Methylation of 1,2,3-Thiadiazole 5-Oximes and 5-*N*-Phenylhydrazones

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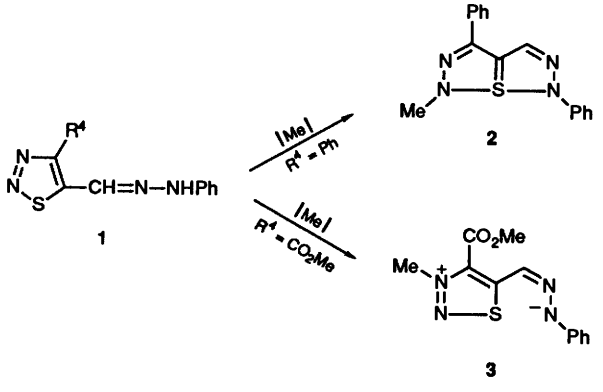
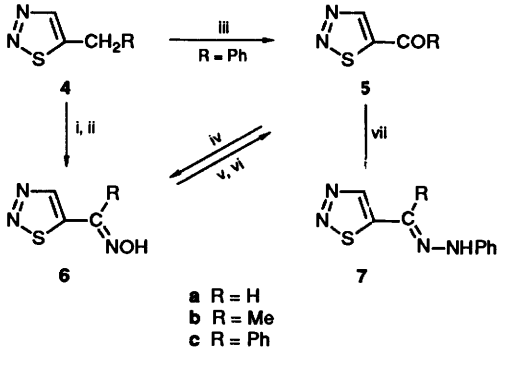
1,2,3-Thiadiazoles unsubstituted at the 4-position and bearing an oxime or phenylhydrazone function at the 5-position have been prepared and treated with Meerwein's reagent. In all cases studied, preferential methylation occurs at N-3 yielding the mesoionic compounds **9** and **12**. The parent oxime **6a** also furnishes the N-2 methylated product **8a** in substantial amounts. In contrast, when the methylation of oxime **6a** is carried out with diazomethane or with methyl iodide, the nitrone **10a** and the oxime ether **11a** are formed. The isomeric structures of the reaction products were distinguished by their ^{13}C NMR and mass spectra.

We have previously reported[1,2] that 1,2,3-thiadiazole-5-carbaldehyde phenylhydrazones **1** are methylated either at N-2 or N-3, depending on the nature of the R^4 substituent, Thus, the tetraazathiapentalene **2** is obtained from compound **1** when R^4 = Ph, whereas the mesoionic compound **3** results when R^4 is an ester function.



Since thiapentalenes[3] and mesoionic compounds[4] are of general interest, we have extended this research to the methylation of 1,2,3-thiadiazole 5-oximes and compared the results with those of the corresponding *N*-phenylhydrazones. In all cases studied the thiadiazole ring was unsubstituted at the 4-position.

The known parent oxime **6a**[5] was prepared by the reported procedure of nitrosation of 5-methyl-1,2,3-thiadiazole **4a** with isopentyl nitrite in the presence of potassium ethoxide (Scheme 1). This compound was identified as the *Z*-isomer since the



Scheme 1 *Reagents:* i, $C_5H_{11}{}^iONO$–EtOK; ii, HCl; iii, CrO_3 or $K_2Cr_2O_7$; iv, NH_2OH; v, $NaHSO_3$; vi, HCl; vii, $PhNHNH_2$

NMR spectrum in dimethyl sulfoxide solution shows an imine ($^1J_{CH}$ 188 Hz)[6] and a C-5 resonance (δ_C 139) which is shifted upfield by *ca.* 14 ppm compared with 1,2,3-thiadiazole-5-carbaldehyde **5a** (δ_C 153.3 in $CDCl_3$) due to a combination of the substituent (*ca.* 4 ppm) and the γ-effect (*ca.* 10 ppm).[7] The aldehyde **5a** was obtained from the oxime **6a** by cleavage with sodium bisulfite.[8]

Compound **6b** was similarly prepared by nitrosation of the readily available thiadiazole **4b** and transformed into the ketone **5b** by the bisulfite method. In the case of compound **6c**, the active methylene compound **4c** was oxidized to the ketone **5c** and then converted into the oxime **6c**. The NMR spectra in dimethyl sulfoxide solution revealed that the oximes **6b** and **6c** are present in the *Z*-configuration (γ-effect of C-5) although small amounts of the *E*-isomers are also observed.

The *N*-phenylhydrazones **7a–c**, derived from the aldehyde **5a** or the ketones **5b, c** by treatment with phenylhydrazine, were found to exist exclusively in the *E*-configuration. For instance, compound **7a** manifests in the ^{13}C NMR spectrum an imine ($^1J_{CH}$ 171 Hz),[6] and a C-5 absorption (δ_C 153) at the same position as that of the aldehyde **5a**. The spectral data are summarized in Table 1.

