Methylation of 2-Acylamido-1,3,4-thiadiazoles. An Infrared, Proton and Carbon Nmr Study

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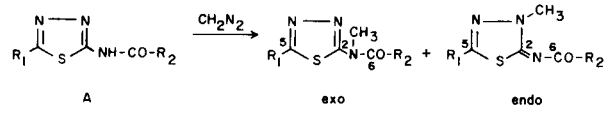
Received January 21, 1980

The site of methylation in 2-acylamido-1,3,4-thiadiazoles can be determined by ir and Carbon-13 nmr spectroscopy.

J. Heterocyclic Chem., 17, 1469 (1980).

2-Amino-1,3,4-thiadiazoles are ambident compounds and may be acylated (1) or alkylated either at the exocyclic NH_2-group or at the endocyclic NH, depending on the conditions of the reaction. The determination of the site of reaction may be accomplished by spectroscopic means, *i.e.*, ir, ^{1}H-nmr or ^{13}C-nmr spectroscopy. In this investigation we apply the three spectroscopic methods to the problem of finding the site of methylation in acylamido-1,3,4-thiadiazoles.

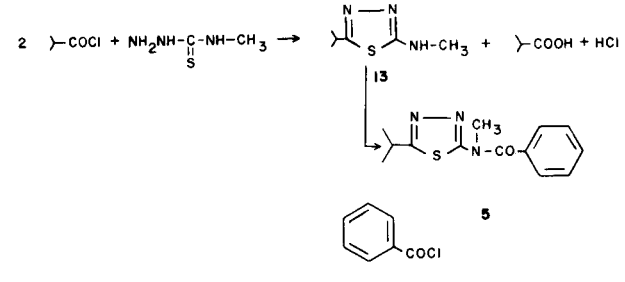
The compounds necessary for this study were synthesised as isomer mixtures by treating the acylamido-1,3,4-thiadiazoles with diazomethane. The pure isomers were separated using column chromatography and are presented in the following scheme (compounds **1-12**)



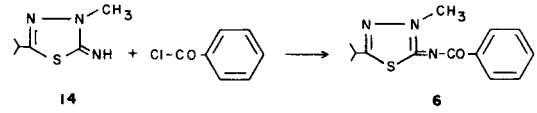
R_1	R_2	A	exo	endo
methyl	phenyl	**1**	**2**	**3**
i-propyl	phenyl	**4**	**5**	**6**
i-propyl	ethyl	**7**	**8**	**9**
t-butyl	*t*-butyl	**10**	**11 (a)**	**12**

(a) Compound **11** could not be synthesised by the above route, probably due to the steric crowding by the *t*-butyl group.

An alternative route to the exo-compounds involves the acylation of the 5-alkyl-2-*N*-methylamino-1,3,4-thiadiazole. The isolation of a single product after treatment of 5-isopropyl-2-*N*-methylamino-1,3,4-thiadiazole (**13**) with benzoyl chloride, which is identical to compound **5**, offered further proof that the correct spectroscopic structure assignment had been made for the two isomers obtained from the diazomethane methylation.



This structure assignment was further verified by the fact that the endo-compounds could also be prepared as single products by the acylation of 5-alkyl-3-methyl-2-imino-1,3,4-thiadiazolines. Thus, the benzoylation of 5-isopropyl-3-methyl-2-imino-1,3,4-thiadiazoline (**14**) yielded a single product, which was identical to compound **6**.



The relevant spectroscopic data (^{13}C shifts and coupling constants, ^{1}H-shifts and ir frequencies of the CO stretching vibration) are given in Tables I and II. For the purpose of the unifying discussion average values of characteristic data are given in Table III. The determination of the ^{1}H-nmr and ir data is straightforward. The assignment of the carbon shifts is less trivial, usually requiring proton coupled spectra. The absolute value of the long range carbon-proton coupling constants and of the multiplicity characterises each carbon signal uniquely. In compound **10**, C-5 was assigned by partial deuteration of NH. Carbons C-2 and C-6 experience isotope shifts of 0.13

Table I

Ir (a) and ^{1}H-Nmr (b) Data

Compound	ν (CO)	δ (CH_3N)	δ (R_1)		δ (R_2)	
2	1660	3.70	2.71		(f)	
3	1610	3.95	2.45		(g)	
4	1675		3.41	1.48	(g)	
5	1665	3.70	3.42	1.45	(f)	
6	1610	4.00	3.17	1.37	(g)	
7	1695		3.40	1.47	2.80	1.33
8	1675	3.77	3.38	1.43	2.72	1.27
9	1610	3.88	3.16	1.35	2.57	1.22
10	1685		1.48 (d)		1.46 (d)	
12	1620	3.92	1.39 (e)		1.28 (e)	

(a) The ir spectra are recorded in solution (carbon tetrachloride or chloroform); values given are in cm^{-1}. Column 2 describes the stretching vibration of the acyl CO bond. (b) ^{1}H-Nmr spectra are recorded in deuteriochloroform. The table gives the shifts (in ppm *vs.* TMS) of the newly introduced CH_3 group (column 3). The other columns contain shifts of the substituents in a self explanatory way. (d)(e) Assignments with the same index may be interchanged. (f)(g) See text.

