# Reactivity of 2-Amino-1,3,4-thiadiazoles. Nucleophilic Behaviour of some 2-Amino-1,3,4-thiadiazoles: Model Compounds



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The ambident nucleophilic behaviour of some 2-amino-5-*H*-1,3,4-thiadiazoles in alkylation, acylation and nitrosation reaction has been verified. The structures assigned to the 2-amino-1,3,4-thiadiazoles (**1a-i**) and to the $\Delta^2$-1,3,4-thiadiazolines (**2a-e**) agree with the spectral data.

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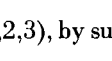
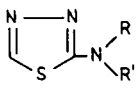
We have pointed out in our research on the synthesis and reactivity of 1,3,4-thiadiazoles the bidentate nucleophilic behaviour of some 2-amino-5-R-1,3,4-thiadiazoles

(R = $C_6H_5CO$-, Br-,  ) (1,2,3), by subjecting them to acetylation, alkylation, benzoylation and nitrosation reactions.

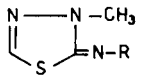
In order to verify an eventual influence of the 5-R-substituetns on the nucleophile-like behaviour of these cyclic thiamidines, it was thought necessary to subject the 2-amino-5-*H*-1,3,4-thiadiazoles (**1a-e**) to the same reactions (see Scheme 1). Some of these substrates have already

SCHEME 1



1 a-i

a : R=R'=H
b : R=H ; R'=$CH_3$
c : R=H ; R'=NO
d : R=H ; R'=$COCH_3$
e : R=H ; R'=$COC_6H_5$
f : R=R'=$CH_3$
g : R=$CH_3$ ; R'=NO
h : R=$CH_3$ ; R'=$COCH_3$
i : R=$CH_3$ ; R'=$COC_6H_5$



2 a-e

a : R=H
b : R=$CH_3$
c : R=NO
d : R=$COCH_3$
e : R=$COC_6H_5$

been reported in literature, however, the structures and the spectral data have not yet been clearly established (4).

The $\Delta^2$-1,3,4-thiadiazoline (**2a**) has been synthetized and subjected to the same electrophilic substitution reactions in order to have at disposal disubstituted model compounds which are necessary for the assignment of the structure to the thiadiazolines substrates obtained (5).

Methylation of **1a** with methyl iodide gave 4-methyl-5-imino-$\Delta^2$-1,3,4-thiadiazoline hydroiodide, from which the corresponding base **2a** can be freed by treatment with bases (7); according to the alkylation reaction of 2-amino-1,3,4-thiadiazoles, it proceeds on the ring nitrogen atom in position 3 (8) because of its higher nucleophilicity with respect to the exocyclic nitrogen atom (1) (see Scheme 2). The action of nitrous acid on **1a** gave the 2-nitrosoamino-1,3,4-thiadiazole (**1c**) (7) while acylation (acetylation and benzoylation) afforded the thiadiazoles **1d** (7,9) and **1e**, respectively.

Methylation with methyl iodide of 2-methylamino-1,3,4-thiadiazole (**1b**) proceeds, in this case too, on the ring nitrogen atom in position 3, giving the thiadiazoline **2b** (10), whereas nitrosation and acylation proceed on the nitrogen exocyclic atom giving, respectively, the thiadiazoles **1g**, **1h** (11) and **1i**.

The substrate **1c** was recovered unchanged after nitrosation reaction, but it was decomposed by benzoylation. Acetylation gave rise to cleavage of the nitroso group so that monoacetyl derivative **1d** was obtained. Methylation under different conditions gave, with very poor yield, a mixture of the thiadiazole **1d** and of the thiadiazoline **2c** (preparative tlc silicagel GF 254, cyclohexane-ethyl acetate 1:1).

Attemtps to perform nitrosation or acetylation of the thiadiazole **1d** failed, the starting material being recovered unchanged. Attempted benzoylation results in extensive decomposition. Reaction of the same substrate with diazomethane gave a mixture of the thiadiazole **1h** and thiadiazoline **2d** (1).

