Reactivity of 2-Amino-1,3,4-thiadiazoles. Methylation Reactions of Some 2-Amino-5-benzoyl-1,3,4-thiadiazoles

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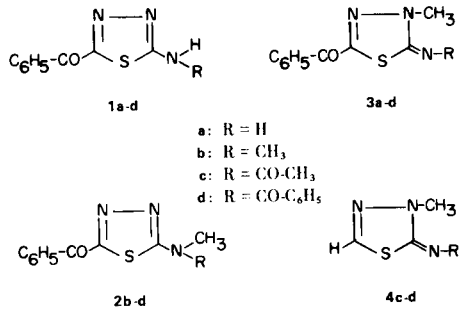
Methylation reactions of 2-amino-5-benzoyl-1,3,4-thiadiazoles **1a-d** are reported as a function of alkylating agents (methyl iodide, dimethyl sulfate-potassium carbonate, diazomethane, dimethyl-sulfate-sodium methoxide). Methylation occurs at both the ring nitrogen in position 3 and the exocyclic nitrogen atom.

The alkylation reaction of 2-amino-1,3,4-thiadiazoles proceeds on the ring nitrogen atom in position 3 (1) because of its higher nucleophilicity with respect to the exocyclic nitrogen atom (2). In the same position 3 the 2-acylamino-1,3,4-thiadiazoles are alkylated by alkyl halides in alkaline medium (3). However, an example of methylation has been reported (4) where the type of base used influences the alkylation direction (5). On the other hand it is known that for other heterocyclic amines, the selectivity of the attack by an alkylating electrophilic agent is determined by its nature and other factors (*i.e.*, steric effects, hydrogen bonding, solvent) which can modify the nucleophilic properties of the reaction centers and, consequently, the nature of alkylation products (6).

Since we are investigating the reactivity of the 2-amino-1,3,4-thiadiazoles (7,8), we thought it of interest to study the methylation reaction as a function of the substrate, alkylating agent and reaction medium.

In this work we report results concerning the substrates 2-amino- (**1a**), 2-methylamino- (**1b**), 2-acetylamino- (**1c**) and 2-benzoylamino- (**1d**)-5-benzoyl-1,3,4-thiadiazoles and the alkylating systems: a) methyl iodide in methanol, b) dimethyl sulphate-potassium carbonate in acetone, c) diazomethane in ether-dioxane, d) dimethyl sulphate-sodium methoxide in methanol. In Table I are reported the results obtained. From the table it is possible to deduce that the methylation with methyl iodide in methanol, when proceeding, concerns exclusively the ring nitrogen atom in position 3 giving good yields of the thiadiazolines **3a** and **3b**. The same reaction fails with the **1c** and **1d** compounds (see below).

With dimethyl sulphate-potassium carbonate in acetone, the methylation reaction proceeds preferentially on the ring nitrogen atom; in fact, the exocyclic nitrogen atom



also exhibits a reactivity, even with variable yields. From **1a-d** it is possible to obtain the thiadiazolines **3a-d** together with the thiadiazoles **2b-d**. Compound **1a** does not give the monoalkylation compound **1b**, but the dialkylation products **2b** (traces) and **3b** together with **3d** (9). It must

SCHEME I

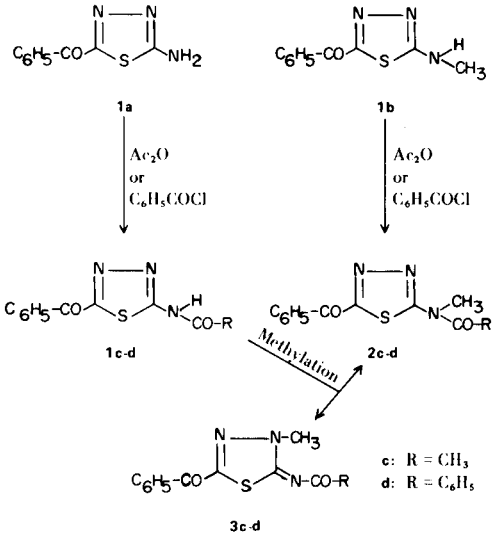


Table I

Methylation Products of 1,3,4-Thiadiazoles **1a-d** (yields %)

