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1,2,4-Thiadiazolo[2,3-*a*]pyridinium chlorides undergo a very facile base promoted transformation to give bispyridylimino-1,2,4-thiadiazolidines. The unequivocal structural assignment of these last compounds was achieved by spectroscopic  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{15}\text{N}$  two dimensional methods.

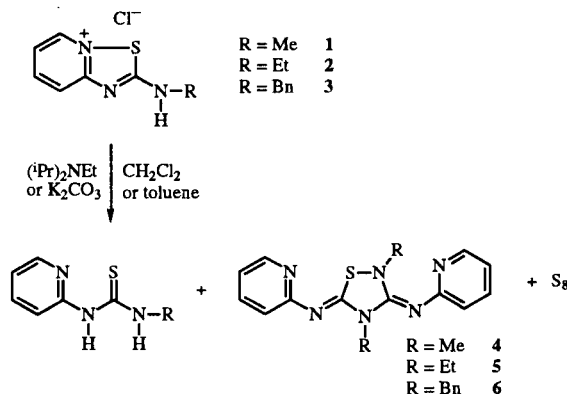
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Recently, we have described the applications of thiadiazolo heteroarylium salts in heterocyclic synthesis [1]. The high reactivity of 1,2,4-thiadiazolo[2,3-*a*]pyridinium chlorides against electrophiles has been shown to be an easy and efficient synthetic pathway to many five membered heterocycles bearing pyridylimino substituents [2]. Continuing with our studies on these heteroarylium salts, we report here the behaviour of 1,2,4-thiadiazolo[2,3-*a*]pyridinium chlorides in basic medium.

2-Alkyl or 2-benzylamino-1,2,4-thiadiazolo[2,3-*a*]pyridinium salts **1-3** [2] are white solids and perfectly stable, the same as their solutions in dichloromethane or toluene at room or reflux temperature. However, when a weak base, potassium carbonate or a tertiary amine is present, a facile transformation proceeds to give sulfur and a mixture of two compounds which, after a careful analytical and spectroscopic study, could be isolated and characterized as the corresponding *N*-alkyl or *N*-benzyl-*N'*-(2-pyridyl)thiourea and its oxidation derivative, the thiadiazolidine compounds **4-6** (Scheme 1). These last heterocycles are structurally related with Hector's bases which are known since 1890 and were obtained by oxidation of thioureas with peroxides. The

oxidizing power of the thiadiazolopyridinium chlorides **1-3** was established by standard methods, *e.g.*, liberation of iodine from iodide.

Scheme 1



It is known that structurally interesting molecules can be synthesized from the oxidation of *N*-alkyl-*N'*-phenylthioureas [3]. There are sixteen possible different isomeric 1,2,4-thiadiazolidine derivatives from these reactions due

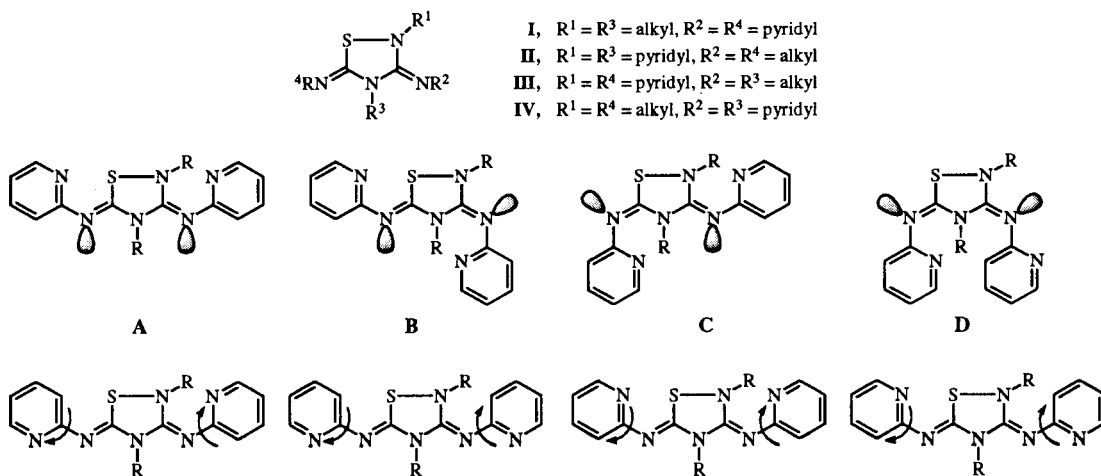
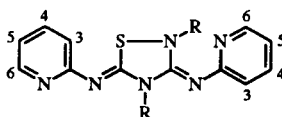


Figure 1.