On the benzoyl derivative **1e**, treatment with acetic anhydride affords removal of the benzoyl group and yields the acetyl derivative **1d**. Alkylation with diazomethane again produced a mixture of the thiadiazole **1i** and the thiadiazoline **2e** (1), whereas **1e** is unreactive towards nitrous acid, and decomposition is observed in attempting benzoylation with benzoyl chloride.

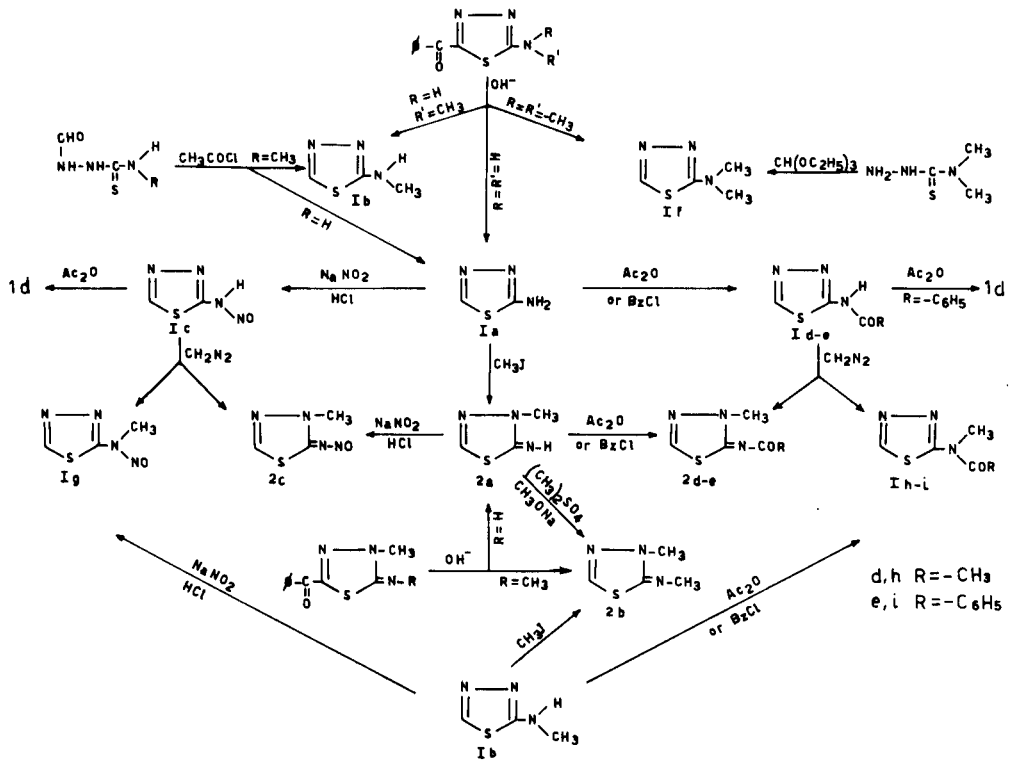
The thiadiazoline **2a** readily undergoes alkyaltion, nitrosation, acetylation and benzoylation, yielding the thiadiazolines **2b**, **2c**, **2d** and **2e**, respectively.

The above results allowed us to assign unambiguously the structure of 1,3,4-thiadiazoles to products **1c-e** and the structure of $\Delta^2$-1,3,4-thiadiazoline to products **2a-e** which, therefore, can be considered model compounds.

The above results show also that all these substrates behave, similarly to the substrates previously considered (1,2,3), as bidentate nucleophiles, according to the hypothesis of a tautomerism between the 2-amino-1,3,4-thiadiazole and 5-imino-$\Delta^2$-1,3,4-thiadiazoline forms.

The spectral data (ir, nmr) and the elemental analyses gave a further support for the postulated structures.

SCHEME 2



## EXPERIMENTAL

Melting points were determined using a Kofler hotplate and are uncorrected. Ir spectra (nujol mull) were recorded on a Perkin-Elmer Infracord 137 instrument. Nmr spectra (60 MHz) were obtained using a Jeol C-60 H spectrometer with TMS as internal standard. The structure of all products described was established by elemental analyses and by their spectroscopic data, as well as by comparison (ir spectra, melting points, mixed melting points) with authentic samples when available. Elemental analyses data are given only for new compounds, previously unreported.

