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Spectral Assignments and Reference Data

^{1}H, ^{13}C, ^{15}N and ^{19}F NMR study of acetylation products of heterocyclic thiosemicarbazones

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Novel 2-acetylamino-4-acetyl-5-aryl(heteryl)-1,3,4-thiadiazolines, 2-acetylamino-5-aryl(heteryl)-1,3,4-thiadiazoles, and some of their salts were prepared and studied by multinuclear ^{1}H, ^{13}C, ^{15}N, ^{19}F and 2D NMR spectroscopy. The acetylation of thiosemicarbazones is accompanied by ring closure to form the corresponding 1,3,4-thiadiazolines and 1,3,4-thiadiazoles. ^{15}N NMR spectroscopy is a unique method for the identification of thiadiazole pyridinium salts. Copyright © 2007 John Wiley & Sons, Ltd.

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KEYWORDS: 1,3,4-thiadiazolines; 1,3,4-thiadiazoles; heterocyclization; acetylation; NMR spectroscopy; B3LYP/6-311G+ method

INTRODUCTION

Acetylation of thiosemicarbazones of the aromatic and heterocyclic series by acetic anhydride has been investigated with the aim of preparing new heterocyclic compounds of the thiadiazole series. The unremitting interest in substituted thiadiazoles is caused by their remarkable biological properties such as antitubercular, antifungal, antibacterial and hypoglycemic activity.[1–4]

There are some known methods for the synthesis of substituted 1,3,4-thiadiazolines and 1,3,4-thiadiazoles based on thiosemicarbazones and thiobenzohydrazine.[4–11] Some 1,3,4-thiadiazolines were obtained from diaryl and aryl cycloalkyl ketones via the corresponding thiosemicarbazones.[4] 2,4-Substituted 5,5-pentamethylene-4,5-dihydro-1,3,4-thiadiazole was prepared by the reaction of cyclohexanone thiosemicarbazone with acetic anhydride in the presence of acetyl chloride by heating in pyridine.[5,6] 1,4-Diphenylthiosemicarbazide under long storage with formaldehyde in dioxane afforded 4-phenyl-2-phenylamino-1,3,4-thiadiazoline.[7] Substituted 4-carbamoyl-2-ureido-4,5-dihydro-1,3,4-thiadiazoles were prepared by the cyclization reaction of thiosemicarbazones of benzaldehyde, furan-2-aldehyde, acetone, cyclopentanone, and cyclohexanone with isocyanates under heating.[8] Thiobenzoylhydrazones were cyclized under prolonged heating in chloroform to give 2,5-substituted 1,3,4-thiadiazoles.[9] The reaction of thiosemicarbazones of benzaldehyde, formaldehyde, acetone, and acetophenone with acetic anhydride under heating (100 °C) led to 4-acetyl-2-acetylamino-Δ^2-1,3,4-thiadiazolines and 4-acetyl-2-amino-Δ^2-1,3,4-thiadiazolines.[10] Substituted 2,3-dihydro-1,3,4-thiadiazoles were synthesized in benzene by the reaction of *N*′-phenylthiobenzoylhydrazine with aliphatic, aromatic, and heterocyclic aldehydes and ketones in the presence of trimethylsilylchloride in benzene.[11] Some data on the acetylation reaction of thiosemicarbazones have been reported in ashort communication.[12]

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RESULTS AND DISCUSSION

The acetylation of thiosemicarbazones of 4-methoxybenzaldehyde (**1a**), pyridine-4-aldehyde (**1b**), pyridine-3-aldehyde (**1c**), pyridine-2-aldehyde (**1d**), thiophene-2-aldehyde (**1e**), furan-2-aldehyde (**1f**), indole-3-aldehyde (**1g**), and isatine (**1h**) by acetic anhydride (**2**) has been investigated in the present work in order to prepare promising biologically active compounds. The reactions involved the cycle closure (addition of mercapto group across the CH=N bond) and simultaneous acetylation across the NH group of the ring and the NH_2 group of the open chain to give 2-acetylamino-4-acetyl-5-aryl(heteryl)-1,3,4-thiadiazolines **(3a–h)** (Scheme 1):