0022-152X/80/071469-04$02.25

Table II

^{13}C-NMR Data (in DMSO-d_6)

Compound No.	δ (C2)	δ (C5)	δ (C6)	δ (C5′) (a)	δ (C6′) (b)	Δ (c)	δ (CH_3)	^{3}J (C2, CH_3)
1	159.4	159.4	165.1	150.1	−4.6	9.3	—	—
2	160.8	161.9	169.8	152.6	0.1	8.2	38.4	
3	165.8	154.2	173.8	144.9	4.1	20.9	37.4	2.5
4	159.0	170.2	165.2	150.1	−4.5	8.9	—	—
5	159.5	171.9	169.3	151.8	0.4	7.7	38.0	2.6
6	164.8	164.2	172.7	144.1	3.0	20.7	37.4	2.4
7	157.8	170.0	172.0	149.9	−5.2	7.9	—	—
8	159.3	171.5	173.1	151.4	−4.1	7.9	34.3	2.7
9	163.6	163.6	182.1	143.5	4.9	20.1	37.2	2.0
10	158.8	173.2	176.5	151.1	−4.4	7.7	—	—
12	164.4	166.6	186.6	144.5	5.7	19.9	37.1	2.0

(a) δ (C5′) is δ (C5) reduced by the increment for the substituent at C5 (increments used are those for benzene, *viz.*, 9.3, 20.1, 22.1 ppm for methyl, *i*-propyl and *t*-butyl, respectively). (b) δ (C6′) is δ (C6) reduced by the shift of the corresponding acid (169.7, 177.2, 180.9 ppm for benzoic, propionic and pivalic acids, respectively). (c) Δ = δ (C2) − δ (C5′).

Table III

Summary of Averaged Values of Characteristic Ir and ^{13}C-Nmr Data (individual data see Tables I and II)

	δ (CO)	δ (C2)	δ (C5′)	δ (C6′)	Δ
exo (NH)	1685	158.8	150.3	−4.7	8.5
(NCH_3)	1667	159.9	151.9		8.0
endo	1612	164.6	144.2	4.4	20.4

and 0.10 ppm, respectively, to higher field, while C-5 is not affected. In the proton coupled spectrum C-2 is a singlet.

Discussion.

A simple means to assign the structure of the product is ir spectroscopy. In the endo series, where the CO double bond is conjugated with the exocyclic CN double bond, the CO stretching vibration occurs at *ca.* 1610 cm^{-1}. The isolated CO vibration in the starting acylamido compound and in the corresponding exo-methylated products (exo NH and exo NCH_3), however, appear at least 50 cm^{-1} to shorter wave lengths (see Tables I and III), thus allowing an easy distinction between the two series of compounds. The vibrations of the heterocyclic ring are not easily assigned and are not very useful for a unique distinction.

The shifts of the three carbon atoms (C-2, C-5, C-6) indicated in the table vary over a considerable range, depending on the type of the substituents R_1, R_2 and the site of substitution (see Tables II and III). In contrast to the ir spectra, the carbon nmr spectra are very similar for the two compounds in the exo series (exo NH and exo NCH_3). The difference in the electronic structure between the exo and the endo series manifests itself clearly in the shifts of the carbon atoms. The δ value of C-2 is seen to be around 164.6 ppm for the endo series and around 159.9 ppm for the exo series (NH and NCH_3). In order to have comparable information from C-5, its shift must be corrected for the effect of the substituent R_1. Substituent effects for benzene were used and the resulting shifts are included in Tables II and III as δ (C-5′). They group around 144.2 ppm for the endo and 151.9 ppm for the exo series. The scatter around the average values is much smaller than the gap between the two series for both C-2 and C-5′ and this allows a safe assignment of the site of substitution even when only one compound is available.