Methylation of **1a-e** and of **2a**.

Compound **1a** (1.01 g., 0.01 mole) in anhydrous methanol (40 ml.) and methyl iodide (0.035 mole) were heated at reflux for 24 hours. After concentration (under reduced pressure) and filtration, the residue washed with methanol-ligroin, gave **2a**·HI (2.1 g., yield 92%), m.p. 235-238° (ethanol)(7). Compound **2a**·HI, suspended in a little water and treated with diluted ammonia gave **2a** (0.95 g., yield 85%), which was identical in all respects with an authentic sample (6).

Compound **1b** (1.15 g., 0.01 mole) following the procedure above gave **2b**·HI (2.25 g., yield 87%), m.p. 233-235° [lit. (10), m.p. 232-233°]. Compound **2b**·HI suspended in a little water and treated with diluted ammonia gave **2b** (1 g., yield 77%), m.p. 46-48° [lit. (10), oil]. It was identical in all respects with an authentic sample (6).

Compound **1c** (1.3 g., 0.01 mole) suspended in dioxane (50 ml.) was treated with an ethereal solution of diazomethane. After filtration and removal of the solvents, the residue gave, in very poor yield, a mixture of **1g** and **2c** (preparative tlc silicagel GF 254 cyclohexane-ethylacetate 2:1).

Compound **1g** had ir: 3049 $cm^{-1}$ (CH); nmr (deuteriochloroform): 3.18-3.57 δ (2s, 6H, 2 x $NCH_3$), 8.91-9.03 δ (2s, 2H, 2 x CH).

*Anal.* Calcd. for $C_3H_4N_4OS$: C, 25.01; H, 2.80; N, 38.89. Found: C, 24.85; H, 2.82; N, 39.00.

Compound **2c** had ir: 3012 $cm^{-1}$ (CH); nmr (deuteriochloroform): 4.07 δ (s, 3H, $NCH_3$), 8.42 δ (s, 1H, CH).

*Anal.* Calcd. for $C_3H_4N_4OS$: C, 25.01; H, 2.80; N, 38.89. Found: C, 24.90; H, 2.78; N, 39.15.

Compound **1d** (1.43 g., 0.01 mole) following the procedure above gave a mixture of **1h** (0.55 g., yield 35%) and **2d** (0.78 g., yield 50%), which can be separated by preparative tlc (silicagel GF 254, cyclohexane-ethylacetate 2:1). Compounds **1h** and **2d** were identical in all respects with an authentic sample (11) and (1).

Compound **1e** (2.05 g., 0.01 mole) following the procedure above gave a mixture of **1i** (0.57 g., yield 25%) and **2e** (1.38 g., yield 61%), which can be separated by preparative tlc (silicagel GF 254, cyclohexane-ethylacetate 2:1). Compound **1i** had m.p. 119-121° (ligroin); ir: 2994 (CH) and 1629 $cm^{-1}$ (C=O); nmr (deuteriochloroform): 3.28 δ (s, 3H, $NCH_3$), 7.52-7.70 δ (m, 5H, Ar-H), 8.98 δ (s, 1H, CH).

*Anal.* Calcd. for $C_{10}H_9N_3OS$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.85; H, 4.05; N, 19.20.

Compound **2e** was identical in all respects with an authentic sample (1).

Compound **2a** (1.15 g., 0.01 mole) was dissolved in anhydrous methanol (20 ml.) and a methanolic solution of sodium methoxide (0.3 g. of sodium in 20 ml. of methanol) and dimethylsulphate (1 ml.) were added. The reaction mixture was refluxed for 1 hour, the solvent distilled off, the residue diluted with water and extracted with chloroform to give **2b** (0.15 g., yield 10%).

Acetylation of **1a-e** and of **2a**. General Procedure.

The heterocyclic compound (0.01 mole) dissolved in 5 ml. of pyridine and 0.0125 mole of acetic anhydride were refluxed for 30 minutes. Upon dilution with water, the crude product preci-

pitated out. The residue was taken up with water and filtered.