The reaction of pyridine-4-aldehyde thiosemicarbazone (**1b**), with acetic anhydride at 100 °C for 2 h resulted in a mixture of 2-acetylamino-4-acetyl-5-(pyridyl-4)-1,3,4-thiadiazoline (**3b**) (37% yield) and 2-acetylamino-5(pyridyl-4)-1,3,4-thiadiazole (**4a**) (25% yield). The reaction at a temperature of 120 °C for 5 h led to only one product (**4a**) in 63% yield.

The cyclization of thiosemicarbazones **1a, 1c, 1d, 1e**, and **1f** with acetic anhydride under heating (75–80 °C) for 3–4 h gave 2-acetylamino-4-acetyl-5-aryl(heteryl)-1,3,4-thiazolines (**3a, 3c–f**) in 98–40% yields. The reaction did not involve the formation of 1,3,4-thiadiazoles (**4**). The reaction of indole-3-aldehyde thiosemicarbazone (**1g**) with acetic anhydride under heating (80 °C) for 3 h resulted in 2-acetylamino-4-acetyl-5-(3-indolyl)-1,3,4-thiadiazoline (**3g**) in 90% yield. The product decomposed under long heating at higher temperatures to give both 2-acetylamino-1,3,4-thiadiazole (**5**) and an unidentified product.

The heating of 3-isatine thiosemicarbazone (**1h**) with acetic anhydride at 115–120 °C for 4 h led to the cyclization and the formation of the intermediate **A.** The latter was acetylated across the NH and NH_2 groups to give spiro[2-acetylamino-4-acetyl-1,3,4-thiadiazole-5,3′-*N*-acetylindol-2-one] (**3h**) in 74% yield (Scheme 2). The IR spectra of all compounds showed absorption bands of C–S bonds, (690–695 cm^{-1}), C=N (1580–1590 cm^{-1}), C=O (1630–1640, 1690–1710 cm^{-1}), and NH (3150–3210 cm^{-1}).

In the ^{1}H NMR spectrum of thiadiazole **5** (Table 1), the low-field signal (9.13 ppm) is related to a proton in the position 5, whereas in the ^{13}C NMR spectrum without proton decoupling there is a significant C-5 signal splitting characteristic of these cyclics ($^{1}J_{C-H} = 212$ Hz).

As seen from Table 1, the signal of methyl protons in the $NHCOCH_3$-fragment is in a high-frequency region (2.1–2.3 ppm) compared to that of the acetyl group protons (2.0–2.10 ppm) and does not depend much on the substituent in the thiadiazolyl fragment at position 5. The chemical shifts of the NH group proton in both thiadiazolines (**3**) and thiadiazoles (**4**) are hardly sensitive to the effect of the heterocyclic substituent in the position 5 (Table 1). The position of resonance signals of H-5 and C-5 in the proton and carbon spectra of the thiadiazolyl (**3**) series changes insignificantly depending on the substituent in this position ($\Delta\delta = 0.4$ and 6 ppm, respectively), whereas in the heteroaromatic system **4,** the effect of substituent is much higher ($\Delta\delta$ C-5 = 12 ppm, Table 1). Thus, the chemical shifts of the heterocycle nuclei in the thiadiazoles are more sensitive to substituent effects than those in thiadiazolines.