Methylation of the parent oxime **6a** with 1.1 equiv. of Meerwein's reagent in dichloromethane, followed by deprotonation of the resulting salts, furnished the N-2 methyl derivative **8a** and the mesoionic compound **9a** in 13.5 and 25% yields respectively after chromatographic separation. According to the NMR spectrum of the crude reaction mixture, 26.5% of compound **8a** (δ 4.0) and 47% of **9a** (δ 4.5) were present in addition to 26.5% of a two-fold methylated product (δ 4.2 and 4.7) which could not be isolated.

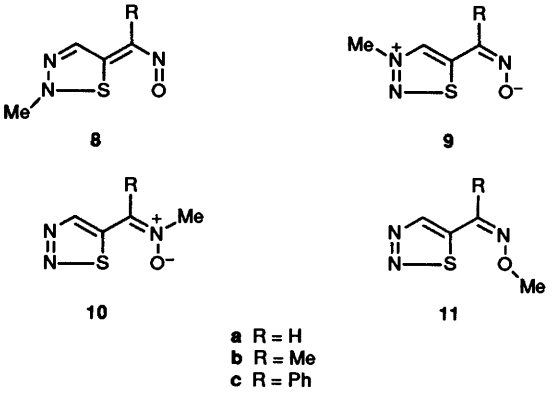
In contrast, when the methylation of oxime **6a** was carried out with an excess of diazomethane in diethyl ether, the nitrone **10a** and the oxime ether **11a** were obtained as the sole reaction products in 19 and 39% yield (ratio 1:2 by NMR). The same products, but in reversed proportion (ratio *ca.* 2:1 by NMR), were obtained when compound **6a** was refluxed with an excess of methyl iodide in acetonitrile; compounds **10a** and **11a** were isolated in 28 and 18% yields, respectively. From these results we conclude that the nature of the methylating reagent has a dramatic influence on the position of attack at the heterocycle.

The ketoximes **6b** and **6c** failed to give N-2 methylated derivatives when treated with 1.5 equiv. of Meerwein's reagent, but furnished preferentially the mesoionic compounds **9b, c**, isolated in 41–42% yield. In the case of the oxime **6b**, a small amount (<2%) of the impure nitrone **10b** was also isolated.

The structures of the reaction products were elucidated on the basis of their NMR and mass spectra. Thus, compound **8a** does not show a $M^{\bullet+} - N_2$ fragment typical of thiadiazoles in the

Table 1 Selected ^{13}C chemical shifts of the heterocycles

Compd.	Solvent	C-4	C-5	C=O	C=N	Me
5a	$CDCl_3$	149.8	153.3	179.3		
5b	$CDCl_3$	148.1	154.7	187.8		29.7
5c	$CDCl_3$	149.0	153.1	184.5		
6a(*Z*)	$(CD_3)_2SO$	149.4	139.0		135.9	
6b(*Z*)	$(CD_3)_2SO$	148.3	140.3		142.7	18.2
6c(*Z*)	$(CD_3)_2SO$	148.9	140.4		146.7	
7a(*E*)	$(CD_3)_2SO$	144.9	153.6		124.8	
7b(*E*)	$(CD_3)_2SO$	144.0	158.2		132.3	14.3
7c(*E*)	$(CD_3)_2SO$	144.5	157.1		134.1	
8a	$CDCl_3$	135.8	139.1		140.3 (C–N)	38.4
9a	$(CD_3)_2SO$	134.9	142.4		137.3	45.9
9b	$(CD_3)_2SO$	134.6	142.8		143.8	15.5, 45.9
9c	$(CD_3)_2SO$	135.2	141.7		148.9	45.9
10a	$(CD_3)_2SO$	148.0	142.3		128.2	51.4
10b	$(CD_3)_2SO$	148.8	144.3		135.7	15.8, 47.9
11a	$CDCl_3$	149.0	139.3		135.0	63.4
12a	$CDCl_3$	128.5	140.9		121.8	45.3
12b	$CDCl_3$	127.7	139.1		130.1	18.0, 45.6
12c	$(CD_3)_2SO$	131.2	138.8		132.6	45.4



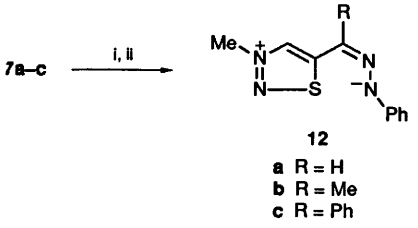
mass spectrum; instead a prominent peak at *m/z* 43 (71%) is present, attributable to MeN_2^+ or $CHNO^{\bullet+}$. That the methyl substituent is located on the thiadiazole ring is also evident from the position of the C-4 resonance in the ^{13}C NMR spectrum, which has shifted from δ 149.4 in **6a** to δ 135.8 in **8a** (Table 1). This shielding of *ca.* 14 ppm indicates a structural variation of the ring skeleton. The methyl group is located on N-2 since its carbon atom (δ 38.4) does not couple with 4-H.