Substrate	MeI	Me_2SO_4-K_2CO_3	CH_2N_2	Me_2SO_4-MeONa
1a	**3a** (82)	**2b** (tr.), **3a** (10) **3b** (15) **3d** (6)	no react.	**2b** (2), **1d** (13)
1b	**3b** (60)	**2b** (3), **3b** (40)	no react.	**2b** (28)
1c	no react.	**2c** (42), **3c** (54)	**2c** (28), **3c** (52)	**1a** (25), **3c** (2) **1b** (11), **4c** (25)
1d	no react.	**2d** (4), **3d** (79)	**2d** (7), **3d** (62)	**4d** (59)

be noted that the 2-acylamino compounds **1c** and **1d** give methylation products with high yields. The ratio between exocyclic nitrogen to the ring nitrogen atom methylation is nearly 1:1 in the case of 2-acetylamino **1c** and much less for the 2-benzoylamino **1d**, and this because of steric and electronic effects (11).

Also with diazomethane, the **1c** and **1d** methylation proceeds at both the ring nitrogen atom and acylamino group. The thiadiazolines **3c-d** and thiadiazoles **2c-d** are obtained. The yield of the methylation products is good and the ratio of exocyclic to the ring nitrogen atom methylation is higher for the 2-acetylamino **1c** than for the benzoylamino **1d** (12).

In alkaline medium (dimethyl sulfate-sodium methoxide) the methylation reaction becomes more complicated because of the benzoyl group displacement (10) both in the substrates and reaction products, together with cleavage of acetyl group (see below) or cleavage of the thiadiazole ring itself (10). Only the main products are reported in the Table I. The ring nitrogen atom in position 3 does not show any reactivity for compounds **1a** and **1b**, for which methylation only at the exocyclic nitrogen is observed [in the **1a** case dialkylation takes place and **1d** is also found (13)]. The yield of methylation products is rather low since 50% of **1a** and 30% of **1b** do not react. The 2-dimethylamino compound **2b** obtained from **1a** and **1b** is, as far as we know, the first example for such a type of substrate. Methylation of **1c** and **1d** occurs at the ring nitrogen atom giving **3c** (and the corresponding **4c** from the alkaline displacement of the benzoyl group) and **4d** derived in the same way from the unisolated **3d**. Compound **1c** also gives the deacylated product **1a** and its methyl derivative **1b**. The last product came from the deacylation of the unisolated **2c**, since **1b** is never obtained from **1a**.

The whole of our results allows us to point out the following: a) in the 2-amino or 2-alkylamino derivatives (**1a** and **1b**) the ring nitrogen atom is the more nucleophilic center (14) because of conjugative interaction between ring and side-chain nitrogen atoms, so explaining the behaviour of **1a** and **1b** towards methyl iodide; b) 2-acylamino derivatives (**1c** and **1d**) do not react with methyl iodide because the conjugative interaction between the exocyclic nitrogen atom and carbonyl amidic group decreases the nucleophilicities of the reaction centers. (See ir stretchings of amidic C=O); c) in the case of methylation reactions with dimethyl sulphate in alkaline medium (potassium carbonate or sodium methoxide), an inverted reactivity is observed, *i.e.*, acylamino derivatives lead to methylation products with higher total yields than **1a** or **1b**, and this because of a change in the methylation mechanism. Since the reaction is base-induced, methylation is favoured for compounds with acidic hydrogens (2-acylamino derivatives). Moreover, when sodium methoxide is used, a change in the reaction center is observed for **1a** and **1b**, methylation occurring at exocyclic nitrogen only (16); d) in the case of the reaction with diazomethane, obviously methylation occurs only for compounds containing acidic hydrogens, *i.e.*, **1c** and **1d**.