The heterocyclic ring in the position 5 poorly influences the ^{15}N screening constant of the thiadiazoline ring nitrogen atoms **3**. The position of the resonance signals of pyridinic nitrogen atom N-3 is changed from −113 to −117 ppm region, whereas the signals of pyrrolic type nitrogen atoms N-4 (from −192 to −199 ppm) are shifted to lower frequencies by ~80 ppm (Table 1), which is a well-known fact in ^{15}N NMR.[13] Because of serious structural changes, quite a different picture is observed in ^{15}N NMR spectra in going from thiadiazolines to thiadiazoles: the ring nitrogen atom signals show a dramatic high-frequency shift (by more than 100 ppm). Disruption of the aromaticity in the thiadiazolines decreases the screening of ^{15}N nucleus of cyclic nitrogen atoms. Since both these nitrogen atoms in the thiadiazoles are the 'pyridine' nitrogen atoms, a problem of assigning their signals appears. As known from the literature,[13] the $\delta^{15}N$ value of nitrogen atoms of unsubstituted thiadiazole is −10 ppm and depends much on the presence of the substituent in the positions 2 and 5 (Scheme 3):

^{15}N NMR signals of the compounds studied were measured by 2D HMBC ^{1}H–^{15}N method or direct method of accumulation. The

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Spectral Assignments and Reference Data

Table 1. NMR spectrum parameters (δ, ppm and J, Hz) of 5-substituted 2-acetylamino-4-acetyl-1,3,4-thiadiazolines (**3**) and 5-substituted 2-acetylamino-1,3,4-thiadiazoles (**4, 5**) and their salts (**6–11**) (DMSO-d_6)

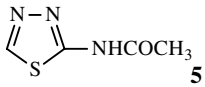
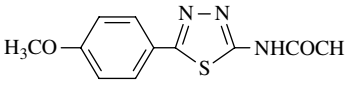
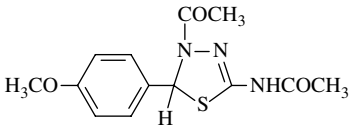
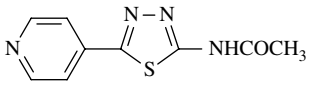
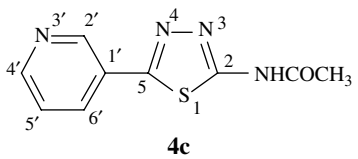
Compound 1	δ^1H 2	δ^{13}C 3	δ^{15}N 4
 **5**	2.19 CH_3 9.13 H-5 12.60 NH –	22.49 q CH_3 $^1J = 129.0$ 148.54 d C-5 $^1J = 212.0$ 158.56 C-2 $^2J = 4.0$ 168.70 C═O $^2J = 6.4$	−19.9 N-4 −55.5 N-3 −242.3 NH –
 **4a**	2.21 CH_3 3.83 CH_3O 7.05 d H-3′, 5′ $^3J = 8.8$ 7.81 d H-2′, 6′ $^3J = 8.8$ 11.4 br NH	22.40 d CH_3 $^1J = 129.4$ 55.73 d CH_3O $^1J = 144.6$ 115.13 C-3′, 5′ $^1J = 161.6$, $^2J = 4.7$ 123.68 C-1′ $^2J = 7.2$ 128.68 C-2′, 6′ $^1J = 161.0$, 158.04 C-2, 161.52 C-4′ 162.08 C-5, 168.83 C═O	– – – – – – –
 **3a**	2.03 CH_3 2.17 CH_3(NH) 3.72 OCH_3 6.77 H-5 6.88 d H-2′, 6′, $^3J = 8.5$ 7.17 d H-3′, 5′ $^3J = 8.5$ 11.7 br NH – –	21.94 q CH_3 $^1J = 129.0$ 22.45 q CH_3(NH) $^1J = 129.0$ 55.22 q OCH_3 $^1J = 144.2$ 65.68 C-5 dt $^1J = 159.5$, $^3J = 4.0$ 114.05 dd C-3′, 5′ $^1J = 160.6$, $^3J = 4.8$ 126.70 ddd C-2′, 6′ $^1J = 158.2$, $^{2,3}J = 6.8$,3.6 133.56 dd C-1′ $^2J = 8.4$, $^2J = 7.2$ 146.06 d C-2 $^2J = 4.1$, 159.12 d C-4′ 4′ $^2J = 8.8$ 167.33 q C═O $^2J = 6.3$ 169.39 qd C═O(NH) $^2J = 6.5$, $^3J = 2.9$	−113.5 N-3 −194.8 N-4 −243.8 NH – – – – – – – –
 **4b**	2.34 CH_3 7.89 d H-2′, 6′ $^3J = 5.8$ 8.72 H-3′, 5′ $^3J = 5.8$ 11.85 NH –	22.32 q CH_3 $^1J = 129.8$ 120.69 dd C-2′, 6′ $^1J = 167.0$, $^2J = 10.0$ 137.14 dd C-1′ 150.61 dd C-3′, 5′ $^1J = 180.9$, $^2J = 10.8$ 159.48 C-5 159.53 d C-2 $^2J = 4.4$ 168.81 C═O $^2J = 6.8$	−59.8 Npyr −241.7 NH – – – – –
 **4c**	2.23 CH_3 7.55 dd H-5′ $^3J = 8.1$ $^3J = 4.5$ 8.32 H-6′ $^3J = 8.1$ 8.70 dd H-4′ $^3J = 4.5$ $^4J = 1.5$ 9.12 H-2′ $^4J = 1.5$ 12.73 NH	22.38 q CH_3 $^1J = 129.3$ 124.25 ddd C-5′ $^1J = 165.9$, $^2J = 8.2$ 126.46 dd C-1′ $^2J = 10.0$ $^2J = 1.7$ 134.33 dt C-6′ $^1J = 167.0$, $^2J = 5.6$ 147.35 dd C-4′ $^1J = 181.0$, $^2J = 12.1$ 151.11 dd C-2′ $^1J = 180.2$, $^2J = 10.8$ 158.90 C-5 158.96 C-2, 168.77 C═O $^2J = 6.9$	−52.8 Npyr −243.0 NH – – – – – – –

