**i**).

In order to determine whether with other leaving groups than the sulfonamide, it was possible to get better results, a similar elimination reaction was attempted with the *trans*-*N*,*N*-dimethyl-2-(*p*-methoxyphenyl)-3-(hydroxymethyl)pyrrolidinium salt **5**. This salt was prepared by alkylation of the 3-(hydroxymethyl)-2-(*p*-methoxyphenyl)-1-methylpyrrolidine with iodomethane.[9] When the salt **5** was heated at 150 °C for 6 h, just 10% of the salt reacted and although the ^{1}H NMR spectrum of the crude product showed signals in the olefinic region that could be assigned to the corresponding elimination product, the complex mixture decomposed when chromatographic purification was attempted and we could not establish whether the fragmentation reaction with the dimethylalkylamine as the leaving group had occurred.

The structures of compounds **1**–**3** were elucidated spectroscopically. NMR coupling constants of *ca.* 15 Hz, confirmed the *trans* olefinic double bond of sulfonamides **3**. In addition, NOE irradiation techniques confirmed the *trans* configuration of the sulfonamide **3c**. In the irradiation experiments of both olefinic hydrogens no enhancement of the other olefinic signal was observed indicating the *trans* configuration. Irradiation of the olefinic signal at δ 6.35 produced a positive NOE effect to the allylic methylene and the methyl group of the *p*-toluenesulfonyl substituent.

These experimental results could be explained by competitive attack of the sulfonyl chlorides on the alcohol or amine functions. When the nucleophilic attack of the nitrogen takes place, the tertiary amine would be reversibly converted into a sulfonamide salt **Int1** (Scheme 2). Electron-releasing aromatic substituents at C2 of the pyrrolidine ring and the good leaving group character of the arenesulfonamide favour the heterolytic cleavage of the N1–C2 bond and formation of the carbonium ion **Int2**. Finally the elimination of the protonated formaldehyde from this cationic intermediate, analogous to the Grob fragmentation[10] or the retro-Prins-type reaction,[11] allows the conversion of the salt into the alkene **3** (Scheme 2).

Computational results

The molecular mechanism for the fragmentation of the sulfonamide salt **Int1**, obtained from *trans*-3-(hydroxymethyl)-2-phenyl-1-methylpyrrolidine (R = Me, R′ = Ph) with benzenesulfonyl chloride and trimethylamine as a base to give the sulfonamide **3**, has been studied by PM3 semiempirical methods.

It is important to realize that the finding of one TS does not exclude the possibility of alternative reaction paths having other TSs. In order to discriminate between alternative reaction channels, an extensive exploration of the PES for this fragmentation process has been carried out. This study has rendered two intermediates, **Int1** and **Int2**, and two TSs, **TS1** and **TS2**, corresponding to a stepwise mechanism (see Scheme 2). The possibility of processes occurring in which the acidic hydrogen of the alcohol group is previously removed by trimethylamine has been discarded because they have higher energies. However, the transition structure corresponding to that formed in the concerted process by simultaneous ring cleavage and extrusion of formaldehyde has not been found as a stationary point.

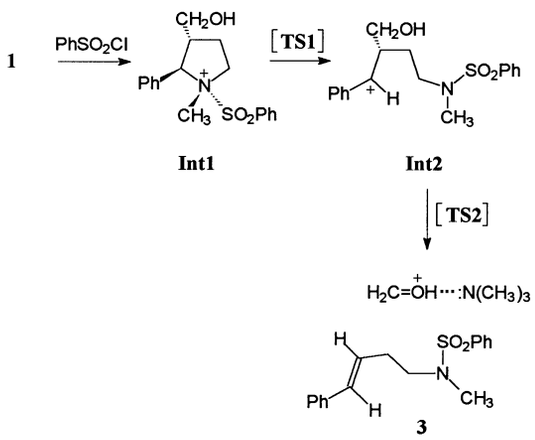
Table 2 shows the results of the geometries and the TV for **TS1** and **TS2**. Fig. 1 shows the transition structures **TS1** and **TS2** involved in the formation of the cationic intermediate **Int2**, and the extrusion of protonated formaldehyde, respectively. In Table 3, we report the PM3 calculated heats of formation and relative energies of the optimized geometries with and without solvent effect.