The mesoionic compounds **9a**, **b**, **c** also lack the $M^{\bullet+} - N_2$ fragment in their mass spectra, but show an abundant *m/z* 43 peak for MeN_2^+. In the ^{13}C NMR spectra, the C-4 atoms are shifted upfield compared with the oximes **6a–c** (see Table 1), and the *N*-methyl carbons resonate as a double quartet due to coupling with 4-H ($^3J_{CH} \cong 1.5$ Hz). Furthermore, the positions of the methyl hydrogens (δ 4.5) and methyl carbon resonances (δ 46), as well as the $^1J_{CH}$ coupling constants (144 Hz) agree with values published for similar mesoionic compounds.[2,9]

The nitrone **10a** exhibits the expected $M^{\bullet+} - N_2$ fragment at *m/z* 115 (13%) as well as a diagnostic peak at *m/z* 42 (100%) for $H\overset{+}{C}{=}NMe$ in the mass spectrum. In the ^{13}C NMR spectrum, the methyl resonates as a double quartet at δ 51.4 ($^1J_{CH}$ 143 Hz, $^3J_{CH}$ 2 Hz). The *Z*-configuration of nitrone **10a** was determined by a homonuclear NOE experiment. Thus, selective irradiation of the R hydrogen atom at δ 8.93 causes an increase of the 4-H (δ 9.4) and methyl hydrogens (δ 3.98), indicating a *cis* relationship of these atoms.

The structure of the oxime ether **11a** was easily established on the basis of the similarity of the C-4 (δ 149), C-5 (δ 139) and C=N (δ 135) carbon resonances with those of **6a**, and on the position of the OCH_3 resonance at δ_C 63. In the mass spectrum, fragments are observed at *m/z* 115 (26%) for $M^{\bullet+} - N_2$ and at *m/z* 45 (88%) for $MeON^{\bullet+}$.

For comparison with the nitrones we have also methylated the hydrazones **7a–c** with Meerwein's reagent in dichloromethane. In all cases single products were obtained in high yields, to which the mesoionic structures **12a–c** are assigned on the basis of criteria discussed above for compounds **9a–c** (Table 1). The upfield shielding of the C-4 resonances (δ 128–131), compared with the starting hydrazones (δ 144–145), indicates an increased electron density at this carbon atom by delocalization of the negative charge.



Scheme 2 *Reagents:* i, Me_3OBF_4; ii, K_2CO_3

Experimental

IR spectra were recorded on a Perkin-Elmer spectrometer, ^1H and ^{13}C NMR spectra on a Bruker WM-250 or AMX-400 spectrometer, and mass spectra (EI) on a Kratos MS50 TC instrument operating at 70 eV.

The known thiadiazoles **4a–c** were prepared by the method of Hurd and Mori,[10] and the oxime **6a** by the procedure of Benschop.[5]

1,2,3-*Thiadiazole-4-carbaldehyde* **5a**.—To a solution of oxime **6a** (1.29 g, 10 mmol) in ethanol (40 cm^3) was added aqueous sodium bisulfite (2.6 g in 10 cm^3), and the whole was refluxed overnight. After removal of the solvent, the residue was mixed with concentrated hydrochloric acid (20 cm^3) and dichloromethane (20 cm^3) and stirred for 60 h. The dichloromethane layer was collected and the aqueous phase was further extracted with dichloromethane (20 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated to give the aldehyde **5a** (0.56 g, 49%) as an oil; ν_{max}(neat)/cm^{-1} 1690s (CO); $\delta_H(CDCl_3)$ 9.2 (1 H, br s, 4-H) and 10.3 (1 H, br s, CHO); $\delta_C(CDCl_3)$ 149.8 (C-4, $^1J_{CH}$ 192), 153.3 (C-5, $^2J_{CH}$ 13, 34) and 179.3 (CO, $^1J_{CH}$ 189, $^3J_{CH}$ 2); *m/z* 114 ($M^{\bullet+}$, 1.5%), 86 ($M^{\bullet+} - N_2$ or CO, 29), 85 (12), 58 ($M^{\bullet+} - N_2 - CO$, 100) and 57 (68) ($M^{\bullet+}$, 113.9888. $C_3H_2N_2OS$ requires *M*, 113.9887).

5-*Acetyl*-1,2,3-*thiadiazole* **5b**.—This compound was similarly prepared from the oxime **6b** and purified by column chromatography on silica gel with diethyl ether as the eluent (yield 47%); ν_{max}(neat)/cm^{-1} 1700s (CO); $\delta_H(CDCl_3)$ 2.71 (3 H, s, Me) and 9.04 (1 H, s, 4-H); $\delta_C(CDCl_3)$ 29.7 (Me, $^1J_{CH}$ 129), 148.1 (C-4, $^1J_{CH}$ 192), 154.7 (C-5, $^2J_{CH}$ 13, $^3J_{CH}$ 1.6) and 187.8 (CO, $^2J_{CH}$ 6.5, $^3J_{CH}$ 1); *m/z* 128 ($M^{\bullet+}$, 2%), 100 ($M^{\bullet+} - N_2$, 2), 58 (14) and 43 ($MeCO^+$, 100).