Table 1a  
<sup>1</sup>H Chemical Shift (ppm) of 1,2,4-Thiadiazolidines 4-6



Compound	(N2)R	(N4)R	(N5) Pyridine				(N3) Pyridine			
			H-3	H-4	H-5	H-6	H-3	H-4	H-5	H-6
4 R = Me	2.82 (s)	3.60 (s)	7.32 (ddd)	7.67 (td)	6.92 (td)	8.27 (ddd)	6.85 (dd)	7.47 (td)	6.72 (td)	8.23 (ddd)
5 R = Et	1.02 (t) 3.23 (c)	1.36 (t) 4.27 (c)	7.35 (dd)	7.70 (td)	6.90 (td)	8.35 (dd)	6.80 (dd)	7.50 (td)	6.70 (td)	8.25 (dd)
6 [a] R = Bz	4.51 (s)	5.47 (s)	7.20 (m)	7.60 (m)	6.86 (m)	8.16 (m)	6.40 (d)	7.20 (m)	6.62 (td)	8.16 (m)

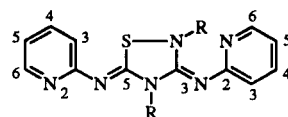
[a] H-Ar: 7.08-7.54 ppm.

Table 1b  
<sup>1</sup>H Coupling Constants (Hz) of 1,2,4-Thiadiazolidine 4-6

Compound	(N5) Pyridine						(N3) Pyridine					
	J <sub>H6-H5</sub>	J <sub>H6-H4</sub>	J <sub>H6-H3</sub>	J <sub>H5-H4</sub>	J <sub>H5-H3</sub>	J <sub>H4-H3</sub>	J <sub>H6-H5</sub>	J <sub>H6-H4</sub>	J <sub>H6-H3</sub>	J <sub>H5-H4</sub>	J <sub>H5-H3</sub>	J <sub>H4-H3</sub>
4	5.4	1.7	0.9	7.2	1.1	8.3	5.3	2.0	0.9	6.1	1.0	8.2
5 [a]	5.4	1.4	—	6.8	1.0	8.3	4.8	1.9	—	6.3	1.0	7.8
6	—	1.7	—	—	—	8.7	6.1	—	—	—	1.0	8.1

[a] J<sub>N2-CH<sub>2</sub>CH<sub>3</sub></sub> = 7.3; J<sub>N4-CH<sub>2</sub>CH<sub>3</sub></sub> = 6.8 Hz.

Table 2  
<sup>13</sup>C Chemical Shift (ppm) of 1,2,4-Thiadiazolidines 4-6



Compound	(N2)R	C-3	(N4)R	C-5	(N5) Pyridine					(N3) Pyridine				
					C-2	C-3	C-4	C-5	C-6	C-2	C-3	C-4	C-5	C-6
4 R = Me	32.1	161.0	33.6	160.4	156.6	116.1	138.1	119.4	147.8	148.3	115.6	137.2	117.3	139.8
5 R = Et	40.2	161.1	41.0	159.7	157.0	116.7	138.0	119.4	148.1	146.4	115.7	137.3	116.9	140.4
6 [a] R = Bz	47.8	160.2	49.3	159.8	156.6	116.6	138.0	119.6	147.4	145.9	116.7	136.9	117.8	139.8

[a] C-Ar: 126.9, 127.1(6), 127.2(1), 128.1(9), 128.1(8), 128.4, 128.6.

to the different substituents on the thiadiazolidine ring and the *E/Z* disposition of the imino bond (Figure 1). Three of these isomers could be obtained and were isolated by means of column chromatography or solubility differences [4]. Additionally, if the phenyl moiety is replaced by a heteroaryl group, which is the case herein described, the free rotation around the C-N bond increases the possible conformations in the final isomer.

The structural elucidation of thiadiazolidines 4-6 was accomplished by the usage of two-dimensional nmr methods. Initially, thiadiazolidine 5 was selected for this study.

Analytical data for compound 5 indicated a composition compatible with a C<sub>16</sub>H<sub>18</sub>N<sub>6</sub>S molecular formula.

The structural confirmation of 5 was established by the unequivocal assignment of its <sup>1</sup>H and <sup>13</sup>C spectra through the concerted use of COSY [5], HMQC [6], HMBC [7], and <sup>13</sup>C coupled spectra.