The **TS1** is formed by ring cleavage of pyrrolidine. The study of the TV of this TS shows that this process is mainly associated with the cleavage of the N1–C2 bond (2.326 Å) and the rehybridization of N1 and C2 centres, which both change from sp^3 to sp^2 (Table 3). The perpendicular arrangement of the

Table 3 PM3 heats of formation and relative energies in kcal mol^{-1} of the stationary points for molecular mechanism of the fragmentation of benzenesulfonamide salt of 3-(hydroxymethyl)-2-phenyl-1-methylpyrrolidine in the gas phase and Cl_2CH_2

	ΔH_f/kcal mol^{-1} in gas phase	ΔE^a/kcal mol^{-1}	ΔH_f/kcal mol^{-1} in Cl_2CH_2	ΔE^a/kcal mol^{-1}
Int1	92.09	0	45.41	0
TS1	113.49	21.40	65.59	20.19
Int2	102.63	10.54	53.53	8.12
TS2	111.12	19.04	72.76	27.35

[a] Relative energy respect to **Int1**.



Scheme 2

phenyl substituent on C2 relative to the N1–C2 bond in **TS1** stabilizes the cleavage of this bond and the formation of the benzylic cation **Int2** (N1–C2–C6–C7 dihedral angle of 91.6°). These results are in agreement with the fact that electron-releasing groups on C2 favour the cleavage process (see Experimental section).

The **TS2** corresponds to the process of C3–C9 bond cleavage and subsequent extrusion of protonated formaldehyde. The study of the TV of **TS2** shows that this process is mainly associated with bond cleavage of the C3–C9 bond (2.047 Å). The values for C9–O10 and O10–H11 bond lengths for **TS2** are 1.291 and 1.009 Å, respectively. These values indicate that the deprotonation of formaldehyde occurs in a later step. Thus, the formation of a hydrogen bond between the acidic hydrogen of the alcohol group and nitrogen atom of trimethylamine (bond length H11–N12, 1.700 Å) stabilizes the formation of the **TS2** and facilitates the extrusion of protonated formaldehyde.

The activation energy for step 1 (21.4 kcal mol^{-1}) is higher than for step 2 (8.5 kcal mol^{-1}) in the gas phase. The relative energies of **TS1** and **TS2** relative to **Int1** are 21.4 and 19.0 kcal mol^{-1}, respectively (Table 3). In this case the reversibility of the first step and similar values of **TS1** and **TS2** energies do not allow a clear assignment of the rate-determining step.

The study of the solvent effect on the reaction mechanism has been carried out by optimization of the stationary points found in gas phase by the COSMO option included in the MOPAC93 program. Table 3 shows the PM3 calculated heats of formation and relative energies of the optimized geometries in dichloromethane. An analysis of the geometrical parameters indicates that there are no large modifications in the geometry of the stationary points, and in the case of transition structures, only small modifications are detected (bond length: N1–C2 2.259 Å for **TS1** and C3–C9 2.035 Å for **TS2**).[12] The polar solvents stabilize charged species giving heats of formation lower than in the gas phase. In this case, the inclusion of the solvent effect produces a larger stabilization for **TS1** than **TS2**, and in dichloromethane the activation energy for the two steps are 20.2 and 19.2 kcal mol^{-1}, respectively. However the energies