The difference between C-2 and C-5′ is 8.5 and 8.9 ppm for the exo NH and exo NCH_3 compounds, respectively, and rises to 20.4 ppm in the endo series. This increase is obtained by shifting C-2 and C-5 in opposite directions by almost the same amount (*ca.* 6 ppm). The shift of the carbonyl carbon also reflects the site of substitution. In order to eliminate the influence of the different acid parts, the shift of the carbonyl of the acid has been subtracted and the resulting difference is indicated in Tables II and III as δ (C-6′). Methylation at the endo-cyclic nitrogen shifts the carbonyl to lower field by 8 to 10 ppm. This is probably due to the reduced mesomeric interaction of the electron pair on nitrogen with the carbonyl π-system due to the formation of the exocyclic double bond. Exo methylation shifts the carbonyl carbon to lower field, *ca.* 4.5 ppm and *ca.* 1 ppm for benzamide and propionamide, respectively.

There is only a small range of the carbon shift of the N-CH_3 group. The unusual shift of the methyl group in compound **8** is probably due to a γ-effect of the CH_2-group in R_2.

The coupling constants ^{3}J (H_3C, C-2) between the protons of the introduced methyl group and C-2 do not show a significant variation with the substitution site.

The basic difference in the electronic structure of the

ring in the two series is not strongly reflected in ^{1}H-nmr data since protons are present only in the substituents. The difference in shift of corresponding signals for the two series of compounds is comparatively small. The methyl group introduced on alkylation appears at lower field in the endo series than in the exo series in all cases. The difference is only a few tenths of a ppm. Compounds **1** to **6** are benzoyl amides. In the exo derivatives **2** and **5** the ^{1}H-nmr spectrum of the aromatic ring appears essentially as a slightly broadened singlet, indicating that the CO group is significantly turned out of the plane of the benzene ring (f in Table I, column $\delta(R_2)$) In the other benzoyl derivates studied, the two protons next to the CO group are shifted to lower field by *ca.* 0.8 ppm relative to the meta and para protons due to the anisotropy of the carbonyl group (g in Table I, column $\delta(R_2)$).

Conclusion.

Ir and carbon nmr are useful methods for the determination of the methylation site in acylamido thiadiazoles. The observed effects are large and can be explained by well known arguments. They reflect the difference in electronic structure and the methods can therefore be generalised to other reaction products. The success of the methods depends on the correct assignment of the relevant absorption which may be hampered by overlapping signals. Since the inherent resolution in carbon nmr is better than in ir that method is likely to be applicable for wider classes of compounds.

EXPERIMENTAL

The spectra were recorded on the following instruments: ir, Perkin-Elmer PE 457; ^{1}H-nmr, Varian T-60 (60 MHz); ^{13}C-nmr Bruker WP 80 (20 MHz). Melting points were measured on a Tottoli melting point apparatus and are uncorrected. Tlc was carried out on Merck silica gel 60 F 254.

The 5-alkyl-2-acylamido-1,3,4-thiadiazoles were prepared by acylation of the corresponding 5-alkyl-2-amino-1,3,4-thiadiazoles (2).

General Method of Preparation of 5-Alkyl-2-acylamido-1,3,4-thiadiazoles.

The 5-alkyl-2-amino-1,3,4-thiadiazole (1 mole) was suspended in pyridine (50 ml.) and the suspension cooled to 0-10°. To this was added under efficient stirring and cooling the acid chloride (1 mole). The resulting solution was stirred at 0-10° for a further 1 hour and then at room temperature for between 2 and 6 hours. The reaction mixture was concentrated to half its volume and poured into water (1 litre), previously acidified to *p*H 2 with 2*N* sulphuric acid. The resulting precipitate was filtered, washed neutral with water, dried and recrystallised from ethanol to give the 5-alkyl-2-acylamido-1,3,4-thiadiazole as a colourless crystalline solid.

Methylation of 5-Alkyl-2-acylamido-1,3,4-thiadiazoles.

1) Methylation of 5-Methyl-2-benzoylamido-1,3,4-thiadiazole (**1**).

To a well stirred solution of 5-methyl-2-benzylamido-1,3,4-thiadiazole (**1**) (11.0 g., 0.05 mole) in dioxane (100 ml.) was added dropwise a solution of diazomethane (*ca.* 0.1 mole) in ether (100 ml.). The reaction mixture was stirred at room temperature for a further 24 hours. The solvents were removed under reduced pressure to give 10.2 g. of a beige solid, shown by tlc to consist of two components. These were separated by column chromatography over silica using 3% methanol in chloroform as eluant. Fraction 1 consisted of compound **3** (5.8 g., 50%), m.p. 148-150°. Fraction 2 consisted of a colourless solid (0.5 g.) which was recrystallised from toluene (15 ml.) to give compound **2** (0.45 g., 3.9%) m.p. 182-184°.