The COSY spectrum of 5 revealed two four-spin and two five-spin systems, corresponding to different pyridine and ethyl moieties. These fragments were assigned with a proton-carbon direct heteronuclear chemical shift correlation (HMQC) spectrum. The assignment of the remaining quaternary carbons and, what is more important, the positions of pyridine and ethyl moieties, however, needs to employ long-range couplings. In the <sup>13</sup>C coupled spectrum of 5, one quaternary carbon shows a three-bond coupling

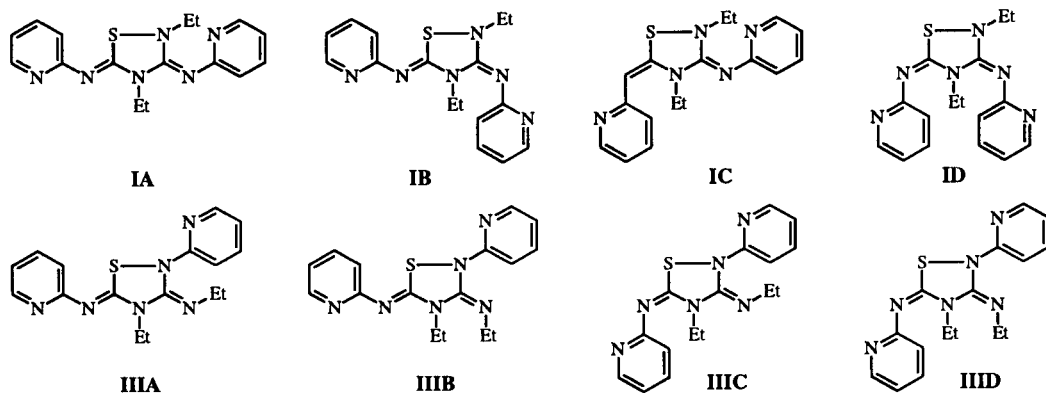


Figure 2.

with only one methylene group, while the other quaternary carbon shows three-bond coupling with both methylenes present in the structure. This fact allow us to discard two position isomers (Formulas II and IV in Figure 1).

However, the two remaining position isomers (Formulas I and III) could be shown four geometric isomers each one due to *E/Z* configuration of the imino bond (Figure 2).

Interestingly nOe difference experiments were observed. Thus, irradiation in the upfield methylene signal (3.23

ppm) shows nOe only in the signals corresponding to H-3 and H-6 of one pyridine ring. Therefore, proximity between both alkyl groups does not exist, and conformations **IIIb** and **IIId** can be discarded. Moreover, irradiation of the downfield methylene signal (4.27 ppm) does not produce an nOe. Therefore, only one pyridine ring and one ethyl moiety are spatially close. This finding is incompatible with structures **Ic**, **Id** and **IIIC**, but three possible isomers, **Ia**, **Ib** and **IIIA** still remain.

Quaternary carbons could be unequivocally assigned by comparison of the coupled  $^{13}\text{C}$  spectra registered with and without irradiation on the protons of the methylene groups. Thus, irradiation of the signal at  $\delta = 3.23$  only modified the multiplicity of one quaternary carbon  $\delta = 146.4$ , whilst irradiation at  $\delta = 4.27$  affects both quaternary thiadiazolidine carbons. This three-bonds scalar coupling found ruled out structure **Ib**, but the remaining isomers **Ia** and **IIIA** were justified by all the experimental data.

The solution for this problem was found in a long-range heteronuclear ( $^1\text{H}/^{15}\text{N}$ ) chemical shifts correlation (HMBC) spectrum of **5**. The two methyl groups of the ethyl moieties exhibit only one response correlating with two pyrrolic-type nitrogen atoms, which definitively confirms that structure **Ia** is the one isolated in our reaction.

The structural elucidation of **4** and **6** were analyzed and the spectroscopic data were assigned in a manner similar to that described in the assignment of the spectra of **5**. The  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts and coupling constants of compounds **4-6** are summarized in Tables 1 and 2.