5-*Benzoyl*-1,2,3-*thiadiazole* **5c**.—A solution of compound **4c** (1.76 g, 10 mmol) in acetic acid (5 cm^3) was mixed with chromium trioxide (2 g, 20 mmol) dissolved in acetic acid–water (5:3 cm^3) and refluxed for 4 h. The reaction mixture was poured into water (100 cm^3) and extracted three times with dichloromethane (50 cm^3). The combined extracts were washed with aqueous sodium hydroxide (2 g in 150 cm^3), dried ($MgSO_4$) and evaporated to give ketone **5c** (1.28 g, 67%), m.p. 80 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 1645s (CO); $\delta_H(CDCl_3)$ 7.5–7.95 (5 H, 3 m, Ph) and 9.07 (1 H, s, 4-H); $\delta_C(CDCl_3)$ 129.0, 129.2,

134.4 and 136.6 (Ph), 149.0 (C-4, $^1J_{CH}$ 194), 153.1 (C-5, $^2J_{CH}$ 13) and 184.5 (CO); *m/z* 190 ($M^{\bullet+}$, 2%), 105 ($PhCO^+$, 100) and 77 (Ph^+, 55) (Found: C, 56.7; H, 3.1. $C_9H_6N_2OS$ requires C, 56.84; H, 3.16%).

Methyl 1,2,3-*Thiadiazol-5-yl Ketone Oxime* **6b**.—To a solution of potassium (1.6 g, 40 mmol) in absolute ethanol–diethyl ether (7:10 cm^3) was added at −5 °C isopentyl nitrite (2.6 g, 22 mmol) and compound **4b** (2.3 g, 20 mmol), and the whole was stirred at room temperature for 3 h. The precipitated yellow potassium salt was dissolved in water and then acidified with aqueous hydrochloric acid (1 mol dm^{-3}) to pH 3. The precipitate was filtered off and dried to give the oxime **6b** (1.76 g, 61%), m.p. 194 °C (EtOH–H_2O); δ_H[$(CD_3)_2SO$]: *Z*-isomer; 2.5 (3 H, s, Me), 9.4 (1 H, s, 4-H) and 11–14 (br, OH); *E*-isomer; 2.4 (s) and 9.2 (s) (*Z*:*E* 8:1); δ_C[$(CD_3)_2SO$]: *Z*-isomer; 18.2 (Me, $^1J_{CH}$ 129.5), 140.3 (C-5, $^2J_{CH}$ 13, $^3J_{CH}$ 3.5), 142.7 (C=N, $^2J_{CH}$ 7, $^3J_{CH}$ 1) and 148.3 (C-4, $^1J_{CH}$ 192); *E*-isomer; 12.6 (Me) and 146.0 (C-4); *m/z* 143 ($M^{\bullet+}$, 28%), 115 (10), 85 ($M^{\bullet+}$ − MeC=NOH, 58), 74 (96), 58 (30) and 57 ($MeC{\equiv}NO^{\bullet+}$, 100) (Found: C, 33.5; H, 3.4. $C_4H_5N_3OS$ requires C, 33.56; H, 3.52%).

Phenyl 1,2,3-*Thiadiazol-5-yl Ketone Oxime* **6c**.—Compound **5c** (2 g, 10.5 mmol) and aqueous sodium acetate (1 g in 10 cm^3) were added to a solution of hydroxylamine hydrochloride (1 g, 14.4 mmol) in ethanol (100 cm^3), and the whole was refluxed for 1 h. Then, water (100 cm^3) was added to the hot reaction mixture and the oxime **6c** (1.69 g, 78%) was obtained upon cooling, m.p. 229 °C (decomp.) (EtOH); δ_H[$(CD_3)_2SO$] 7.5–7.7 (5 H, m, Ph), 9.0 (1 H, s, 4-H), 13.85 (1 H, br, OH) [Note: the *E*-isomer is also present in small amounts, δ_H 9.45 (4-H)]; δ_C[$(CD_3)_2SO$] 128.5, 128.8, 129.7 and 134.1 (Ph), 140.4 (C-5, $^2J_{CH}$ 13), 146.7 (C=N) and 148.9 (C-4, $^1J_{CH}$ 193); *m/z* 205 ($M^{\bullet+}$, 23%), 160 ($M^{\bullet+}$ − N_2 − OH, 28), 147 (42), 116 (34), 104 (100) and 77 (Ph^+, 100) (Found: C, 52.7; H, 3.3. $C_9H_7N_3OS$ requires C, 52.67; H, 3.44%).

Synthesis of the Hydrazones **7a–c**.—*General procedure.* To a warm solution of compound **5** (5 mmol) in ethanol (10 cm^3) was added phenylhydrazine (1 equiv.) and acetic acid (1 drop). The reaction mixture was left overnight at room temperature to give crystals of the hydrazone **7**.