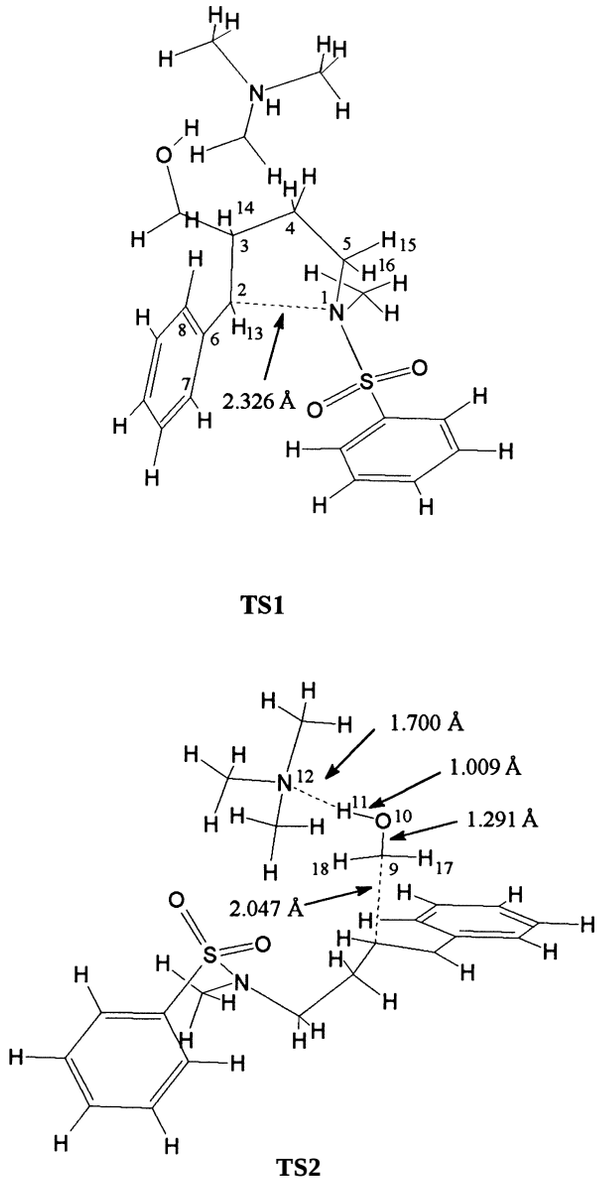


Fig. 1 Geometries of transition structures **TS1** and **TS2**

of **TS1** and **TS2** relative to **Int1** are 20.2 and 27.3 kcal mol^{-1}, and in dichloromethane, the second step is the rate determining step of the cleavage process. This result is in concordance with the dipole moment obtained for **TS1** and **TS2** in the gas phase (6.51 and 4.51 Debyes, respectively), since the solvent effect is higher for species with larger dipole moment.[12] We can conclude that the solvent effect modifies the energy profile of the reaction, but maintains the stepwise character of the global process.

Conclusions

From this study, we can conclude that sulfonyl chlorides react with 3-(hydroxymethyl)pyrrolidines **1** by competitive attack on the alcohol or amine, with formation of sulfonated alcohols or sulfonamide salts and it is determined by the nature of substituents on C2 of the pyrrolidine and the type of the sulfonyl chloride. The fragmentation of arenesulfonamide salts proceeds by a stepwise mechanism with formation of a benzylic carbonium intermediate, which by an irreversible extrusion of protonated formaldehyde in a basic medium, gives rise to the fragmentation of arenesulfonamide salts until completion.

More effective electron-releasing groups (C_6H_5 < *p*-CH_3–C_6H_4 < *p*-CH_3O–C_6H_4) decrease the activation energy of the ring cleavage step, and favour the formation of the sulfon-

Table 4 Yields and spectroscopic data of products **1**[a]

	δ_H	δ_C	ν/cm^{-1}	Yield (%)
1a	1.60 (m, 2 H), 2.00 (s, 3 H), 2.20 (m, 1 H), 2.65 (m, 4 H), 3.60 (dd, *J* 11 and 5.5, 1 H), 3.70 (dd, *J* 11 and 5.5, 1 H), 7.3 (s, 5 H)	26.2 (t), 40.1 (q), 49.6 (d), 55.7 (t), 63.3 (t), 73.9 (d), 127.1 (d), 127.7 (d), 128.2 (d), 141.2 (s)	3460	86
1b	1.62 (m, 1 H), 2.05 (s, 3 H), 2.15 (m, 3 H), 2.25 (s, 3 H), 2.78 (d, *J* 8, 1 H), 3.16 (m, 2 H), 3.4 (dd, *J* 10.6 and 6.6, 1 H), 3.5 (dd, *J* 10.6 and 4.8, 1 H), 7.15 (d, *J* 8, 2 H), 7.44 (d, *J* 8, 2 H)	20.8 (q), 24.9 (t), 38.5 (q), 47.6 (d), 55.3 (t), 61.7 (t), 79.1 (d), 128.3 (d), 129.3 (d), 132.7 (s), 138.2 (s)	3440	87
1c	1.80 (m, 1 H), 2.00 (m, 1 H), 2.10 (s, 3 H), 2.60 (m, 1 H), 3.10 (m, 3 H), 3.45 (m, 3 H), 3.65 (s, 3 H), 6.65 (d, *J* 9, 2 H), 7.10 (d, *J* 9, 2 H)	26.1 (t), 40.0 (q), 49.6 (d), 54.9 (q), 55.6 (t), 63.7 (t), 73.5 (d), 113.6 (d), 128.8 (d), 133.3 (s), 158.7 (s)	3450	87
1j	1.55 (m, 1 H), 1.94 (m, 3 H), 2.90 (d, *J* 12.8, 1 H), 2.95 (m, 1 H), 2.99 (d, *J* 8, 1 H), 3.44 (dd, *J* 10.6 and 6.2, 1 H), 3.48 (br s, 1 H), 3.53 (dd, *J* 10.6 and 5.1, 1 H), 3.67 (d, *J* 12.8, 1 H), 3.71 (s, 3 H), 6.82 (d, *J* 8.8, 2 H), 7.17 (m, 5 H), 7.3 (d, *J* 8.8, 2 H)	26.0 (t), 49.7 (d), 52.0 (t), 55.0 (q), 57.6 (t), 63.9 (t), 71.5 (d), 113.7 (d), 126.5 (d), 127.9 (d), 128.5 (d), 128.8 (d), 134.4 (s), 139.2 (s), 158.7 (s)	3440	85
1k	1.80 (m, 2 H), 2.25 (m, 2 H), 3.20 (m, 3 H), 3.70 (m, 3 H), 3.95 (m, 1 H), 7.30 (m, 5 H), 7.40 (m, 5 H)	26.4 (t), 50.1 (d), 52.3 (t), 57.9 (t), 64.5 (t), 72.4 (d), 126.8 (d), 127.4 (d), 128.0 (d), 128.1 (d), 128.6 (d), 128.7 (d), 139.4 (s), 142.8 (s)	3450	92

