Synthesis of a Phenylazo-derivative of a 1,2,3-Thiadiazolium methylide. C-13/N-15 NMR Characterization and Crystal Structure Analysis

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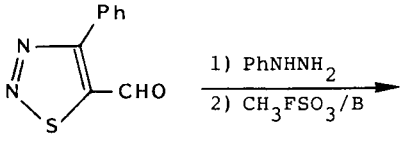
Received August 27, 1990

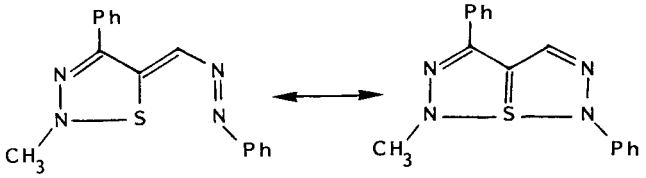
The *N*-phenylhydrazone derived from 4-methoxycarbonyl-1,2,3-thiadiazole-5-carbaldehyde **6** is methylated at the N-3 position, yielding the mesoionic compound **8**. The C-13 and N-15 nmr data, as well as the results from a crystal structure analysis, indicate that the molecule is best represented by the resonance forms **8A** and **8B**. Comparison is made with the previously synthesized thiadiazole derivative **2** which possesses thiapentalene characteristics.

J. Heterocyclic Chem., **28**, 477 (1991).

Methylation of 1,2,3-thiadiazoles can occur either at the N-2 or at the N-3 position [1,2]. In a previous paper we reported that the *N*-phenylhydrazone of 4-phenyl-1,2,3-thiadiazole-5-carbaldehyde **1** is methylated by methyl fluorosulfonate at N-2, yielding a thiadiazole derivative **2** with thiapentalene structural properties [3]. Indeed, the X-ray crystal analysis of **2** indicated a long S-NMe bond (1.78 Å) together with a short S...NPh contact distance (1.97 Å), and a nearly linear N-S...N arrangement (168.1°).



1



2

In continuation of this work we have replaced the phenyl substituent of **1** by an ester function in order to evaluate its effect on the position of methylation of the corresponding hydrazone.

4-Methoxycarbonyl-1,2,3-thiadiazole-5-carbaldehyde **6** was obtained by the sequence outlined in Scheme 1. A similar approach has already been used by Looker and Wilson [4] for the synthesis of the ethyl ester analogue, however, without much success since the product was isolated as an impure oil in low yield. In our hands, **6** was obtained as yellow needles in 47% yield.

The aldehyde **6** was converted into the *N*-phenylhydrazone **7** and then methylated with methyl fluorosulfonate or Meerwein's reagent. In both cases, a dark-red crystalline product was isolated in high yield (80 and 87%), corresponding to the mesoionic structure **8**. Thus, the methyl substituent in **8** is located at a different position from that in **2**. This is evidenced by the *N*-methyl resonances at δ 4.5 in the ^{1}H nmr spectrum and at δ 48 in the ^{13}C nmr spectrum with a coupling constant $^1J_{CH}$ = 145 Hz [5]. In contrast, compound **2** exhibits resonances at δ_H = 4.0 and δ_C = 37.3 with $^1J_{CH}$ = 139.5 Hz. The C-4 absorption of **8** (δ 127.5) is shielded by 18 ppm compared with the hydrazone **7** (δ 145.2), due to an increased electron density at this carbon atom by delocalization of the negative charge (see resonance structures).

The contribution of the two canonical forms **8A** and **8B** is further corroborated by the ^{15}N nmr spectrum (Table 1). Indeed, the hydrazone C=N and NPh nitrogen resonances of **7** at δ 351.9 and 161.4 have shifted downdfield to δ 405.3 and 351.6 respectively in **8**. Their midway position between hydrazones and azo compounds (δ > 500 ppm [6]) is well represented by the resonance forms **8A** and **8B**. Compound **2**, on the contrary, manifests two amino nitrogen resonances (δ 256.6 and 287.3) as well as two imine nitrogen resonances (δ 367.3 and 362.1) in consonance with a thiapentalene structure (Table 1). Further-

