^{1}H NMR and X-Ray Crystallographic Studies of *p*-Toluenesulfonamides of 2,5-Di(pyrrol-2-yl)-pyrrolidines

J. Chem. Research (S), 1999, 312–313
J. Chem. Research (M), 1999, 1373–1396

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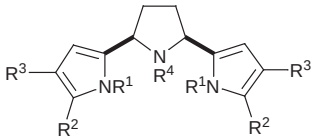
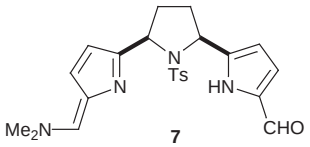
Some pyrrole-*N*-substituted derivatives of *cis*-1-(4-methylphenylsulfonyl)-2,5-di(pyrrol-2-yl)pyrrolidine are prepared, subjected to Vilsmeier formylation and bromination conditions, and products characterised by NMR and in two cases X-ray analysis.

The tosylamide **3** of *cis*-pyrrole trimer[1] **2** can be di-*N*-methylated, giving **4** or di-*N*-(triisopropylsilyl)ated giving **5** using the appropriate halides and sodium hydride as base.



	R^1	R^2	R^3	R^4
2	H	H	H	H
3	H	H	H	Ts
4	Me	H	H	Ts
5	TIPS	H	H	Ts
8	H	CHO	H	Ts
9	Me	CHO	H	Ts
10	TIPS	H	Br	Ts

Vilsmeier formylation of **3** using *N*-methylformanilide and oxalyl chloride, then hydrolysis with sodium hydrogen carbonate, gave dialdehyde **8**. Attempted formylation of **3** using dimethylformamide with phosphorus oxychloride or with oxalyl chloride, followed by treatment with sodium hydrogen carbonate, produced **7**, the structure of which was established by X-ray crystallography; **7** represents an intriguing half-way house in the hydrolysis of the usual Vilsmeier intermediate; it was easily hydrolysed with stronger base to give **8**. Vilsmeier formylation of **4** with dimethylformamide with oxalyl chloride gave diformyl derivative **9** straightforwardly.



7

The doubly TIPS-protected **5** underwent electrophilic substitution with *N*-bromosuccinimide showing different regioselectivity,[2] to give a dibromide **10** in which substitution had taken place in each ring at the least hindered of the two pyrrole β positions.

Structures

An X-ray crystal structure determination of **4** had shown[3] it to be the first representative of an orientation around the sulfonamide unit, different from that which we had earlier demonstrated to be typical[1,4] and which has been frequently exemplified.[5] An X-ray crystallographic determination of the doubly TIPS-protected sulfonamide **5** now shows it too to have the less common sulfonamide geometry, illustrated schematically in Fig. 2.

Having in hand six compounds **3**–**5**, **8**–**10**, all based on the pyrrole trimer nucleus and each having a toluenesulfonamide group attached to the pyrrolidine nitrogen, we were able to discern a pattern in the ^{1}H NMR signals from the toluene group which we believe correlates with the sulfonamide orientation adopted. Crystal structures for compound **3**[1] on the one hand and compounds **4**[3] and **5** on the other, typify the two types of sulfonamide orientation and overall conformation. The toluene ring protons in **3** resonate as AA′XX′ multiplets at δ 7.40 and 7.81 – hemical shifts and chemical shift difference (0.41) typical of toluenesulfonamides; the toluene ring protons of **5** resonate at higher field, δ 7.02 and 7.14, and only 0.12 ppm apart, while the signals from **4** are at δ 7.07 and 7.13, a chemical shift difference of 0.06 ppm.

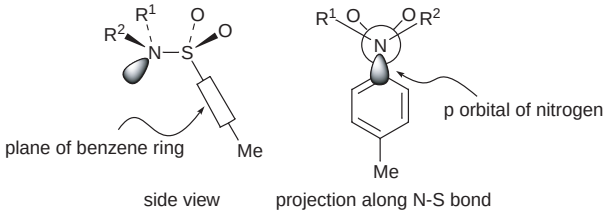


Fig. 2 Alternative geometry of arylsulfonamides

We suggest that the observation of higher than normal chemical shifts, and in particular, a small difference (0.0–0.18 ppm) between the shifts of the *ortho* and *meta* protons of the toluene unit, corresponds to a sulfonamide orientation as illustrated schematically in Fig. 5 and that larger, more 'normal' differences (0.29–0.41) indicate a sulfonamide configuration and molecular conformation corresponding to Fig. 6.

Further confirmation for these explanations came from the observation of nOe enhancements in studies of compounds **4**, **5**, **9**, and **10** between pyrrole protons and toluene ring protons. No such enhancements were observed for **3** and **8**.