[a] Spectra were recorded at 60 MHz (^{1}H in $CDCl_3$, compounds **1a**, **1c**, **1k**).

Table 5 Yields and spectroscopic data of products **2**[a]

	δ_H	δ_C	ν/cm^{-1}	Yield (%)
2a	1.51 (m, 1 H), 1.94 (s, 3 H), 2.00 (m, 1 H), 2.18 (m, 2 H), 2.27 (s, 3 H), 2.63 (d, *J* 8, 1 H), 3.03 (t, *J* 9, 1 H), 3.79 (dd, *J* 10 and 5, 1 H), 3.87 (dd, *J* 10 and 4.4, 1 H), 7.10 (m, 5 H), 7.18 (d, *J* 8.4, 2 H), 7.60 (d, *J* 8.4, 2 H)	20.8 (q), 25.2 (t), 39.3 (q), 46.3 (d), 54.7 (t), 70.0 (t), 72.4 (d), 126.9 (d), 127.0 (d), 127.1 (d), 127.8 (d), 129.2 (d), 132.2 (s), 139.8 (s), 144.1 (s)	1350, 1150	48
2b	1.50 (m, 1 H), 1.80 (m, 1 H), 2.05 (s, 3 H), 2.20 (m, 2 H), 2.25 (s, 3 H), 2.40 (s, 3 H), 3.00 (m, 2 H), 3.85 (m, 2 H), 7.15 (m, 6 H), 7.65 (d, *J* 8.4, 2 H)	20.6 (q), 21.1 (q), 25.2 (t), 39.5 (q), 46.2 (d), 54.9 (t), 70.1 (t), 72.5 (d), 127.3 (d), 127.4 (d), 128.8 (d), 129.4 (d), 132.4 (s), 136.3 (s), 136.8 (s), 144.8 (s)	1350, 1120	26
2e	1.50 (m, 1 H), 1.98 (s, 3 H), 2.00 (m, 1 H), 2.30 (m, 2 H), 2.70 (d, *J* 9.1, 1 H), 3.07 (t, *J* 8.8, 1 H), 3.65 (s, 3 H), 3.82 (dd, *J* 10 and 5, 1 H), 3.91 (dd, *J* 10 and 4.4, 1 H), 6.85 (d, *J* 8.8, 2 H), 7.1 (d, *J* 8.8, 2 H), 7.60 (m, 3 H), 7.8 (m, 2 H)	25.3 (t), 39.7 (q), 46.3 (d), 54.9 (q), 55.0 (t), 70.8 (t), 72.5 (d), 113.7 (d), 126.9 (d), 127.5 (d), 128.6 (d), 128.8 (d), 132.5 (s), 135.0 (s), 158.9 (s)	1350, 1120	48
2f	1.50 (m, 1 H), 2.00 (s, 3 H), 2.38 (m, 3 H), 2.70 (d, *J* 8, 1 H), 3.00 (t, *J* 8, 1 H), 3.80 (s, 3 H), 3.90 (dd, *J* 10.6 and 6, 1 H), 4.00 (dd, *J* 10.6 and 5, 1 H), 6.80 (d, *J* 9, 2 H), 7.05 (d, *J* 9, 2 H), 7.70 (m, 4 H)	25.7 (t), 40.0 (q), 46.7 (d), 55.2 (q), 55.4 (t), 71.3 (t), 72.8 (d), 113.9 (d), 128.7 (d), 129.2 (d), 132.4 (s), 132.5 (d), 134.8 (s), 1441. (s), 159.0 (s)	1350, 1120	32