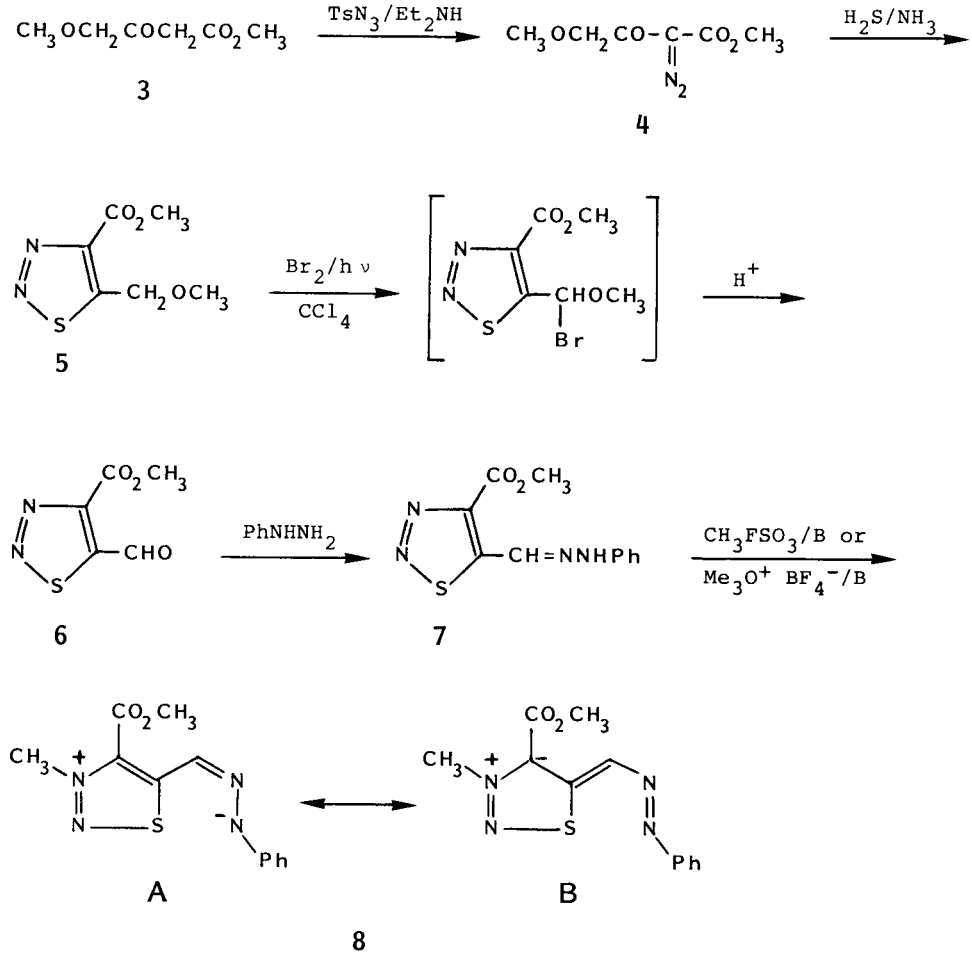
Table 1

^{15}N NMR Data [a] for 2 and 8 in Deuteriochloroform

Compound [b]	N-2	N-3	N-7 ($^2J_{NH}$Hz)	N-8 ($^3J_{NH}$Hz)
2	256.5	367.3	362.1 (11.5)	287.3 (3)
8	362.4	257.5	405.3 (11.5)	351.6

[a] δ Values from liquid ammonia quoted, using nitromethane as external reference. [b] The numbering used is shown in Figure 1.

Scheme 1



more, the large values of the $^2J_{NH}$ coupling constants for N-7 in both **2** and **8** reveal a *cis*-orientation of hydrogen with the nitrogen lone pair [7]. In contrast, **7** exists in the *E*-configuration ($^2J_{CH} \leq 2$ Hz).

A single crystal X-ray analysis of **8** has been carried out and confirms the *Z*-configuration about the C6-N7 bond (Figure 1). The heteroallyl substituent (C6-N7-N8) is coplanar with the thiadiazole ring with a maximum deviation from the best plane through the eight atoms of 0.03 Å. The phenyl ring is twisted 3° out of this plane. The N2-S1...N8 system is nearly linear (170°) and consists of a normal covalent S1-N2 bond (1.70 Å) and a weakly interacting S1...N8 contact (2.21 Å). The equal C4-C5 and C5-C6 bond lengths (1.40 Å) provide further evidence that both **A** and **B** contribute to the structure of **8**.

