Synthesis of 1,2,3-Thiadiazole-5-carbaldehydes and their Conversion into 6aλ⁴-Thia-1,2,5,6-tetraazapentalenes

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A convenient method for the synthesis of the virtually unknown 1,2,3-thiadiazole-5-carbaldehydes consists in monobromination of the 5-methyl derivatives, followed by treatment with sodium azide and decomposition in concentrated sulfuric acid (**6** → **7** → **9** → **10**). These compounds can be transformed *via* methylation of the corresponding hydrazones **12** into 6aλ⁴-thia-1,2,5,6-tetraazapentalenes **13**.

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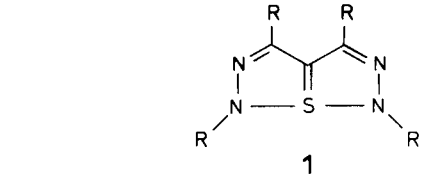
6aλ⁴-Thia-1,2,5,6-tetraazapentalenes **1** are delocalized 10π-electron systems which are characterized by single bond/no bond resonance, represented by the canonical structures **1a** and **1b**. They have been prepared by Perrier and Vialle from bis(arylhydrazones) of β-diketones and SCl_2 (or S_2Cl_2), and by Reid *et al.* from other thiapentalenes (*e.g.* **2**) by the interaction of arenediazonium tetrafluoroborate [1,2].

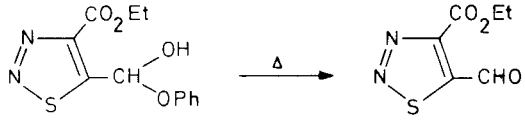


1

1a 1b

2 3

Based on our knowledge that 1,2,3-thiadiazoles can be methylated at both the N-2 and N-3 positions [3], we surmised that methylation of the hydrazones **3** would provide a third and attractive method for the synthesis of **1**. However, the corresponding aldehydes constitute a virtually unknown class of heterocycles although **5** has been reported to be formed as an impure oil by vacuum distillation of the hemiacetal **4** [4].

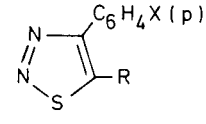


4 5

We now describe a general method for the synthesis of 1,2,3-thiadiazole-5-carbaldehydes and the conversion of a representative example into a 6aλ⁴-thia-1,2,5,6-tetraazapentalene.

The method starts with the readily available 5-methylthiadiazoles **6a-c** which are brominated with one equivalent of *N*-bromosuccinimide under free radical conditions to give **7a-c** in 47, 42 and 13% yield respectively. The low yield in the last case is probably due to inhibition of the radical reaction by the nitrophenyl group, since a large amount of starting material was recovered. With two equivalents of *N*-bromosuccinimide a mixture of the monobromides **7b,c** and dibromides **8b,c** were obtained.

The monobromides were then converted into the azides **9a-c** and decomposed in concentrated sulfuric acid. The latter reaction proceeds *via* a protonated nitrene which undergoes a 1,2-hydrogen shift to an imine, followed by hydrolysis [5]. The aldehydes **10a-c**, thus obtained were fully characterized by spectral methods (see Table 1). They are sensitive to bases, giving the deformylated products **11a-c**, analogous to 1,2,3-triazole-5-carbaldehydes [6], tetrazole-5-carbaldehydes [7] and the well-known example of chloral.



a : X = H
b : X = Cl
c : X = NO_2

	R
6	CH_3
7	CH_2Br
8	$CHBr_2$
9	CH_2N_3
10	CHO
11	H
12	CH=N–NHPh

When the phenylhydrazone **12a**, derived from **10a**, was methylated with methyl fluorosulfonate, red needles of **13**

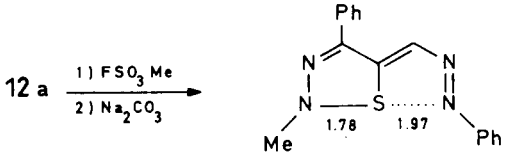
Table 1

NMR Chemical Shifts of the Heterocycles [a]