Furthermore, the nature of the solvent (*i.e.*, hydrogen-bonding or not) influences the course of the methylation in all the reactions studied. This aspect in the methylation reaction we are extensively studying.

The structures were assigned on the basis of analytical, ir, nmr data and by comparison with compounds of well known structure. Compounds **1a**, **1b**, **2b** and **3a-d** were prepared as we have previously reported (7). The acetylation and benzoylation of **1a**, gives **1c** and **1d**, while **1b** gives **2c** and **2d** respectively. The latter compounds are also obtained, together with **3c-d**, by methylation of **1c** and **1d**, so supporting the assigned structures (see Scheme I). Compounds **4c** and **4d** were prepared by acetylation and benzoylation of the 4-methyl-5-imino-Δ^2-1,3,4-thiadiazoline (17).

EXPERIMENTAL

Melting points were determined using a Kofler hotplate and are uncorrected. Ir spectra (nujol mull) were determined 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. Preparative scale tlc was performed on silica

gel GF_{254} with ethylacetate-cyclohexane 1:1 as solvent.

All methylation products obtained were identified by analytical and spectroscopic data and by comparison with authentic samples (ir spectra, melting points, mixed melting points). Analytical data are reported only for the new compounds.

Model Compounds:

Preparation of **1c-d** and **2c-d**: General Procedure.

Compounds **1c-d** and **2c-d** were prepared by acetylation and benzoylation of **1a** and **1b** as follows: a mixture of 2-amino- (or 2-methylamino)-5-benzoyl-1,3,4-thiadiazoles (**1a** or **1b**) (0.01 mole), pyridine (10 ml.) and acetic anhydride (0.02 mole), or benzoyl chloride (0.012 mole), was refluxed for 1 hour. After cooling, water was added and the product filtered (nearly quantitative yield).

2-Acetylamino-5-benzoyl-1,3,4-thiadiazole (**1c**).

This compound had m.p. 291-292° (acetic acid); ir: 3086 (NH) and 1695, 1634 cm^{-1} (C=O); nmr (DMSO-d_6): 2.26 δ (s, 3H, $COCH_3$), 7.40-8.50 δ (m, 5H, Ar-H), 12.00 δ (br.s., 1H, NH).

Anal. Calcd. for $C_{11}H_9N_3O_2S$: C, 53.44; H, 3.67; N, 17.00. Found: C, 53.47; H, 3.71; N, 16.93.

2-Benzoylamino-5-benzoyl-1,3,4-thiadiazole (**1d**).

This compound had m.p. 244-245° (ethanol-acetic acid 1:1); ir: 3115 (NH) and 1667, 1639 cm^{-1} (C=O); nmr (DMSO-d_6): 7.30-8.50 δ (m, 10H, Ar-H), 13.4 δ (br.s., 1H, NH).

Anal. Calcd. for $C_{16}H_{11}N_3O_2S$: C, 62.13; H, 3.59; N, 13.59. Found: C, 62.20; H, 3.69; N, 13.46.

2-Methyl-2-acetylamino-5-benzoyl-1,3,4-thiadiazole (**2c**).

This compound had m.p. 198° (ethanol); ir: 1768, 1634 cm^{-1} (C=O); nmr (deuteriochloroform): 2.47 δ (s, 3H, $COCH_3$), 3.85 δ (s, 3H, $N\text{-}CH_3$), 7.30-8.60 δ (m, 5H, Ar-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.23; H, 4.24; N, 16.25.

2-Methyl-2-benzoylamino-5-benzoyl-1,3,4-thiadiazole (**2d**).