2g	1.50 (m, 1 H), 1.98 (s, 3 H), 2.00 (m, 1 H), 2.20 (m, 1 H), 2.45 (m, 1 H), 2.60 (d, *J* 9, 1 H), 3.10 (m, 1 H), 3.68 (s, 3 H), 4.1 (d, *J* 6, 2 H), 6.70 (d, *J* 9 Hz, 2 H), 7.03 (d, *J* 9, 2 H), 7.90 (d, *J* 9, 2 H), 8.24 (d, *J* 9, 2 H)	25.7 (t), 39.8 (q), 46.5 (d), 53.4 (t), 55.1 (q), 72.2 (t), 73.0 (d), 113.8 (d), 124.2 (d), 127.1 (d), 128.2 (d), 131.9 (s), 148.1 (s), 152.0 (s), 159.1 (s)	1350, 1120	36
2h	1.80 (m, 1 H), 2.05 (s, 3 H), 2.20 (m, 3 H), 2.83 (s, 3 H), 3.18 (m, 2 H), 3.55 (m, 3 H), 3.74 (s, 3 H), 4.08 (d, *J* 5.8, 2 H), 6.80 (d, *J* 8.8, 2 H), 7.25 (d, *J* 8.8, 2 H)	25.8 (t), 37.1 (q), 39.4 (q), 46.7 (d), 55.1 (q), 55.4 (t), 70.4 (t), 73.2 (d), 113.9 (d), 128.8 (d), 132.4 (s), 159.1 (s)	1350, 1100	70
2i	1.75 (m, 1 H), 2.05 (s, 3 H), 2.25 (m, 3 H), 2.30 (s, 3 H), 2.83 (s, 3 H), 3.05 (m, 2 H), 4.10 (d, *J* 6, 2 H), 7.20 (m, 4 H)	21.0 (q), 25.9 (t), 37.1 (q), 39.4 (q), 46.8 (d), 55.4 (t), 70.5 (t), 73.5 (d), 127.7 (d), 129.2 (d), 137.6 (s)	1350, 1120	83
2j	1.59 (m, 1 H), 1.99 (m, 1 H), 2.18 (m, 1 H), 2.35 (m, 1 H), 2.39 (s, 3 H), 2.90 (d, *J* 12.8, 1 H), 2.95 (m, 1 H), 3.00 (d, *J* 8, 1 H), 3.65 (d, *J* 12.8, 1 H), 3.74 (s, 3 H), 6.82 (d, *J* 8.8, 2 H), 7.20 (m, 9 H), 7.68 (d, *J* 8.8, 2 H)	21.4 (q), 25.2 (t), 46.6 (d), 51.7 (t), 55.0 (q), 57.4 (t), 70.5 (t), 70.7 (d), 113.8 (d), 126.6 (d), 127.7 (d), 127.9 (d), 128.4 (d), 128.6 (d), 129.6 (d), 132.8 (s), 133.1 (s), 139.0 (s), 144.5 (s), 158.9 (s)	1360, 1180	85
2k	1.80 (m, 1 H), 2.25 (m, 3 H), 2.35 (s, 3 H), 3.12 (m. 3 H), 3.8 (m, 3 H), 7.12 (m, 12 H), 7.64 (m, 2 H)	21.6 (q), 25.6 (t), 46.7 (d), 51.9 (t), 57.7 (t), 70.7 (t), 71.3 (d), 127.6 (d), 127.9 (d), 128.1 (d), 128.6 (s), 129.8 (s), 130.5 (s), 144.8 (s)	1350, 1120	92

[a] Spectra were recorded at 60 MHz (^{1}H in $CDCl_3$, compounds **2b**, **2i**, **2k**).

amides **3** against the sulfonated alcohols **2**. Sulfonamides with electron-withdrawing substituents also decrease the activation energy of this step, but this effect is not so well reflected in the ratio sulfonamide:sulfonated alcohol because at the same time they increase the rate of *O*-sulfonylation.