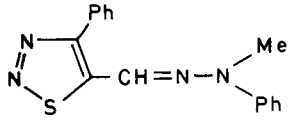
Compound	Solvent	^{1}H NMR R	^{13}C NMR C-4	C-5	R
6a	$CDCl_3$	2.7 (s)	159.6	146.5	10.5
6b	$CDCl_3$	2.75 (s)	158.4	146.7	10.5
6c	$CDCl_3$	2.8 (s)	157.2	148.6	10.7
7a	$CDCl_3$	4.8 (s)	159.5	148.0	19.2
7b	$CDCl_3$	4.78 (s)	158.4	148.2	18.9
7c	$CDCl_3$	4.7 (s)	157.1	149.9	18.3
8b	$CDCl_3$	6.8 (s)	154.1	155.2	23.7
8c	$CDCl_3$	6.78 (s)	152.9	156.8	23.0
9a	$CDCl_3$	4.8 (s)	159.2	146.1	46.0
9b	$CDCl_3$	4.8 (s)	158.2	146.4	45.8
9c	$CDCl_3$	5.0 (s)	156.8	148.5	45.8
10a	$CDCl_3$	10.1 (s)	163.3	147.1	181.8
10b	$CDCl_3$	10.2 (s)	162.1	147.4	181.3
10c	$CDCl_3$	10.3 (s)	160.5	149.0	180.5
11a	$CDCl_3$	8.7 (s)	162.7	129.9	
11b	$CDCl_3$	8.7 (s)	161.7	130.1	
11c	$CDCl_3$	8.9 (s)	160.4	132.5	
12a	DMSO-d_6	8.1 (s)	155.9	148.1	124.7 (C=N)
13	$CDCl_3$	4.0 (s)	142.7	133.0	129.2
		8.8 (s)			

[a] The aromatic carbon and hydrogen atoms are omitted.

were isolated is 31% yield after chromatography and crystallization from toluene/ether. Thus, methylation occurred at the N-2 position of the thiadiazole.



13



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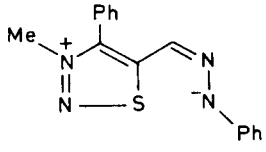


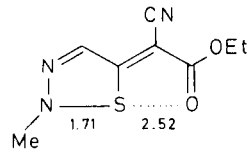
15

The alternative structures **14** and **15** are rejected by a consideration of the nmr spectra (Table 1). Indeed, in the ^{13}C nmr spectra, the thiadiazole C-4 and C-5 resonances of **12a** at δ 155.9 and 148.1 are shifted to δ 142.7 and 133.0 in the product, indicating a structural variation of the ring system. This is not consistent with structure **14**.

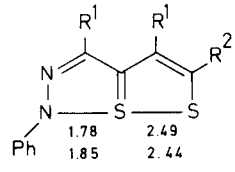
A differentiation between **13** and **15** can be made by inspection of the *N*-methyl absorptions in the spectra. For structure **15** we should expect the *N*-methyl to resonate at about δ 4.4 in the ^{1}H nmr spectrum and at about δ 45 in the ^{13}C nmr spectrum with a coupling constant $^1J_{CH}$ of about 145 Hz [8]. The values found (δ_H = 4.0, δ_C = 37.3, $^1J_{CH}$ = 139.5 Hz), on the contrary, are diagnostic for structure **13**. Furthermore, our product exhibits a multiplet absorption for the phenyl protons attached to the thiadiazole ring due to coplanarity with the heterocycle. For **15**, steric hindrance between the phenyl and methyl substituents would force the phenyl ring to rotate out of the plane of the heterocycle, resulting in a singlet resonance.

Confirmation of structure **13** was obtained by a single crystal X-ray analysis [9], which showed that the molecule adopts a *Z*-confirguration about the exocyclic C=C bond necessary for a thiapentalene structure. The short S...N contact distance (1.97 Å), together with the long S-N bond (1.78 Å) indicates a fairly strong interaction. Furthermore, the N-S...N atoms are located in a nearly linear arrangement (169.1°).

It is interesting to compare the crystallographic data of **13** with those of **16** and **17a,b** which have also a 1,2,3-thiadiazole skeleton [10,11]. The N-S distance in **16** corresponds to a normal covalent bond length, indicating virtually no bonding between sulfur and oxygen. In **13** and **17a,b**, on the contrary, the elongation of the N-S bond points to a thiapentalene structure.



16



17

a : R^1 = Me, R^2 = H

b : R^1 = H, R^2 = t-Bu

EXPERIMENTAL

The heterocycles mentioned below gave ir, ^{1}H nmr, ^{13}C nmr and mass spectra consistent with their structures (see also Table 1). The methylthiadiazoles **6a,b** were prepared by the method of Hurd and Mori [12], whereas **6c** was obtained by nitration of **6a** in 56% yield.

4-Aryl-5-bromomethyl-1,2,3-thiadiazoles **7a-c**.