1,2,3-*Thiadiazole-5-carbaldehyde phenylhydrazone* **7a**. Yield 78%, m.p. 184 °C (EtOH); δ_H[$(CD_3)_2SO$] 6.8–7.4 (5 H, t + d + t, Ph), 8.20 (1 H, s, CH=N), 9.05 (1 H, s, 4-H) and 11.2 (1 H, br, NH); δ_C 112.6, 120.4, 129.1 and 143.6 (Ph), 124.8 (CH=N, $^1J_{CH}$ 171), 144.9 (C-4, $^1J_{CH}$ 192) and 153.6 (C-5, $^2J_{CH}$ 13); *m/z* 204 ($M^{\bullet+}$, 100%), 175 ($M^{\bullet+}$ − N_2 − H, 42), 148 ($M^{\bullet+}$ − 2 N_2, 22), 131 (24), 123 ($PhNS^{\bullet+}$, 27), 117 (21), 105 (PhN_2^+, 15), 91 ($PhN^{\bullet+}$, 37.5), 77 (Ph^+, 70) and 65 (61) (Found: C, 53.1; H, 4.0. $C_9H_4N_4S$ requires C, 52.93; H, 3.95%).

5-*Acetyl*-1,2,3-*thiadiazole phenylhydrazone* **7b**. Yield 63%, m.p. 123 °C; δ_H[$(CD_3)_2SO$] 2.38 (3 H, s, Me), 6.8–7.4 (5 H, 2 m, Ph), 9.05 (1 H, s, 4-H) and 9.94 (1 H, s, NH); δ_C[$(CD_3)_2SO$] 14.3 (Me, $^1J_{CH}$ 129), 113.2, 120.4, 129.1 and 144.4 (Ph), 132.3 (C=N), 144.0 (C-4, $^1J_{CH}$ 191) and 158.2 (C-5, $^2J_{CH}$ 13, $^3J_{CH}$ 4); *m/z* 218 ($M^{\bullet+}$, 84%), 189 ($M^{\bullet+}$ − N_2 − H, 15), 157 (11), 148 (20), 123 (35), 105 (PhN_2^+, 44), 91 ($PhN^{\bullet+}$, 52), 85 (29), 77 (Ph^+, 100) and 65 (69) (Found: C, 55.15; H, 4.6. $C_{10}H_{10}N_4S$ requires C, 55.03; H, 4.62%).

5-*Benzoyl*-1,2,3-*thiadiazole phenylhydrazone* **7c**. Yield 87%, m.p. 164 °C (EtOH); δ_H[$(CD_3)_2SO$] 6.9–7.7 (10 H, 5 m, 2 Ph), 8.06 (1 H, br, NH) and 8.30 (1 H, s, 4-H); δ_C[$(CD_3)_2SO$] 113.5 121.8, 128.3, 129.4, 130.3, 130.5, 130.6 and 142.8 (Ph), 134.1 (C=N), 144.5 (C-4, $^1J_{CH}$ 191) and 157.1 (C-5, $^2J_{CH}$ 12); *m/z* 280 ($M^{\bullet+}$, 59%), 251 ($M^{\bullet+}$ − N_2 − H, 17), 219 (16), 147 (54), 123 ($PhNS^{\bullet+}$, 100), 91 ($PhN^{\bullet+}$, 52) and 77 (Ph^+, 95) (Found: C, 64.3, H, 4.2. $C_{15}H_{12}N_4S$ requires C, 64.29; H, 4.29%).

Methylation of Oxime **6a**

A. With Meerwein's Reagent.—A suspension of oxime **6a** (1.0 g, 7.8 mmol) and trimethyloxonium tetrafluoroborate (1.3 g, 8.4 mmol) in dry dichloromethane (20 cm^3) was stirred at room temperature for 2 days. The solvent was removed and the residue was treated with aqueous sodium hydrogen carbonate (0.84 g, 10 mmol in 20 cm^3) which resulted in gas evolution (CO_2). The mixture was stirred for 15 min, after which water was distilled off under reduced pressure and the residue was chromatographed on silica gel with chloroform–methanol (first 10:1, then 5:1) as the eluent, giving compounds **8a** (200 mg) and **9a** (280 mg, 25%). Compound **8a** proved to be impure and was further chromatographed on silica gel with ether as the eluent (150 mg, 13.5%).

2-*Methyl*-5-*nitrosomethylene*-1,2,3-*thiadiazole* **8a**. M.p. 178 °C; δ_H($CDCl_3$) 4.1 (3 H, s, Me) and 8.8 and 9.25 (2 H, 2 s, 2 CH=); δ_C($CDCl_3$) 38.4 (Me, $^1J_{CH}$ 141), 135.8 (C-4, $^1J_{CH}$ 196), 139.1 (C-5, $^2J_{CH}$ 14) and 140.3 (CNO, $^1J_{CH}$ 192.5); *m/z* 143 ($M^{\bullet+}$, 100%), 128 ($M^{\bullet+}$ − Me, 23), 70 ($M^{\bullet+}$ − MeN_2 − NO, 42), 69 (35), 61 (12), 57 (25) and 43 (MeN_2^+ or $HCNO^{\bullet+}$, 71) (Found: C, 33.7; H, 3.45. $C_4H_5N_3OS$ requires C, 33.56; H, 3.52%).