When *O*-sulfonylation takes place exclusively, sulfonated

alcohols **2** are obtained in high yields. However, when *N*-sulfonylation takes place exclusively, sulfonamides **3** are obtained in low yields, probably due to competitive reactions of the carbonium ion. When sulfonated alcohols and sulfonamides are obtained simultaneously, overall yields are in agreement with these two processes.

Experimental

General material and methods

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ with a Perkin-Elmer 843 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Bruker AC 250 spectrometer in $CDCl_3$. The 60 MHz spectra (indicated in the experimental) were run on a Perkin-Elmer R-24 spectrometer. Chemical shifts (δ) are reported in ppm with TMS as internal standard: *J* values are quoted in Hz. High resolution mass spectra (HRMS) were recorded on a VG-Autospec, TRIO 1000 Fisons instrument. Microanalyses were performed at CSIC, Barcelona.

General procedure for the preparation of *trans*-1-alkyl-2-aryl-3-(hydroxymethyl)pyrrolidines 1

The corresponding *trans*-1-alkyl-5-aryl-4-carboxypyrrolidin-2-one [13] (0.03 mol) in dry THF (200 ml) was slowly added to lithium aluminium hydride (0.06 mol) in dry THF (100 ml). The reaction mixture was refluxed for *ca.* 3 h under Ar and allowed to cool to room temperature. Methanol (10 ml), water (1 ml g^{-1} of $LiAlH_4$), 50% aqueous sodium hydroxide solution (1 ml g^{-1} of $LiAlH_4$) and water (3 ml) were then added. After filtration, the gel was washed with dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum to give the corresponding *trans*-1-alkyl-2-aryl-3-(hydroxymethyl)pyrrolidines that were used without further purification. Yields and spectral data of pyrrolidines **1** are reported in Table 4.

General procedure [14] for the preparation of sulfonated alcohols 2 and sulfonamides 3

The corresponding sulfonyl chloride **4** (0.022 mol) was added dropwise to a solution of the different 3-(hydroxymethyl)-pyrrolidines **1** (0.02 mol) and triethylamine (0.022 mol) in dichloromethane (50 ml) at 0 °C at a rate that does not cause the temperature of the reaction mixture to exceed 15 °C. The reaction mixture was stirred at room temperature for *ca.* 7 h. The mixture was washed with 10% aqueous sodium hydroxide (3 × 25 ml). This phase was extracted with dichloromethane, the combined organic phases were dried with Na_2SO_4 and concentrated. Separation of the residue by column chromatography on silica gel using dichloromethane as eluent gave the sulfonated alcohols **2** (see yields and spectral data in Table 5) and/or the sulfonamides **3**. Unreacted alcohols (5–12%) were obtained in all cases in the chromatographic process and traces of these alcohols were detected as impurities in the isolated compounds which were difficult to eliminate.

***N*-Methyl-*N*-[(*E*)-4-phenylbut-3-en-1-yl]-*p*-toluensulfonamide (3a).** Yield 3%. ν_{max}/cm^{-1} 1340 and 1160; δ_H 2.30 (s, 3 H), 2.31 (m, 2 H), 2.66 (s, 3 H), 3.13 (t, *J* 7, 2 H), 6.03 (dt, *J* 15.7 and 7, 1 H), 6.33 (d, *J* 15.7, 1 H), 7.20 (m, 7 H) and 7.58 (d, *J* 8, 2 H); δ_C 21.3 (q), 31.5 (t), 34.7 (q), 49.7 (t), 126.0 (d), 126.8 (d), 127.1 (d), 127.2 (d), 128.3 (d), 129.5 (d), 132.1 (d), 134.5 (s), 137.0 (s) and 143.1 (s); CI-MS $(M + 1)^+$ 3.16.1367. $C_{18}H_{22}NO_2S$ requires $(M + 1)^+$, 316.1371.