Compound **6** (50 mmoles), freshly crystallized *N*-bromosuccinimide (1.1 equivalents) and dibenzoyl peroxide (100 mg) were heated in 800 ml of dry carbon tetrachloride for 24 hours. The warm mixture was filtered into 1 liter of water and the organic layer was washed three times with 300 ml of water and dried over magnesium sulfate. The filtrate was evaporated and the residue was crystallized from ether.

5-Bromomethyl-4-phenyl-1,2,3-thiadiazole (**7a**).

This compound was obtained in 47% yield, mp 115°.

Anal. Calcd. for $C_9H_7BrN_2S$ (mol wt 255): C, 42.37; H, 2.76. Found: C, 42.32; H, 2.69.

5-Bromomethyl-4-(*p*-chlorophenyl)-1,2,3-thiadiazole (**7b**).

This compound was obtained in 42% yield, mp 114° (chloroform/ether).

Anal. Calcd. for $C_9H_6BrClN_2S$ (mol wt 289): C, 37.33; H, 2.09. Found: C, 37.23; H, 1.99.

5-Bromomethyl-4-(*p*-nitrophenyl)-1,2,3-thiadiazole (**7c**).

This compound was obtained in 13% yield after chromatographic separation from unreacted **6c** with dichloromethane as the eluent, mp 160°.

Anal. Calcd. for $C_9H_6BrN_3O_2S$ (mol wt 300): C, 36.02; H, 2.01. Found: C, 36.12; H, 2.08.

Note: When 2.2 equivalents of *N*-bromosuccinimide were used in the bromination of **6b,c**, a mixture of the monobromides **7b,c** and the dibromides **8b,c** were obtained which were separated by column chromatography on silica gel with carbon tetrachloride (for **8b**) or dichloromethane (for **8c**) as the eluent.

4-(*p*-Chlorophenyl)-5-dibromomethyl-1,2,3-thiadiazole (**8b**).

This compound was obtained in 21% yield, mp 140° (chloroform/ether).

Anal. Calcd. for $C_9H_5Br_2ClN_2S$ (mol wt 368): C, 29.34; H, 1.37. Found: C, 29.48; H, 1.39.

5-Dibromomethyl-4-(*p*-nitrophenyl)-1,2,3-thiadiazole (**8c**).

This compound was obtained in 15% yield, mp 184° (chloroform/ether).

Anal. Calcd. for $C_9H_5Br_2N_3O_2S$ (mol wt 379): C, 28.52; H, 1.33. Found: C, 28.53; H, 1.25.

4-Aryl-5-azidomethyl-1,2,3-thiadiazoles **9a-c**.

Compound **7** (10 mmoles) was stirred with 4 equivalents of sodium azide at room temperature in a two-phase system of dichloromethane (30 ml)-water (10 ml), containing tetrabutylammonium bromide (0.3 g) and a catalytic amount of sodium iodide. After a reaction time of 12 hours, an aqueous solution of sodium thiosulfate (1 g in 50 ml) was added and the whole mixture was extracted with chloroform. The extracts were dried and after concentration and addition of ether, the product was crystallized by cooling.

5-Azidomethyl-4-phenyl-1,2,3-thiadiazole (**9a**).

This compound was obtained in 68% yield, mp 101° dec.

Anal. Calcd. for $C_9H_7N_5S$ (mol wt 217): C, 49.76; H, 3.25. Found: C, 49.70; H, 3.23.

5-Azidomethyl-4-(*p*-chlorophenyl)-1,2,3-thiadiazole (**9b**).

This compound was obtained in 66% yield, mp 111° dec.

Anal. Calcd. for $C_9H_6ClN_5S$ (mol wt 252): C, 42.95; H, 2.40. Found: C, 43.04; H, 2.38.

5-Azidomethyl-4-(*p*-nitrophenyl)-1,2,3-thiadiazole (**9c**).

This compound was obtained in 67% yield, mp 148° dec.

Anal. Calcd. for $C_9H_6N_6O_2S$ (mol wt 262): C, 41.22; H, 2.31. Found: C, 41.38; H, 2.34.

4-Aryl-1,2,3-thiadiazole-5-carbaldehydes **10a-c**.

A solution of **9** (*ca* 6 mmoles) in 20 ml of concentrated sulfuric acid was stirred at room temperature for 5 days. Then, the mixture was poured into 50 ml of ice-cooled water and the whole was extracted three times with 10 ml of chloroform. The extracts were dried over magnesium sulfate, evaporated and the residue crystallized from ether.

4-Phenyl-1,2,3-thiadiazole-5-carbaldehyde (**10a**).

This compound was obtained in 59% yield, mp 69°.