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.77; H, 4.14; N, 19.16; S, 14.62. Found: C, 54.68; H, 4.02; N, 19.23; S, 14.48.

Compound **2**.

Compound **2** was synthesized as described in 1) above.

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.64; H, 4.76; N, 18.02; S, 13.74. Found: C, 56.51; H, 4.84; N, 17.99; S, 13.55.

Compound **3**.

Compound **3** was synthesized as described in 1) above.

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.64; H, 4.76; N, 18.02; S, 13.74. Found: C, 56.53; H, 4.68; N, 18.01; S, 13.64.

2) Methylation of 5-Isopropyl-2-benzoylamido-1,3,4-thiadiazole (**4**).

Using the above method 5-Isopropyl-2-benzoylamido-1,3,4-thiadiazole (**4**) (10.75 g., 0.05 mole) gave after reaction and chromatography (2% methanol in chloroform) compound **6** (6.1 g., 47%), m.p. 73-75° and compound **5** (2.95 g., 23%) m.p. 47-50° (after recrystallisation from petroleum ether).

Anal. Calcd. for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.99; S, 12.96. Found: C, 58.02; H, 5.23; N, 17.05; S, 12.65.

Compound **5**.

Compound **5** was synthesized as described in 2) above.

Anal. Calcd. for $C_{12}H_{13}N_3OS$: C, 59.75; H, 5.79; N, 16.08; S, 12.26. Found: C, 59.93; H, 5.65; N, 15.72; S, 11.73.

Compound **6**.

Compound **6** was synthesized as described in 2) above.

Anal. Calcd. for $C_{12}H_{13}N_3OS$: C, 59.75; H, 5.79; N, 16.08; S, 12.26. Found: C, 59.93; H, 5.65; N, 15.72; S, 11.73.

3) Methylation of 5-Isopropyl-2-propionamido-1,3,4-thiadiazole (**7**).

5-Isopropyl-2-propionamido-1,3,4-thiadiazole (**7**) (10.0 g., 0.05 mole) gave under the above methylation conditions, 10.1 g. of a yellow oil. Chromatography over silica using petroleum ether/ethyl acetate 1:1 afforded compound **9** (6.5 g., 61.3%) as a colourless liquid and 2.5 g. of a colourless solid. Recrystallisation of this solid from petroleum-ether yielded compound **8** (2.0 g., 18.9%) m.p. 70-73°.

Anal. Calcd. for $C_8H_{13}N_3OS$: C, 48.22; H, 6.57; N, 21.09; S, 16.09. Found: C, 48.31; H, 6.48; N, 20.97; S, 15.95.

Compound **8**.

Compound **8** was synthesized as described above.

Anal. Calcd. for $C_9H_{15}N_3OS$: C, 50.68; H, 7.09; N, 19.71; S, 15.03. Found: C, 50.68; H, 7.28; N, 19.57; S, 14.89.

Compound **9**.

Compound **9** was synthesized as described above.

Anal. Calcd. for $C_9H_{15}N_3OS$: C, 50.68; H, 7.09; N, 19.71; S, 15.03. Found: C, 50.39; H, 6.97; N, 19.80; S, 14.90.

4) Methylation of 5-*t*-Butyl-2-pivaloylamido-1,3,4-thiadiazole (**10**).

5-*t*-Butyl-2-pivaloylamido-1,3,4-thiadiazole (**10**) (12.0 g., 0.05 mole) gave after treatment with diazomethane a mixture of starting material (**10**) and endo-product (**12**). Compound **12** was more easily prepared by treating compound **10** (24.1 g., 0.1 mole) and potassium *t*-butoxide (11.2 g., 0.1 mole) in *t*-butanol (150 ml.) at 50° with methyl iodide (15.0 g., 0.1 mole) in *t*-butanol (50 ml.) and heating the resulting mixture under reflux for 15 hours. The reaction mixture was filtered hot. The filtrate was poured onto ice (600 g.), the *p*H adjusted to 7 with dilute hydrochloric acid and extracted with ether. The ether extract was washed several times with water, dried and evaporated to give 26.3 g. of a yellow oil. This oil was chromatographed over silica using 25% ethyl acetate in petroleum ether as eluant. Fraction 1 consisted of compound **12** (18.1 g., 71.0%) as a colourless liquid. Fraction 2 consisted of starting material (**10**) (3.2 g.).

Compound **10**.

Compound **10** was obtained as described above.

Anal. Calcd. for $C_{11}H_{19}N_3OS$: C, 54.74; H, 7.93; N, 17.41; S, 13.28. Found: C, 54.68; H, 7.71; N, 17.29; S, 12.10.