We rationalise these X-ray and spectroscopic results in the following way. In the compounds which have pyrrole *N*-hydrogen there is a favourable conformation (Fig. 6) in which hydrogen bonding between each of the sulfonamide oxygen atoms and a pyrrole *N*-hydrogen is present. In the compounds which adopt the alternative conformation, there is no *N*-hydrogen, so this favourable interaction is not available. In this situation, the molecules adopt an alternative conformation (Fig. 5) which is favoured by two factors: (i) the nitrogen substituents are located on the outside of the molecule, (ii) the alternative sulfonamide geometry allows an energetically favourable $\pi-\pi$ interaction between the electron-deficient toluene ring and the electron-rich pyrrole nuclei, leading to the observed nOe and chemical shift phenomena discussed above.

It is interesting that the crystal structure of **7** shows that, although the orientation around the sulfonamide unit corresponds to that in **3** (as illustrated in Fig. 2), in this case there is no hydrogen bond from the one pyrrole *N*-hydrogen to a sulfoxide oxygen, as observed for **3**. Instead, there is a hydrogen bond between the pyrrole *N*-hydrogen and the

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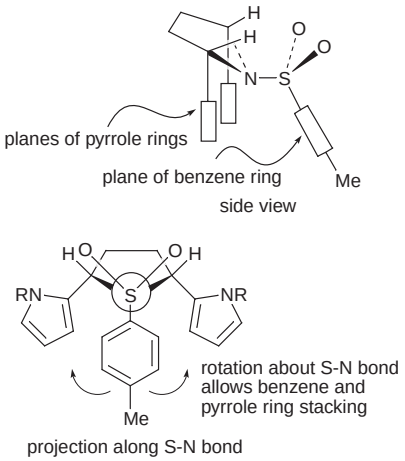

Fig. 5 Orientation corresponding to $\Delta\delta = 0.0-0.18$

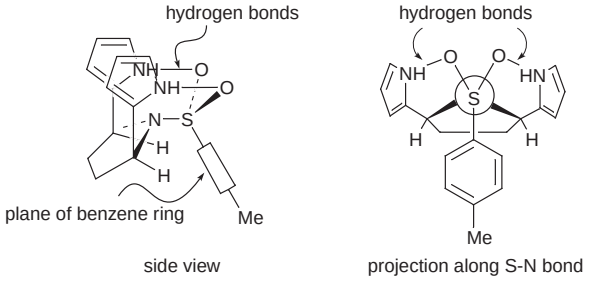

Fig. 6 Orientation corresponding to $\Delta\delta = 0.29-0.41$

imine type nitrogen of the pyrrolenine ring, the hydrogen to imine nitrogen distance being 1.91 Å.

X-Ray crystallography

A suitable sample of **5** was crystallised from CH_2Cl_2– hexane. The structure was solved by direct methods and developed using Fourier techniques. The asymmetric unit contained two molecules. There was disorder over two sites in a number of fragments of the structure–occupancies of each part were constrained to sum to 1. Non-hydrogen atoms were refined anisotropically except for some of the disordered atoms. H atoms were included in calculated positions, using the riding model.

Crystal Data for **5**.—Colourless, tabular, triclinic. space group $P\bar{1}$, $M = 668.13$: $V = 3985.0(13)$Å^3; $a = 15.190(3)$, $b = 19.958(4)$ Å, $c = 14.433(3)$ Å; $Z = 4$, $D_c = 1.113\,g\,cm^{-3}$; h, 0–18, k, −24 to 23, l, −17 to 17. $R = 0.0608$, $wR(F^2) = 0.1941$.

A suitable sample of **7** was prepared by crystallisation from ethanol. The crystal ($0.25 \times 0.15 \times 0.02$) was small and weakly diffracting. The crystal structure was solved by direct methods.

Crystal Data for **7**.—Colourless, plate, monoclinic, space group $P2_1/c$, $M = 438.58$; $V = 2174.9(16)$ Å^3; $a = 17.439(4)$, $b = 10.214(6)$, $c = 12.300(6)$ Å; space group $P2_1/c$; $Z = 4$; $D_c = 1.339\,g\,cm^{-3}$; h, −21 to 21, k, −12 to 0, l, 0–14. $R = 0.1440$, $wR(F^2) = 0.3714$.

Y.Z. was an EPSRC-funded post-doctoral assistant: we thank the EPSRC for their support for this work and the SERC for funds for the purchase of the Rigaku AFC-5R diffractometer.

Techniques used: IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, X-ray crystallography

References: 19

Schemes: 2

Fig. 1: Typical geometry of arylsulfonamides

Fig. 3: ORTEP plot of the structure of **7**

Fig. 4: ORTEP plot of the structure of **5**

Table 1: Chemical shifts of toluene ring protons in $CDCl_3$

Table 2: Crystal and refinement details for **5** and **7**

Table 3: Positional parameters and U_{eq} for **5**

Table 4: Bond lengths (non-hydrogen atoms) in **5**

Table 5: Bond angles (non-hydrogen atoms) in **5**

Table 6: Positional parameters and U_{eq} for **7**

Table 7: Bond lengths (non-hydrogen atoms) in **7**

Table 8: Bond angles (non-hydrogen atoms) in **7**

Received, 17th December 1998; Accepted, 2nd February 1999
Paper E/8/09533G

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