3-*Methyl*-1,2,3-*thiadiazolium*-5-*nitrosomethylide* **9a**. M.p. 192 °C; δ_H[$(CD_3)_2SO$] 4.5 (3 H, s, Me), 9.4 (1 H, s, CH=N) and 9.6 (1 H, s, 4-H); δ_C[$(CD_3)_2SO$] 45.9 (Me, $^1J_{CH}$ 144, $^3J_{CH} \leqslant 2$), 134.9 (C-4, $^1J_{CH}$ 201.5, $^3J_{CH}$ 2.5–3), 137.3 (CNO, $^1J_{CH}$ 191.5) and 142.4 (C-5, $^2J_{CH}$ 14.5, 11.5); *m/z* 143 ($M^{\bullet+}$, 40%), 66 (57), 46 (28), 43 (MeN_2^+ or $HCNO^{\bullet+}$, 100) (Found: C, 33.3; H, 3.4. $C_4H_5N_3OS$ requires C, 33.56; H, 3.52%).

B. With Diazomethane.—To a suspension of oxime **6a** (2 g, 15.5 mmol) in dry diethyl ether (50 cm^3) was added a threefold excess of diazomethane (*ca.* 2 g), dissolved in diethyl ether (80 cm^3),[11] and the mixture was stirred overnight at room temperature. After evaporation of the solvent, the residue was chromatographed on silica gel with diethyl ether–light petroleum (4:1) and then with diethyl ether–methanol (10:1) as the eluents to give compounds **11a** (1 g, 39%) and **10a** (0.42 g, 19%) respectively.

1,2,3-*Thiadiazol*-5-*ylmethylene*(*methyl*)*amine* N-*oxide* **10a**. M.p. 179 °C; δ_H[$(CD_3)_2SO$] 3.98 (3 H, s, Me), 8.93 (1 H, s, CH=N) and 9.4 (1 H, s, 4-H); δ_C[$(CD_3)_2SO$] 51.4 (Me, $^1J_{CH}$ 143, $^3J_{CH}$ 2), 128.2 (CH=N, $^1J_{CH}$ 193), 142.3 (C-5, $^2J_{CH}$ 9, 14) and 148.0 (C-4, $^1J_{CH}$ 193); *m/z* 143 ($M^{\bullet+}$, 29), 115 ($M^{\bullet+}$ − N_2, 13), 70 ($M^{\bullet+}$ − N_2 − MeNO, 11), 67 ($M^{\bullet+}$ − N_2 − SO, 48), 66 (47.5) and 42 (CNO^+, 100) (Found: C, 33.6; H, 3.4. $C_4H_5N_3OS$ requires C, 33.56; H, 3.52%).

5-(*Methoxyiminomethyl*)-1,2,3-*thiadiazole* **11a**. M.p. 60 °C; δ_H($CDCl_3$) 4.25 (3 H, s, Me), 7.98 (1 H, s, CH=N) and 8.94 (1 H, s, 4-H); δ_C($CDCl_3$) 63.4 (Me, $^1J_{CH}$ 145.5), 135.0 (CH=N, $^1J_{CH}$ 186), 139.3 (C-5, $^2J_{CH}$ 11, 14) and 149.0 (C-4, $^1J_{CH}$ 190); *m/z* 143 ($M^{\bullet+}$, 37), 115 ($M^{\bullet+}$ − N_2, 26), 88 (26), 73 (34), 70 (21) and 57 ($HC{\equiv}CS^+$, 100) (Found: C, 33.4; H, 3.4. $C_4H_5N_3OS$ requires C, 33.56; H, 3.52%).

C. With Methyl Iodide.—To a suspension of the potassium salt of oxime **6a** (1 g, 7.4 mmol) in acetonitrile (30 cm^3) was added methyl iodide (10.5 g, 10 equiv.), and the mixture was refluxed for 90 min. After evaporation of the solvent and the excess of methyl iodide, the residue was chromatographed on silica gel with chloroform–methanol (30:1) as the eluent to give compounds **11a** (189 mg, 18%) and **10a** (299 mg, 28%).

Methylation of Oxime **6b**.—A suspension of oxime **6b** (2 g, 14 mmol) and trimethyloxonium tetrafluoroborate (3.1 g, 21

mmol) in dry dichloromethane (50 cm^3) was stirred at room temperature for 2 days. The reaction mixture was treated with aqueous sodium hydrogen carbonate (1.7 g in 75 cm^3) and stirred for 15 min. The dichloromethane layer was collected and the aqueous phase was extracted three times with chloroform. The combined organic layers were dried ($MgSO_4$), evaporated, and the residue chromatographed on silica gel with chloroform–methanol (first 4:1, then 2:3) as the eluent to give unchanged oxime **6b** (230 mg), nitrone **10b** (50 mg, contaminated with oxime **6b**) and compound **9b** (350 mg). The aqueous phase was also subjected to the same chromatographic procedure and yielded a further crop of compound **9b** (550 mg).