***N*-Methyl-*N*-[(*E*)-4-(*p*-tolyl)but-3-en-1-yl]-*p*-toluensulfonamide (3b).** Yield 19%. ν_{max}/cm^{-1} 1340 and 1160; δ_H 2.30 (s, 3 H), 2.40 (s, 3 H), 2.41 (m, 2 H), 2.75 (s, 3 H), 3.15 (t, *J* 8, 2 H), 6.12 (dt, *J* 16 and 8, 1 H), 6.40 (d, *J* 16, 1 H), 7.09 (d, *J* 9, 2 H), 7.25 (m, 4 H) and 7.68 (d, *J* 9, 2 H); δ_C 20.8 (q), 21.1 (q), 31.3 (t), 34.6 (q), 49.6 (t), 124.9 (d), 126.7 (d), 127.0 (d),, 128.9 (d), 129.4 (d), 131.7 (d), 134.1 (s), 134.4 (s), 136.6 (s) and 143.0 (s); HRMS: M^+, 329.1439; $C_{19}H_{23}NO_2S$ requires 329.1449.

***N*-Methyl-*N*-[(*E*)-4-(*p*-methoxyphenyl)but-3-en-1-yl]-*p*-toluensulfonamide (3c).** Yield 32%. Mp 91 °C (from dichloromethane); ν_{max}/cm^{-1} 1340 and 1160; δ_H 2.35 (m, 5 H), 2.75 (s, 3 H), 3.10 (t, *J* 7.5, 2 H), 3.75 (s, 3 H), 5.98 (dt, *J* 15.8 and 7, 1 H), 6.35 (d, *J* 15.8, 1 H), 6.80 (d, *J* 8.8, 2 H), 7.25 (m, 4 H) and 7.68 (d, *J* 8, 2 H); δ_C 21.4 (q), 31.6 (t), 34.8 (q), 49.9 (t), 56.1 (q), 113.8 (d), 123.8 (d), 127.1 (d), 127.2 (d), 129.5 (d), 129.9 (s), 131.5 (d), 134.6 (s), 143.1 (s) and 158.8 (s) (Calc. for $C_{19}H_{23}NO_3S$: C, 65.81; H, 6.75; N, 4.15; S, 8.64. Found: C, 65.65; H, 6.65; N, 4.14; S, 8.56%).

***N*-Methyl-*N*-[(*E*)-4-(*p*-methoxyphenyl)but-3-en-1-yl]-*p*-methoxybenzenesulfonamide (3d).** Yield 26%. Mp 103–105 °C (from hexane–dichloromethane); ν_{max}/cm^{-1} 1340 and 1150; δ_H 2.35 (q, *J* 7.3, 2 H), 2.66 (s, 3 H), 3.05 (t, *J* 7.3, 2 H), 3.70 (s, 3 H), 3.74 (s, 3 H), 5.87 (dt, *J* 16 and 8, 1 H), 6.24 (d, *J* 16, 1 H), 6.73 (d, *J* 8.8, 2 H), 6.86 (d, *J* 9, 2 H), 7.14 (d, *J* 8.8, 2 H) and 7.60 (d, *J* 9.1, 2 H); δ_C 31.6 (t), 34.8 (q), 49.9 (t), 55.2 (q), 55.5 (q), 113.7 (d), 113.8 (d), 123.9 (d), 127.1 (d), 129.1 (s), 129.3 (d), 130.0 (s), 131.5 (d), 158.9 (s) and 162.7 (s) (Calc. for $C_{19}H_{23}NO_4S$: C, 63.15; H, 6.37; N, 3.87; S, 8.86. Found: C, 62.99; H, 6.40; N, 3.86; S, 8.86%).

***N*-Methyl-*N*-[(*E*)-4-(*p*-methoxyphenyl)but-3-en-1-yl]-benzenesulfonamide (3e).** Yield 19%. ν_{max}/cm^{-1} 1350 and 1150; δ_H 2.31 (q, *J* 6.9, 2 H), 2.66 (s, 3 H), 3.03 (t, *J* 6.9, 2 H), 3.66 (s, 3 H), 5.87 (dt, *J* 16 and 8, 1 H), 6.25 (d, *J* 16, 1 H), 6.72 (d, *J* 8.8, 2 H), 7.14 (d, *J* 8.8, 2 H), 7.39 (m, 3 H) and 7.66 (d, *J* 6.7, 2 H); δ_C 31.5 (t), 34.7 (q), 49.8 (t), 55.1 (q), 113.74 (d), 123.6 (d), 127.1 (d), 129.0 (d), 130.0 (s), 131.5 (d), 132.4 (d), 137.5 (s) and 158.8 (s); HRMS: M^+, 331.1243; $C_{18}H_{21}NO_3S$ requires 331.1242.