This compound had m.p. 181-182° (ethanol); ir: 1661, 1634 cm^{-1} (C=O); nmr (deuteriochloroform): 3.78 δ (s, 3H, $N\text{-}CH_3$), 7.30-8.60 δ (m, 10H, Ar-H).

Anal. Calcd. for $C_{17}H_{13}N_3O_2S$: C, 63.15; H, 4.05; N, 13.00. Found: C, 63.21; H, 4.19; N, 12.90.

4-Methyl-5-acetylimino-Δ^2-1,3,4-thiadiazoline (**4c**).

A mixture of 4-methyl-5-imino-Δ^2-1,3,4-thiadiazoline (0.55 g.), pyridine (2 ml.) and acetic anhydride (0.5 ml.) was refluxed for 1 hour. After cooling, the solvent was removed under reduced pressure and the residue was crystallized from ligroin. Recrystallization from ligroin yielded **4c** (0.4 g.), m.p. 116-117° (ligroin); ir: 3067 (CH-) and 1610 cm^{-1} (C=O); nmr (deuteriochloroform): 2.30 δ (s, 3H, $COCH_3$), 3.93 δ (s, 3H, $N\text{-}CH_3$), 8.30 δ (s, 1H, =CH-).

Anal. Calcd. for $C_5H_7N_3OS$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.15; H, 4.42; N, 26.70.

4-Methyl-5-benzoylimino-Δ^2-1,3,4-thiadiazoline (**4d**).

This compound was prepared by the same procedure with the base (0.55 g.), pyridine (2.5 ml.) and benzoyl chloride (0.7 ml.). After cooling, dilution with water and filtration gave **4d** (0.5 g.), m.p. 129-130° (benzene-ligroin 1:1); ir: 3030 (=CH-) and 1597 cm^{-1} (C=O); nmr (deuteriochloroform): 3.99 δ (s, 3H, $N\text{-}CH_3$), 8.27 δ (s, 1H, =CH-), 7.25-8.40 δ (m, 5H, Ar-H).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.71; H, 4.08; N, 19.08.

Methylation with Methyl Iodide in Methanol: General Procedure.

A mixture of thiadiazoles (0.01 mole), anhydrous methanol (25 ml.) and methyl iodide (0.035 mole) was refluxed for 24 hours. After removing the solvent, the residue was taken up with hot water, filtered and neutralized with aqueous ammonium hydroxide 1:1.

Methylation of **1a**.

The neutral solution was extracted with chloroform and the dried extract was evaporated to yield 4-methyl-5-imino-2-benzoyl-Δ^2-1,3,4-thiadiazoline (**3a**) (1.8 g.), m.p. 74-75° (ligroin) (7).

Methylation of **1b**.

The water insoluble fraction (0.6 g.) was starting material **1b**. Neutralization of the water solution gave directly 4-methyl-5-methylimino-2-benzoyl-Δ^2-1,3,4-thiadiazoline **3b** (1.4 g.), m.p. 120-121° (ligroin) (7).

Methylation with Dimethyl Sulphate and Potassium Carbonate. General Procedure.

A mixture of thiadiazoles (0.01 mole), acetone (100 ml.), potassium carbonate (0.01 mole) and dimethyl sulphate (0.01 mole) was heated under reflux for 12 hours. After cooling, the mixture was filtered and the solvent evaporated to dryness under reduced pressure.

Methylation of **1a**.

Extraction with boiling benzene of the residue obtained from evaporation of the solvent, gave a mixture (tlc) of **2b** (trace), **3a**, **3b**, **3d**. The benzene solution was evaporated and the residue treated with boiling ligroin and filtered. Cooling of the ligroin solution gave **3b** (0.35 g.), m.p. 120-121° (ligroin) (7). Tlc of the ligroin solution showed the presence of **2b** (by comparison with authentic sample). The ligroin insoluble fraction (0.67 g.), containing **3a** and **3b** mixture, was treated with acetic anhydride (0.5 ml.) and pyridine (3 ml.) and refluxed for 20 minutes. Water was added, the solvent removed and the residue underwent fractional crystallization from ethanol to yield first **3d** (0.2 g.), m.p. 191° (ethanol) (7) and then, after dilution with water, the acetyl derivative of **3a** (3c) (0.25 g.), m.p. 169-170° (ethanol) (7).