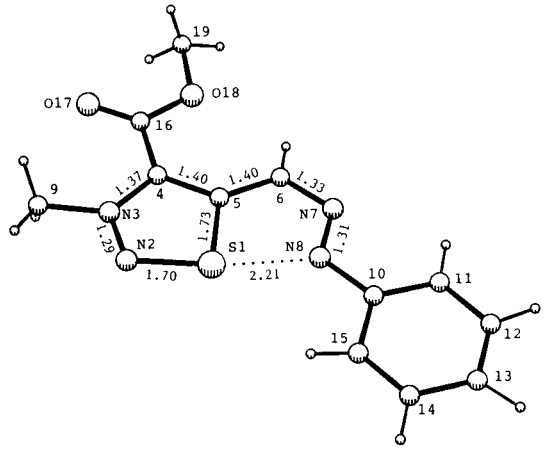
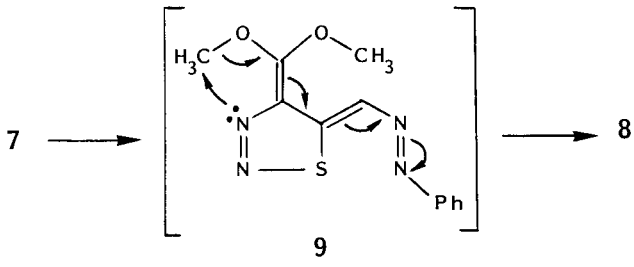


Figure 1. Molecular structure of **8** with numbering scheme and selected bond lengths.

The different behavior of the *N*-phenylhydrazones of **1** and **6** upon methylation is striking and needs clarification. Since this is due only to the replacement of the phenyl by an ester substituent at the 4-position, we may assume that methylation of **7** first occurs at the ester function to give the transient product **9**, followed by an isomerization to **8**. This mechanism cannot operate for the *N*-phenylhydrazone of **1**, where the position of methylation is dictated by

the peculiar thiapentalene stabilization of **2**. It should be noted, however, that methylation at N-3 may have occurred to some extent but escaped isolation, since **2** was obtained only in 31% yield (after extraction, chromatography and crystallization).



EXPERIMENTAL

The ^1H and ^{13}C nmr spectra were recorded on a Bruker WM-250 spectrometer at 250 and 62.9 MHz, respectively, using a 5 mm dual probe. The chemical shifts are reported in ppm relative to TMS as an internal reference.

Natural abundance ^{15}N nmr spectra were recorded on a Brucker WM-250 spectrometer, operating at 25.35 MHz, and equipped with a selective ^{15}N 10 mm probe. The chemical shifts were determined with respect to external nitromethane contained in a 4 mm capillary held centrally in the sample tube. This reference was given a δ value of 380.2 ppm, thus converting the N chemical shifts to the liquid ammonia shielding scale. The spectra of the products were recorded in deuteriochloroform using *ca* 0.2 molar solutions.

The DEPT pulse sequence based on polarization transfer through long-range coupling ($^2J_{NH}$ and $^3J_{NH}$) was used to detect the nitrogens two or three bonds away from the aromatic and aliphatic protons.

Typical acquisition parameters for the DEPT sequence are: spectral width 12.5 KHz (δ 550 → 50 ppm), pulse angle 45°, delay time .05 sec (^nJ = 10 Hz), number of scans 10000 for the ^1H coupled spectra.

The assignment of the nitrogen absorptions of **2** was based on the multiplicity patterns. In the case of **8**, a DEPT spectrum with selective decoupling of the NCH_3 protons was also recorded in order to assign unambiguously N-2 and N-3.

4-Methoxycarbonyl-1,2,3-thiadiazole-5-carbaldehyde (**6**).