The only point remaining unresolved was the relative disposition of the pyridine nitrogen atoms in relation to the thiadiazolidine ring. The semiempirical AMPAC 5.0 [8] full-geometry calculations using the MNDO method predict that one pyridine ring is almost co-planar with the thiadiazolidine ring whilst the other one formed a certain angle with the sulfur heterocycle. This angle's values, which are comprised between 40 and 100°, is governed by the steric interactions between the hydrogens atoms of the different alkyl group attached to the thiadiazolidine

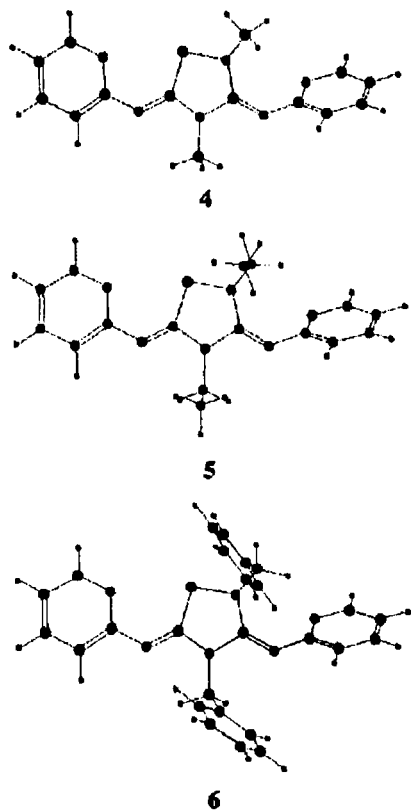


Figure 3. MNDO full optimized structures of thiadiazolidines **4-6** showing the relative disposition of the heterocyclic moieties.

2-position and the pyridine atoms. The structures generated by MNDO calculations are shown in Figure 3.

In conclusion we have described the behaviour of thiazolopyridinium chlorides in basic medium which led to the production of substituted 1,2,4-thiadiazolidines. Their structures have been determined using spectroscopic and theoretical methods.

### EXPERIMENTAL

Melting points were determined with a Reichert-Jung Thermovar apparatus and are uncorrected. Reagents and solvents were purchased from common commercial suppliers. The nmr spectra were recorded on a Bruker AM-200 or a Varian Gemini-200 spectrometers at 200 and 50 MHz for  $^1\text{H}$  and  $^{13}\text{C}$  respectively. The HMQC and HMBC sequences were performed on a Varian Unity-500 operating at 500 MHz.

3,5-[Bis(2-pyridyl)imino]-2,4-dimethyl-1,2,4-thiadiazolidine (4).

To a suspension of 2-methylamino-1,2,4-thiadiazolo[2,3-*a*]pyridinium chloride (5 mmoles) [2] in dichloromethane (20 ml), *N,N'*-diisopropylethylamine (5 mmoles) was added. The reaction mixture was stirred at room temperature for 24 hours. After stirring, the solvent was evaporated to dryness and the residue was purified by column chromatography using dichloromethane:methanol (100:1) as eluent to furnish 164 mg (0.5 mmole, 12%) of compound 4, mp 130-132°.

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{14}\text{N}_6\text{S}$ : C, 56.37; H, 4.69; N, 28.18; S, 10.73. Found: C, 55.98; H, 4.52; N, 28.05; S, 10.90.

3,5-[Bis(2-pyridyl)imino]-2,4-diethyl-1,2,4-thiadiazolidine (5).

*N,N'*-Diisopropylethylamine (5 mmoles) was added to a suspension of 2-ethylamino-1,2,4-thiadiazolo[2,3-*a*]pyridinium chloride (5 mmoles) [2] in dichloromethane (20 ml). The reaction mixture was stirred at room temperature for 24 hours. The solvent

was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using dichloromethane:methanol (100:1) as the eluent to give 554 mg (1.7 mmoles, 34%) of compound 5, mp 136-138°.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{18}\text{N}_6\text{S}$ : C, 58.90; H, 5.52; N, 25.76; S, 9.81. Found: C, 58.64; H, 5.26; N, 25.93; S, 9.72.

3,5-[Bis(2-pyridyl)imino]-2,4-dibenzyl-1,2,4-thiadiazolidine (6).

To a suspension of 2-benzylamino-1,2,4-thiadiazolo[2,3-*a*]pyridinium chloride (5 mmoles) [2] in dichloromethane (20 ml), *N,N'*-diisopropylethylamine (5 mmoles) was added. The reaction mixture was stirred at room temperature for 24 hours. After stirring, the solvent was evaporated to dryness and the residue was purified by column chromatography using dichloromethane:methanol (100:1) as the eluent to provide 203 mg (0.45 mmole, 9%) of compound 6, mp 133-135°.

*Anal.* Calcd. for  $\text{C}_{26}\text{H}_{24}\text{N}_6\text{S}$ : C, 69.31; H, 4.92; N, 18.65; S, 7.11. Found: C, 69.40; H, 4.92; N, 18.51; S, 6.82.

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