Methylation of **1b**.

The residue obtained from evaporation of the solvent was treated with boiling ligroin and filtered. The insoluble ligroin fraction, dissolved in water and neutralized with aqueous ammonium hydroxide (1:1) yielded **3b** (0.8 g.), m.p. 120-121° (ligroin) (7). Cooling the ligroin solution, yielded 0.3 g. of crude mixture which was chromatographed on preparative scale tlc to yield additional **3b** (0.2 g.) and **2b** (0.07 g.), m.p. 102° (aqueous ethanol) (7).

Methylation of **1c**.

The acetone insoluble fraction, washed with water to remove inorganic material, gave **2c** (0.5 g.), m.p. 198° (ethanol), identified with an authentic sample. The acetone solution was evaporated and the residue underwent preparative scale tlc to yield additional **2c** (0.6 g.) and **3c** (1.4 g.), m.p. 169-170° (ethanol) (7).

Methylation of **1d**.

The acetone insoluble fraction, as above, gave **3d** (1.4 g.), m.p. 191° (ethanol) (7). The residue of the acetone solution underwent fractional crystallization from ethanol to yield first additional **3d** (1.15 g.) and then **2d** (0.12 g.), m.p. 181-182° (ethanol).

Methylation with Diazomethane.

Methylation of **1c**.

To a solution of **1c** (1 g.) in dioxane (100 ml.) an excess of ethereal diazomethane was added. After standing 24 hours, the solvent was evaporated and the residue chromatographed on preparative scale tlc, to yield **3c** (0.55 g.), m.p. 169-170° (ethanol) (7) and **2c** (0.30 g.), m.p. 198° (ethanol).

Methylation of **1d**.

By the same procedure **1d** (1 g.) in dioxane (40 ml.), the obtained residue underwent fractional crystallization from ethanol to yield first **3d** (0.65 g.), m.p. 191° (ethanol) (7) and then **2d** (0.07 g.), m.p. 181-182° (ethanol).

Methylation with Dimethyl Sulphate and Sodium Methoxide. General Procedure.

A mixture of sodium methoxide (0.01 mole), anhydrous methanol (40 ml.), thiadiazole derivative (0.01 mole) and dimethyl sulphate (0.01 mole) was refluxed for 8 hours, and then evaporated under reduced pressure. The residue was taken up with water and filtered.

Methylation of **1a**.

The crude water insoluble material was taken up with chloroform and filtered from insoluble starting material (1.05 g.). Removal of the solvent and crystallization of the residue from ligroin gave **2b** (0.05 g.), m.p. 102° (aqueous ethanol) (7). The water solution was extracted with chloroform, the dried extracts were evaporated to dryness and the residue taken up with methanol, filtered to yield **1d** (0.4 g.), m.p. 244-245° (ethanol-acetic acid).

Methylation of **1b**.

The crude water insoluble material was treated with boiling ligroin, starting material filtered off (0.7 g.), and after cooling, **2b** (0.65 g.), m.p. 102° (aqueous ethanol) (7) was obtained.

Methylation of **1c**.

The crude water insoluble material was treated with boiling benzene (15 ml.) and filtered. The insoluble fraction, after crystallization from ethanol gave **1a** (0.52 g.), m.p. 200-201° (ethanol) (7). The benzene solution, after standing, gave **1b** (0.25 g.), m.p. 167-168° (benzene-ligroin) (7). Removal of the benzene solution to dryness, and crystallization of the residue from ligroin, gave **3c** (0.05 g.), m.p. 169-170° (ethanol) (7). The water solution was extracted with chloroform, the dried extracts evaporated and the obtained residue was treated with boiling ligroin. Insoluble starting material (0.07 g.) was filtered off and cooling of the ligroin gave **4c** (0.4 g.), m.p. 116-117° (ligroin).