To an ice-cooled solution of **3** (21.4 g, 146 mmoles) and tosyl azide (28.8 g, 146 mmoles) in ether (100 ml) was added diethylamine (10 ml) and the whole was stirred at 0° for 15 minutes and then at room temperature for 30 minutes. Upon addition of *n*-pentane (150 ml), tosyl amide precipitated and was removed by filtration. The filtrate was evaporated and flash-chromatographed on silica gel with ether-light petroleum (1:1) as the eluent to give methyl methoxyacetyldiazoacetate (**4**) as a pale yellow liquid in 56% yield (14 g).

This compound (7.7 g, 45 mmoles) was cooled to 0° and concentrated ammonium hydroxide (15 ml) was added dropwise for 30 minutes under a continuous stream of hydrogen sulfide. The precipitated 4-ethoxycarbonyl-5-methoxymethyl-1,2,3-thiadiazole (**5**) was filtered off and purified by column chromatography on silica gel with ether as the eluent, yield 79% (6.7 g), mp 48°.

A solution of **5** (2.8 g, 14.9 mmoles) and bromine (2.8 g, 17.8 mmoles) in dry carbon tetrachloride (40 ml) was refluxed for 24 hours under continued illumination with a 500 watt light. After removal of the solvent, the residual oil was chromatographed on silica gel with ether as the eluent. The ether eluates were concentrated, treated with a few drops of light petroleum and cooled to give **6** as yellow needles in 47% yield (1.2 g), mp 45-46°; ir (potassium bromide): 1730 and 1680 cm^{-1} (s, CO); ^1H nmr (deuteriochloroform): δ 4.1 (s, 3H, OCH_3), 10.7 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): δ 53.6 (OCH_3, $^1J_{CH}$ = 148.5 Hz), 151.4 (C-4), 157.4 (C-5, $^2J_{CH}$ = 34.5 Hz), 159.9 (COO, $^3J_{CH}$ = 4 Hz), 182.0 (CHO, $^1J_{CH}$ = 201 Hz); ms: m/z (%) 172 (0.4, $M^{+\cdot}$), 141 (10, $M^{+\cdot}$ -OMe), 116 (23, $M^{+\cdot}$ -N_2 -CO), 98 (9), 85 (100, $M^{+\cdot}$ -COOMe -N_2), 71 (49), 57 (64), 45 (32).

Anal. Calcd. for $C_5H_4N_2O_3S$ (mol wt 172): C, 34.89; H, 2.34. Found: C, 34.88; H, 2.45.

Table 2
Atomic Coordinates (x10^4) and Equivalent Temperature Factors (Å^2)

$$B_{eq} = (8/3)\pi^2\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \vec{a_i}\,\vec{a_j}$$

	x/a	y/b	z/c	B_{eq}
S1	2112(1)	616(0)	407(0)	3.67(1)
N2	2535(2)	599(1)	1952(2)	4.08(3)
N3	3236(2)	-124(1)	2272(1)	3.58(3)
C4	3460(2)	-727(1)	1375(2)	3.34(3)
C5	2901(2)	-415(1)	220(2)	3.23(3)
C6	2942(3)	-781(1)	-960(2)	3.66(3)
N7	2386(2)	-328(1)	-1930(1)	3.65(3)
N8	1832(2)	431(1)	-1609(1)	3.62(3)
C9	3771(4)	-205(2)	3583(2)	4.75(4)
C10	1190(2)	967(1)	-2549(2)	3.63(3)
C11	1001(3)	744(2)	-3774(2)	4.47(4)
C12	301(4)	1326(2)	-4612(2)	5.55(5)
C13	-226(3)	2127(2)	-4240(2)	5.35(4)
C14	-6(4)	2360(2)	-3024(3)	5.63(5)
C15	705(3)	1793(1)	-2188(2)	4.97(4)
C16	4167(2)	-1575(1)	1701(2)	3.69(3)
O17	4560(3)	-1809(1)	2711(2)	5.64(3)
O18	4308(3)	-2054(1)	694(1)	5.19(3)
C19	4969(5)	-2912(2)	882(3)	6.46(6)

Table 3
Bond Lengths (Å)

N2-S1	1.700(2)	C5-S1	1.734(2)
N8-S1	2.209(2)	N3-N2	1.294(2)
C4-N3	1.367(2)	C9-N3	1.477(2)
C5-C4	1.403(3)	C16-C4	1.475(3)
C6-C5	1.401(3)	N7-C6	1.331(3)
N8-N7	1.309(2)	C10-N8	1.402(2)
C11-C10	1.378(3)	C15-C10	1.402(3)
C12-C11	1.388(3)	C13-C12	1.377(4)
C14-C13	1.375(4)	C15-C14	1.374(3)
O17-C16	1.188(2)	O18-C16	1.329(2)
C19-O18	1.448(3)		

4-Methoxycarbonyl-3-methyl-1,2,3-thiadiazolium-5-phenylazomethylide (**8**).