***N*-Methyl-*N*-[(*E*)-4-(*p*-methoxyphenyl)but-3-en-1-yl]-*p*-bromobenzenesulfonamide (3f).** Yield 21%. Mp 110–112 °C (from hexane–dichloromethane); ν_{max}/cm^{-1} 1340 and 1150; δ_H 2.35 (q, *J* 8, 2 H), 2.80 (s, 3 H), 3.15 (t, *J* 8, 2 H), 3.80 (s, 3 H), 5.95 (dt, *J* 15 and 8, 1 H), 6.35 (d, *J* 15, 1 H), 6.85 (d, *J* 9, 2 H), 7.25 (d, *J* 9, 2 H) and 7.60 (s, 4 H); δ_C 31.6 (t), 34.7 (q), 49.9 (t), 55.2 (q), 113.9 (d), 123.5 (d), 127.1 (d), 128.7 (d), 129.7 (s), 131.7 (d), 132.2 (d), 137.0 (s) and 159.0 (s); (Calc. for $C_{18}H_{20}NO_3SBr$: C, 52.68; H, 4.87; N, 3.41; S, 7.80; Br, 19.51. Found: C, 52.65; H, 4.83; N, 3.33; S, 7.75; Br, 19.26%).

***N*-Methyl-*N*-[(*E*)-4-(*p*-methoxyphenyl)but-3-en-1-yl]-*p*-nitrobenzenesulfonamide (3g).** Yield 9%. Mp 95–96 °C (from hexane–dichloromethane); ν_{max}/cm^{-1} 1350 and 1160; δ_H 2.33 (q, *J* 7.1, 2 H), 2.77 (s, 3 H), 3.15 (t, *J* 7.1, 2 H), 3.70 (s, 3 H), 5.79 (dt, *J* 15.7 and 7, 1 H), 6.21 (d, *J* 15.7, 1 H), 6.72 (d, *J* 8.8, 2 H), 7.09 (d, *J* 8.8, 2 H), 7.84 (d, *J* 8.8, 2 H) and 8.17 (d, *J* 8.8, 2 H); δ_C 31.6 (t), 34.6 (q), 49.9 (t), 55.1 (q), 113.9 (d), 123.3 (d), 124.2 (d), 127.1 (d), 128.2 (d), 129.6 (s), 132.0 (d), 144.1 (s), 149.7 (s) and 159.0 (s); (Calc. for $C_{18}H_{20}N_2O_5S$: C, 57.44; H, 5.31; N, 7.44; S, 8.51. Found: C, 57.31; H, 5.26; N, 7.39; S, 8.53%).

***trans*-1,1-Dimethyl-2-(*p*-methoxyphenyl)-3-(hydroxymethyl)-pyrrolidinium iodide (5).** Iodomethane (0.02 mol) was added to a stirred solution of *trans*-1-methyl-2-(*p*-methoxyphenyl)-3-(hydroxymethyl)pyrrolidine **1c** (0.02 mol) in methanol (70 ml) over 30 min period. The flask was cooled with an ice bath to keep the reaction temperature at *ca.* 25 °C. After 1 h the bath was removed and the reaction mixture was allowed to stir at room temperature for 3 days. The solvent was removed under reduced pressure. The solid was triturated and washed with diethyl ether and dried under reduced pressure. Yield: 64%. δ_H([$^2H_6$]DMSO) 2.05 (m, 2 H), 2.75 (s, 3 H), 3.00 (s, 3 H), 3.15 (d, *J* 6, 1 H), 3.30 (m, 2 H), 3.65 (m, 2 H), 3.80 (s, 3 H), 4.60 (d, *J* 12, 1 H), 4.95 (m, 1 H), 7.08 (d, *J* 9, 1 H) and 7.59 (d, *J* 9, 1 H); δ_C([$^2H_6$]DMSO) 28.9 (t), 41.2 (q), 45.1 (q), 50.2 (d), 55.6 (q), 60.3 (t), 64.8 (t), 78.6 (d), 114.6 (d), 120.5 (s), 133.0 (d) and 161.0 (s).

A mixture of the salt **5** (0.008 mol) and sodium hydroxide (0.008 mol) in methanol (30 ml) was heated in an enclosed steel bomb for 6 h at 150 °C. After separation of the unreacted salt (90%), the complex mixture could not be resolved chromatographically.

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