Methylation of **1d**.

The residue obtained from evaporation of the solvent was gently refluxed with water and filtered. The insoluble fraction after crystallization from benzene-ligroin gave **4d** (1.3 g.), m.p. 130-131°. Acidification of the water solution gave starting material (0.6 g.).

REFERENCES

(1) J. Sandstrom, "Advances in Heterocyclic Chemistry," A. R. Katritzky, Ed., Academic Press, Vol. 9, p. 181 (1968) and references cited therein.

(2) E. Testa, G. G. Gallo, F. Fava and G. Weber, *Gazz. Chim. Ital.*, 88, 812 (1958).

(3) G. Pala, *Farmaco* (Pavia), Ed. Sci., 13, 650 (1958); *Chem. Abstr.*, 53, 18947 (1959).

(4) R. W. Young, K. H. Wood, J. A. Eichler, J. R. Vaughan, Jr., and G. W. Anderson, *J. Am. Chem. Soc.*, 78, 4649 (1965).

(5) 2-Acetylamino-5-benzylthio-1,3,4-thiadiazole was methylated at the ring nitrogen atom by methyl bromide and sodium methoxide in methanol, while methyl iodide and potassium *t*-butoxide in *t*-butyl alcohol methylates the nitrogen of the acetylamino group (4).

(6) *Inter alia*, see Kiyotaka Oyama and Ross Stewart, *J. Chem. Soc. Perkin I*, 673 (1973) and references cited therein.

(7) G. Werber, F. Buccheri, and M. L. Marino, *J. Heterocyclic Chem.*, in press.

(8) Work in progress.

(9) The **3d** formation from **1a** can be explained through an intermolecular nucleophilic attack of the amino group of **1a** to the benzoyl group of another molecule with displacement of the thiadiazole ring [see alkaline cleavage of benzoyl-1,3,4-thiadiazoles (10)], and formation of **1d** which, after methylation, would give **3d**. It is not possible to exclude that the nucleophilic attack to the benzoyl group can proceed through the **3a** imino group.

(10) A. Alemagna, T. Bacchetti and C. Rizzi, *Gazz. Chim. Ital.*, 102, 311 (1972).

(11) The benzoyl group in **1d** screens the exocyclic nitrogen atom from attack by alkylating agent more than acetyl group in **1c**. Furthermore, conjugative interaction between phenyl ring and the carbonyl group (for **1d**), decreases the conjugative interaction between exocyclic nitrogen atom and carbonyl group; therefore, in the base-induced reaction (potassium carbonate in acetone) the conjugative interaction between exocyclic and ring nitrogen atom is more favoured for **1d** than for **1c**.

(12) Also in this case steric and electronic effects could explain as to why ratio is higher for **1c** than for **1d** (see reference 11).

(13) The **1d** formation from **1a** can be explained as seen before for **3d** (see reference 9).

(14) Molecular orbital calculations on 2-amino-1,3,4-thiadiazole place the highest electron density on nitrogen atom in position 3 (15).

(15) J. Sandstrom, *Acta Chem. Scand.*, 18, 871 (1964).

(16) These results can be explained by assuming that, in the experimental conditions used (sodium methoxide in methanol), in the **1c** and **1d** cases, the methylation reaction takes place on the substrates in anionic form. Conjugative interaction with adjacent carbonyl group causes a large solvatation in this area, so making the ring nitrogen atom the more nucleophilic center. On the contrary, in the **1a** and **1b** cases, we observe a direct nucleophilic attack (base-assisted) by exocyclic nitrogen atom to the dimethyl sulphate.

(17) M. Freund and C. Meinecke, *Ber.*, 29, 2514 (1896).