Compound **12**.

Compound **12** was obtained as described above.

Anal. Calcd. for $C_{12}H_{21}N_3OS$: C, 56.44; H, 8.29; N, 16.45; S, 12.55. Found: C, 56.72; H, 8.12; N, 16.60; S, 12.22.

5-Isopropyl-2-methylamino-1,3,4-thiadiazole (**13**).

4-Methylthiosemicarbazide (10.5 g., 0.1 mole) was suspended in toluene (50 ml.) and heated to 50°. To this was added isobutyroyl chloride (21.3 g., 0.2 mole) at such a rate as to keep the temperature at 50°. After the addition the mixture was heated at 85° for 2 hours. The two-phase mixture was cooled to 10° whereupon a colourless solid precipitated out, was filtered off, washed with a little cold toluene and dried on the filter to give 15.2 g. of the hydrochloride of **13** as a colourless solid. This was dissolved in water (30 ml.) and neutralised with concentrated ammonia. The oil which separated was extracted with ether. The ether fraction was washed with water, dried and evaporated to give compound **13** (12.1 g., 77.0%) as a yellowish oil; nmr (deuteriochloroform): 1.34 (doublet J = 8 Hz, 6H, $(CH_3)_2CH$-), 3.04 (singlet, 3H, CH_3-N), 3.25 (septuplet, 1H, $-CH(CH_3)_2$), 7.2 (broad singlet, 1H, NH).

Anal. Calcd. for $C_6H_{11}N_3S$: C, 45.83; H, 7.05; N, 26.72; S, 20.39. Found: C, 45.67; H, 7.01; N, 26.99; S, 20.13.

Benzoylation of 5-Isopropyl-2-methylamino-1,3,4-thiadiazole (**13**).

A solution of 5-Isopropyl-2-methylamino-1,3,4-thiadiazole (**13**) (3.14 g., 0.02 mole) in pyridine (50 ml.) was cooled to 10°. Benzoyl chloride (2.8 g., 0.02 mole) was added dropwise, keeping the temperature at 10°. The reaction mixture was stirred at room temperature for 18 hours then poured into water (400 ml.) and extracted with ether. The ether extract was washed with 2*N* sulphuric acid and water, dried and evaporated to give 5.0 g. of a yellow oil which crystallised on standing. Recrystallisation from petroleum ether afforded compound **5** (3.0 g., 58%), m.p. 47-50°.

5-Isopropyl-3-methyl-2-imino-1,3,4-thiadiazole (**14**).

A solution of 2-amino-5-isopropyl-1,3,4-thiadiazole (28.6 g., 0.2 mole) in anhydrous methanol (250 ml.) was heated under reflux for 24 hours with methyl iodide (92.0 g., 0.65 mole). The methanol and excess methyl iodide was evaporated and the resulting solid washed twice with cold acetone. The red filtrate was discarded. The yellow residue was dissolved in methanol (40 ml.) and treated with ether (250 ml.). The hydroiodide of compound **14** precipitated out as a colourless solid (15.4 g., 55%), m.p. 149-153°, and was shown by ^{1}H-nmr spectroscopy to be almost pure material; nmr (deuteriochloroform): 1.36 (doublet, J = 8 Hz, 6H, $(CH_3)_2CH$), 3.20 (septuplet, J = 8 Hz, 1H, $-CH(CH_3)_2$), 4.0 (singlet, 3H, CH_3-N), 9.7 (broad singlet, 2H, NH + HI).

Anal. Calcd. for $C_6H_{11}N_3S \cdot HI$: C, 25.28; H, 4.24; N, 14.74; S, 11.23. Found: C, 25.22; H, 4.31; N, 14.76; S, 11.04.

Benzoylation of 5-Isopropyl-3-methyl-2-imino-1,3,4-thiadiazole (**14**).

A solution of 5-isopropyl-3-methyl-2-imino-1,3,4-thiadiazole hydroiodide (2.85 g., 0.01 mole) in pyridine (50 ml.) was cooled to 10°. Benzoyl chloride (2.8 g., 0.02 mole) was added dropwise, keeping the temperature at 10°. The reaction mixture was stirred at room temperature for 2 hours. The pyridine was evaporated and the residue taken up in ether (100 ml.). The ether solution was washed with water, dilute sulphuric acid and again with water dried and evaporated to give 3.1 g. of a yellow solid. Recrystallisation of this solid from petroleum ether afforded compound **6**, (2.31 g., 88%) as colourless crystals, m.p. 73-74°.

REFERENCES AND NOTES

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