3-*Methyl*-1,2,3-*thiadiazolium*-5-(α-*nitroso*)*ethylide* **9b**. Orange crystals (900 mg, 41%), m.p. 240 °C (EtOH); $\delta_H[(CD_3)_2SO]$ 2.65 (3 H, s, Me), 4.50 (3 H, s, MeN) and 9.8 (1 H, s, 4-H); $\delta_C[(CD_3)_2SO]$ 15.5 (Me, $^1J_{CH}$ 128), 45.9 (MeN, $^1J_{CH}$ 144, $^3J_{CH}$ 1.5), 134.6 (C-4, $^1J_{CH}$ 200, $^3J_{CH}$ 3), 142.8 (C-5, $^2J_{CH}$ 12, $^3J_{CH}$ 3) and 143.8 (CNO, $^2J_{CH}$ 7); *m/z* 157 ($M^{\bullet+}$, 100%), 142 ($M^{\bullet+}$ – Me, 9), 140 (17), 127 (15), 80 (63) and 43 (MeN_2^+, 78) (Found: C, 38.0; H, 4.4. $C_5H_7N_3OS$ requires C, 38.21; H, 4.49%).

α-(1,2,3-*Thiadiazol*-5-*yl*)*ethylidene*(*methyl*)*amine* N-*oxide* **10b**. Obtained as a mixture with oxime **6b** in a ratio of 65:35 (50 mg); $\delta_H[(CD_3)_2SO]$ 2.7 (3 H, s, Me), 4.0 (3 H, s, MeN) and 9.6 (1 H, s, 4-H); $\delta_C[(CD_3)_2SO]$ 15.8 (Me, $^1J_{CH}$ 131), 47.9 (MeN, $^1J_{CH}$ 143), 135.7 (C=N), 144.3 (C-5, $^2J_{CH}$ 14, $^3J_{CH}$ 4, $^4J_{CH}$ 1) and 148.8 (C-4, $^1J_{CH}$ 193).

Methylation of the Oxime **6c**.—A suspension of the oxime **6c** (1 g, 4.9 mmol) and trimethyloxonium tetrafluoroborate (1.09 g, 7.35 mmol) in dry dichloromethane (30 cm^3) was stirred at room temperature for 2 days. The solvent was removed and the residue was treated with aqueous sodium hydrogen carbonate (2 g in 75 cm^3). The whole was extracted three times with chloroform (100 cm^3) and the extracts were dried ($MgSO_4$) and evaporated to give 3-methyl-1,2,3-thiadiazolium-5-(α-nitroso)-benzylide **9c** (450 mg, 42%), m.p. 194–196 °C, orange crystals (EtOH); $\delta_H[(CD_3)_2SO]$ 4.5 (3 H, s, Me), 7.4–7.9 (5 H, 2 t + d, Ph) and 9.85 (1 H, s, 4-H); $\delta_C[(CD_3)_2SO]$ 45.9 (Me, $^1J_{CH}$ 144.6, $^3J_{CH}$ 1.4), 126.6, 128.2, 128.8 and 134.4 (Ph), 135.2 (C-4, $^1J_{CH}$ 201, $^3J_{CH}$ 3), 141.7 (C-5, $^2J_{CH}$ 11) and 148.9 (CNO, $^3J_{CH}$ 4); *m/z* 219 ($M^{\bullet+}$, 82%), 148 (30), 142 ($M^{\bullet+}$ – Ph, 41), 115 (25) and 43 (MeN_2^+, 100) (Found: C, 54.7; H, 4.1. $C_{10}H_9N_3OS$ requires C, 54.78; H, 4.14%).

Methylation of the Hydrazones **7a–c**.—*General procedure*. A suspension of the hydrazone **7** (2 mmol) and trimethyloxonium tetrafluoroborate (2.5 mmol) in dry dichloromethane (20 cm^3) was stirred overnight at room temperature. After removal of the solvent, the residue was dissolved in methanol (20 cm^3) and treated with aqueous sodium hydrogen carbonate (1 g in 50 cm^3). The mixture was extracted three times with chloroform or dichloromethane (50 cm^3), and the combined extracts were dried ($MgSO_4$) and evaporated.

3-*Methyl*-1,2,3-*thiadiazolium*-5-*phenylazomethylide* **12a**. Red crystals (*ca.* 100%, 63% after crystallization), m.p. 156–157 °C ($CHCl_3$–hexane); $\delta_H(CDCl_3)$ 4.2 (3 H, s, Me), 7.0–7.8 (5 H, 2 t + d, Ph) and 8.34 and 8.36 (2 H, 2 s, CH=N and 4-H); $\delta_C(CDCl_3)$ 45.3 (Me, $^1J_{CH}$ 144, $^3J_{CH}$ 1.5), 118.6, 123.9, 129.2 and 151.0 (Ph), 121.8 (CH=N, $^1J_{CH}$ 190), 128.5 (C-4, $^1J_{CH}$ 194) and 140.9 (C-5, $^2J_{CH}$ 11 and 14.5); *m/z* 218 ($M^{\bullet+}$, 68%, 204 (28), 175 ($M^{\bullet+}$ – CH_3N_2, 19), 149 (14), 123 (13), 104 (15), 91 ($PhN^{\bullet+}$, 25), 77 (Ph^+, 73), 65 (37), 58 (11), 51 (31) and 43 (MeN_2^+, 100). (Note: no correct microanalysis was obtained since a residue was formed.)