Compound **1a** (1.01 g.) gave **1d** (1.2 g., yield 84%), m.p. 275-277° [lit. (7), m.p. 268°] (ethanol 60%); ir: 3106 (NH), 3003 (CH) and 1661 $cm^{-1}$ (C=O); nmr (DMSO-$d_6$): 2.18 δ (s, 3H, $COCH_3$), 9.13 δ (s, 1H, CH), 11.40-13.00 δ (br.s, 1H, NH).

*Anal.* Calcd. for $C_5H_7N_3OS$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.40; H, 4.40; N, 26.60.

Compound **1b** (1.15 g.) gave **1h** (1.05 g., yield 67%), m.p. 142-143° [lit. (11), m.p. 142-143°] (ethanol); ir: 3030 (CH) and 1645 $cm^{-1}$ (C=O); nmr (deuteriochloroform): 2.46 δ (s, 3H, $COCH_3$), 3.83 δ (s, 3H, $NCH_3$), 8.95 δ (s, 1H, CH).

Compound **2a** (1.15 g.) gave **2d** (0.85 g., yield 55%), m.p. 116-117° (ligroin). It was identical in all respects with an authentic sample (1).

Compound **1c** (1.3 g.) gave **1d** (0.45 g., yield 31%), which showed no melting point depression when mixed with a sample of pure **1d**, obtained by the acetylation of **1a**.

Compound **1e** (2.05 g.) gave **1d** (0.65 g., yield 45%), which showed no melting point depression when mixed with a sample of pure **1d**, obtained by acetylation of **1a**.

Compound **1d** was recovered unchanged.

Benzoylation of **1a-e** and of **2a**. General Procedure.

The heterocyclic compound (0.01 mole) in pyridine (5 ml.) was refluxed for 15 minutes with benzoyl chloride (0.0125 mole). After dilution with water, following the procedure above, the following were obtained:

Compound **1a** gave **1e** (1.93 g., yield 94%), m.p. 213-214° (ethanol); ir: 3106-3030 (NH,CH) and 1664 $cm^{-1}$ (C=O); nmr (DMSO-$d_6$): 7.50-8.38 δ (m, 5H, Ar-H), 9.26 δ (s, 1H, CH), 11.95 δ (br. s, 1H, NH).

*Anal.* Calcd. for $C_9H_7N_3OS$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.75; H, 3.28; N, 20.60.

Compound **1b** gave **1i** (1.2 g., yield 83%), m.p. 119-121° (ligroin).

Compound **2a** gave **2e** (1.12 g., yield 78%), m.p. 129-130° (benzene-ligroin 1:1).

Compounds **1c**, **1d** and **1e** under the same experimental conditions underwent decomposition.

Nitrosation of **1a-e** and of **2a**. General Procedure.

To a suspension or solution of the compound (0.01 mole) and dilute hydrochloric acid 1:1 was added aqueous sodium nitrite (1.38 g.).

Compound **1a** gave **1c** (1.1 g., yield 85%), m.p. 225° dec. [lit. (7), m.p. 220° dec.]; ir: 3279 (NH) and 3049 $cm^{-1}$ (CH); nmr (DMSO-$d_6$): 4.31 δ (br. s, 1H, NH), 9.30 δ (s, 1H, CH).

*Anal.* Calcd. for $C_2H_2N_4OS$: C, 18.47; H, 1.55; N, 43.08. Found: C, 18.45; H, 1.60; N, 42.88.

Compound **1b** gave **1g** (1.27 g., yield 88%), m.p. 65-67° (water).

Compound **2a** gave **2c** (1.32 g., yield 92%), m.p. 122° (ethanol).

Compounds **1c**, **1d** and **1e** were recovered unchanged.

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(4) M. Freund and C. Meinecke, *Chem. Ber.*, 29, 2511 (1896); G. Yound and W. Eyre, *J. Chem. Soc.*, 79, 54 (1901).

(5) The substrates **1a**, **1b**, **1f**, **2a** and **2b** should be considered as model compounds; their structure was recently confirmed by ourselves (6) (see Scheme 2).

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