Anal. Calcd. for $C_9H_6N_2OS$ (mol wt 190): C, 56.82; H, 3.17. Found: C, 56.88; H, 3.21.

4-(*p*-Chlorophenyl)-1,2,3-thiadiazole-5-carbaldehyde (**10b**).

This compound was obtained in 57% yield, mp 136°C.

Anal. Calcd. for $C_9H_5ClN_2OS$ (mol wt 225): C, 48.12; H, 2.24. Found: C, 47.86; H, 2.31.

4-(*p*-Nitrophenyl)-1,2,3-thiadiazole-5-carbaldehyde (**10c**).

This compound was obtained in 83% yield, mp 138°.

Note: No satisfactory elemental analysis could be obtained (Calcd. C, 45.96; H, 2.14. Found: C, 45.24; H, 2.59). Mass spectrum (high resolution): no $M^{+\cdot}$, $M^{+\cdot} - N_2$ at m/z 206.9990 (Calcd. 206.9990).

4-Aryl-1,2,3-thiadiazoles **11a-c**.

A suspension of **10** (3.5 mmoles) in 10 ml of aqueous sodium hydroxide (1*N*) was stirred at room temperature for 15 minutes. The precipitate was filtered off and crystallized from chloroform/ether.

4-Phenyl-1,2,3-thiadiazole (**11a**).

This compound was obtained in 51% yield (100% before crystallization), mp 78° (lit 78° [13]).

4-(*p*-Chlorophenyl)-1,2,3-thiadiazole (**11b**).

This compound was obtained in 55% yield, mp 138°.

Anal. Calcd. for $C_8H_5ClN_2S$ (mol wt 197): C, 48.86; H, 2.56. Found: C, 48.74; H, 2.66.

4-(*p*-Nitrophenyl)-1,2,3-thiadiazole (**11c**).

This compound was obtained as a pale yellow powder in 49% yield and was identical in all respects with the product obtained by nitration of **11a**. It melts at 180° and resolidifies into colourless needles with mp 225-227°.

4-Phenyl-1,2,3-thiadiazole-5-carbaldehyde Phenylhydrazone (**12a**).

A solution of **10a** (1.9 g, 10 mmoles) and phenylhydrazine (1.13 g, 11 mmoles) in 10 ml of methanol containing 0.5 ml of water and 0.2 ml of concentrated hydrochloric acid was refluxed for 10 minutes. Upon cooling **12a** crystallized out, yield 68% after recrystallization from ethanol, mp 178°.

Anal. Calcd. for $C_{15}H_{12}N_4S$ (mol wt 280): C, 64.26; H, 4.31. Found: C, 64.33; H, 4.41.

1-Methyl-3,6-diphenyl-6aλ⁴-thia-1,2,5,6-tetraazapentalene (**13**).

A solution of **12a** (5 mmoles) and methyl fluorosulfonate (10 mmoles) in 50 ml of dichloromethane was stirred at room temperature for 15 hours. Then, ether was added and the precipitated salt, **13**.$HFSO_3$, was filtered off and washed with ether (yield 86%).

The salt (5 mmoles) was dissolved in a mixture of 750 ml of water and 250 ml of methanol, containing sodium carbonate (1.07 g, 10 mmoles) and stirred at room temperature for 15 minutes. The solution was extracted with benzene and the extracts were washed with water and dried over calcium chloride. After removal of the solvent, the residue was chromatographed on silica gel with toluene as the eluent. After concentration of the eluate and addition of ether, red needles of **13** were obtained in 31% yield, mp 142°; ^1H nmr (250 MHz, deuteriochloroform): δ 4.0 (s, 3H, CH_3), 7.2-7.3, 7.4-7.6 and 7.8-7.9 (three m, 10 aromatic H), 8.8 (s, 1H, = CH); ^{13}C nmr (deuteriochloroform): δ 37.3 (CH_3, $^1J_{CH}$ = 139.5 Hz), 129.2 (=CH, $^1J_{CH}$ = 193 Hz), 133.0 (C-5, $^2J_{CH}$

= 14 Hz), 142.7 (C-4, $^3J_{CH}$ = 4 Hz), 134.0 and 145.5 (Ph C-*ipso*), 119.4 and 127.7 (Ph C-*ortho*), 129.0 and 129.4 (Ph C-*meta*), 125.2 and 128.4 (Ph C-*para*).

Anal. Calcd. for $C_{16}H_{14}N_4S$ (mol wt 294): C, 65.28; H, 4.79. Found: C, 65.16; H, 4.66.

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