3-*Methyl*-1,2,3-*thiadiazolium*-5-(α-*phenylazo*)*ethylide* **12b**. Compound **12b** (94%) was further purified by column chromatography on silica gel with chloroform as the eluent, m.p. 167 °C; $\delta_H(CDCl_3)$ 2.7 (3 H, s, Me), 4.2 (3 H, s, MeN), 7.0–7.8 (2 t + d, Ph) and 8.3 (1 H, s, 4-H); $\delta_C(CDCl_3)$ 18.0 (Me, $^1J_{CH}$ 127), 45.6 (MeN, $^1J_{CH}$ 143), 118.1, 123.1, 129.2 and 150.3 (Ph), 127.7 (C-4, $^1J_{CH}$ 192.5, $^3J_{CH}$ 3), 130.1 (C=N, $^2J_{CH}$ 6.5) and 139.1 (C-5, $^2J_{CH}$ 10.5, $^3J_{CH}$ 3.5); *m/z* 232 ($M^{\bullet+}$, 74), 189 (17, $M^{\bullet+}$ – MeN_2), 127 (12), 104 (27), 91 ($PhN^{\bullet+}$, 14), 77 (Ph^+, 38.5), 51 (20) and 43 (MeN_2^+, 100) (Found: C, 56.9; H, 5.5. $C_{11}H_{12}N_4S$ requires C, 56.87; H, 5.21%).

3-*Methyl*-1,2,3-*thiadiazolium*-5-(α-*phenylazo*)*benzylide* **12c**. Yield 93% (68% after crystallization), m.p. 183–185 °C (PhMe or DMF–H_2O); $\delta_H[(CD_3)_2SO]$ 4.37 (3 H, s, Me), 7.0–7.9 (10 H, 3 t + 2 d, 2 Ph) and 9.56 (1 H, s, 4-H); $\delta_C[(CD_3)_2SO]$ 45.4 (Me, $^1J_{CH}$ 143.5, $^3J_{CH}$ 1.5), 117.8, 123.2, 126.4, 126.5, 128.5, 129.1, 137.3 and 150.3 (Ph), 131.2 (C-4, $^1J_{CH}$ 199, $^3J_{CH}$ 2.5), 132.6 (C=N) and 138.8 (C-5, $^2J_{CH}$ 12); *m/z* 294 ($M^{\bullet+}$, 98%), 293 (67), 251 ($M^{\bullet+}$ – MeN_2, 34), 218 (14), 142 (34), 115 (41), 77 (Ph^+, 94) and 43 (MeN_2^+, 100) (Found: C, 65.4; H, 4.8. $C_{16}H_{14}N_4S$ requires C, 65.53; H, 4.76%).

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References

1 G. L'abbé and A. Frederix, *J. Heterocycl. Chem.*, 1990, **27**, 1415.
2 G. L'abbé, A. Frederix and S. Toppet, *J. Heterocycl. Chem.*, 1991, **28**, 477.
3 Reviews: C. Th. Pedersen, *Sulfur Rep.*, 1980, **1**, 1; N. Lozac'h, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 6, p. 1049.
4 Review: C. A. Ramsden, in *Comprehensive Organic Chemistry*, eds. D. H. R. Barton and W. D. Ollis, Pergamon, Oxford, 1979, vol. 4, p. 1171.
5 H. P. Benschop, G. R. Van den Berg, C. Van Hooidonk, L. P. A. De Jong, C. E. Kientz, F. Berends, L. A. Kepner, E. Meeter and R. P. L. S. Visser, *J. Med. Chem.*, 1979, **22**, 1306.
6 G. E. Maciel, J. W. McIver, N. S. Ostlund and J. A. Pople, *J. Am. Chem. Soc.*, 1970, **92**, 1; G.L'abbé, M. Bruynseels, P. Delbeke and S. Toppet, *J. Heterocycl. Chem.*, 1990, **27**, 2021.
7 G. E. Hawkes, K. Herwig and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1017; C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.*, 1977, **42**, 2614.
8 S. H. Pines, J. M. Chemerda and M. A. Kozlowski, *J. Org. Chem.*, 1966, **31**, 3446.
9 G. L'abbé, P. Vangheluwe, S. Toppet, G. S. D. King and L. Van Meervelt, *Bull. Soc. Chim. Belg.*, 1984, **93**, 405.
10 C. D. Hurd and R. I. Mori, *J. Am. Chem. Soc.*, 1955, **77**, 5359; see also L. Wolff, *Liebigs Ann. Chem.*, 1904, **333**, 1; J. Font, M. Torres, H. E. Gunning and O. P. Strausz, *J. Org. Chem.*, 1978, **43**, 2487; F. Bellesia, R. Grandi, U. M. Pagnoni and R. Trave, *Gazz. Chim. Ital.*, 1981, **111**, 289; M. Pieper, W. Teichert and H. Meier, *Liebigs Ann. Chem.*, 1986, 1334; G. L'abbé, P. Delbeke, W. Dehaen, L. Bastin and S. Toppet, *Bull. Soc. Chim. Belg.*, 1991, **100**, 623.
11 F. Arndt, in *Org. Synth.*, Coll. Vol. II, 1943, 165.

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