A solution of **6** (1 g, 5.8 mmoles) and phenylhydrazine (0.62 g), (5.8 mmoles) in methanol (20 ml) containing 1 ml of acetic acid was refluxed for 10 minutes. Upon cooling, **7** crystallized out as orange needles in 79% yield (1.2 g), mp 198°; ir (potassium bromide): 3230 (m), 1730 cm^{-1} (s, CO); ^1H nmr (dimethyl sulfoxide-d_6, 250 MHz): δ 4.0 (s, 3H, OCH_3), 6.95 (t), 7.10 (d) and 7.35 (t) (5 aromatic H), 8.6 (s, 1H, CH=N), 11.7 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 52.4 (OCH_3), 113.1, 121.5, 129.3 and 142.9 (Ph C_o, C_p, C_m and C_i), 125.3 (CH=N, $^1J_{CH}$ = 178 Hz), 145.2 (C-4), 159.3 (C-5), 160.7 (CO); ^{15}N nmr (dimethyl sulfoxide-d_6): δ 161.4 (NPh), 351.9 (C=N, $^2J_{NH} \leq 2$ Hz, *E*-configuration).

This compound (0.5 g, 1.9 mmoles) was stirred with methyl fluorosulfonate (0.3 ml, 3.8 mmoles) in dry dichloromethane (20 ml) at room temperature for 15 hours. After addition of ether, a precipitate of **8**.$HFSO_3$ was obtained (0.7 g).

This salt (0.7 g, 1.86 mmoles) was dissolved in water-methanol (400 ml, 3:1), containing an excess of sodium carbonate (0.5 g), and the whole was stirred at room temperature for 15 minutes. The precipitated **8** was filtered off and dried, yield 80% (0.42 g), mp 141-142° (dark-red needles from methanol); ir (potassium bromide): 1720 cm^{-1} (s, CO); ^1H nmr (deuteriochloroform, 250 MHz): δ 4.05 (s, 3H, OCH_3), 4.5 (s, 3H, NCH_3), 7.15 (t), 7.40 (t) and 7.70 (d) (5 aromatic H), 8.8 (s, 1H, CH=); ^{13}C nmr (deuteriochloroform): δ 48.0 (NCH_3, $^1J_{CH}$ = 145 Hz), 52.7 (OCH_3), 118.9, 125.0, 129.2 and 149.5 (Ph C_o, C_p, C_m and C_i), 124.9 (CH=N, $^1J_{CH}$ = 195 Hz), 127.5 (C-4), 139.3 (C-5, $^2J_{CH}$ = 13.5 Hz), 159.9 (CO).

Anal. Calcd. for $C_{12}H_{12}N_4O_2S$ (mol wt 276): C, 52.16; H, 4.38. Found: C, 52.20; H, 4.37.

Note: Compound **8** was also obtained when **7** (0.5 g, 1.91 mmoles) was treated with trimethyloxonium tetrafluoroborate (0.3 g, 2 mmoles) in dry dichloromethane (20 ml) at room temperature for 24 hours and then worked up as described above, yield 87%.

Table 4
Bond Angles (°)

C5-S1-N2	92.2(1)	N8-S1-N2	170.1(1)
N8-S1-C5	78.0(1)	N3-N2-S1	110.4(1)
C4-N3-N2	117.9(2)	C9-N3-N2	116.0(2)
C9-N3-C4	126.1(2)	C5-C4-N3	110.7(2)
C16-C4-N3	120.0(2)	C16-C4-C5	129.2(2)
C4-C5-S1	108.7(1)	C6-C5-S1	119.9(2)
C6-C5-C4	131.4(2)	N7-C6-C5	119.4(2)
N8-N7-C6	112.0(2)	N7-N8-S1	110.7(1)
C10-N8-S1	131.8(1)	C10-N8-N7	117.4(2)
C11-C10-N8	125.3(2)	C15-C10-N8	116.1(2)
C15-C10-C11	118.6(2)	C12-C11-C10	119.8(2)
C13-C12-C11	121.1(2)	C14-C13-C12	119.3(2)
C15-C14-C13	120.1(2)	C14-C15-C10	121.0(2)
O17-C16-C4	125.8(2)	O18-C16-C4	110.1(2)
O18-C16-O17	124.1(2)	C19-O18-C16	116.1(2)

Crystal Structure Analysis of **8**.

Compound **8** crystallized from methanol in the space group $P2_1/c$ with a = 7.428(1), b = 15.705(2), c = 10.820(2) Å, β = 90.28(1)°, V = 1262.2(3) $Å^3$, Z = 4, D_x = 1.45 gcm^{-3}. Intensities from a parallelepiped crystal 0.43 x 0.12 x 0.05 mm were measured using a Huber 4-circle diffractometer with graphite-monochromatized CuK_α-radiation (λ = 1.54178 Å). Of the 2264 independent reflections with $\sin\theta/\lambda \leq 0.60$ $Å^{-1}$, 1959 had $I \geq 2.5\sigma(I)$ and were considered as observed. The structure was solved by direct methods (SHELXS 86) [8] and refined by least squares methods [9] to an R-value of 0.042 for the observed reflections. Atomic coordinates, bond lengths and angles are given in Tables 2, 3 and 4. Figure 1 shows a stereoscopic view of the molecule with selected bond lengths.

Acknowledgement.

We thank Professor W. D. Ollis for suggesting the name of the new mesoionic compound **8**. A. F. is indebted to the I.W.O.N.L. (Belgium) for a fellowship. Financial support from the N.F.W.O., F.N.R.S. and the "Ministerie voor Wetenschapsbeleid" is gratefully acknowledged.

REFERENCES AND NOTES

[1] E. W. Thomas in Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, Vol **6**, p 447.

[2] S. Brückner, G. Fronza, L. M. Giunchi, V. A. Kozinski and O. V. Zelenskaja, *Tetrahedron Letters*, **21**, 2101 (1980); S. Auricchio, S. Brückner, L. M. Giunchi, V. A. Kozinsky and O. V. Zelenskaja, *J. Heterocyclic Chem.*, **17**, 1217 (1980); K. Masuda, J. Adachi, H. Nate, H. Takahata and K. Nomura, *J. Chem. Soc., Perkin Trans. I*, 1591 (1981); K. Masuda, J. Adachi, H. Morita and K. Nomura, *Chem. Pharm. Bull.*, **29**, 1743 (1981).

[3] G. L'abbé, A. Frederix, and J.-P. Declercq, *Bull. Soc. Chim. Belg.*, **98**, 949 (1989); G. L'abbé and A. Frederix, *J. Heterocyclic Chem.*, **27**, 1415 (1990).

[4] J. H. Looker and L. W. Wilson, *J. Heterocyclic Chem.*, **2**, 348 (1965).

[5] G. L'abbé, P. Vangheluwe, S. Toppet, G. S. D. King and L. Van Meervelt, *Bull. Soc. Chim. Belg.*, **93**, 405 (1984).

[6] N. A. Porter, G. R. Dubay and J. G. Green, *J. Am. Chem. Soc.*, **100**, 920 (1978); G. C. Levy and R. L. Lichter in Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy, Wiley-Interscience, New York, 1979, p 93.

[7] B. C. Chen, W. von Philipsborn and K. Nagarajan, *Helv. Chim. Acta*, **66**, 1537 (1983); W. von Philipsborn and R. Müller, *Angew. Chem., Int. Ed. Engl.*, **25**, 383 (1986).

[8] G. M. Sheldrick in Crystallographic Computing 3, G. M. Sheldrick, C. Kruger and R. Goddard, eds, Oxford University Press, 1985, pp 175-189.

[9] G. M. Sheldrick, SHELX 76, Program for Crystal Structure Determination, University of Cambridge, England, 1976.