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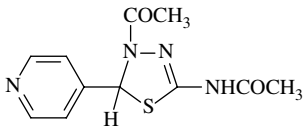
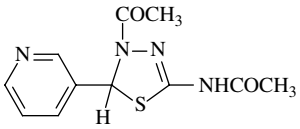
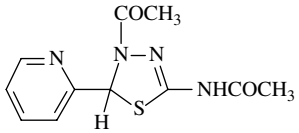
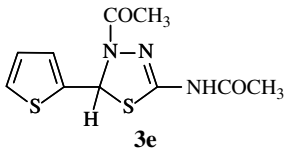
Table 1. (*Continued*)

Compound 1	δ^1H 2	δ^{13}C 3	δ^{15}N 4
 **3b**	2.04 CH_3	21.67 q CH_3 $^1J = 129.0$	−61.4 Npyr
	2.24 CH_3(NH)	22.43 q CH_3(NH) $^1J = 129.8$	−113.6 N-3
	6.85 H-5	64.56 dt C-5 $^1J = 161.4$ $^3J = 4.4$	−198.8 N-4
	7.26 H-2′, 6′	119.87 dm C-2′, 6′ $^1J = 163.6$	−243.6 NH
	$^3J = 5.7$	145.80 d C-2 $^2J = 4.8$	–
	8.56 H-3′, 5′	149.45 t C-1′ $^2J = 6.0$	–
	$^3J = 5.7$	150.06 dd C-3′, 5′ $^1J = 179.8$, $^2J = 11.2$	–
	11.84 br s NH	167.66 q C═O $^2J = 6.4$	–
		169.52 q C═O (NH) $^2J = 6.5$	–
 **3c**	2.04 CH_3	22.33 q CH_3 $^1J = 129.4$	−68.4 Npyr
	2.19 CH_3(NH)	23.17 q CH_3(NH) $^1J = 129.4$	−117.3 N-3
	6.86 H-5	64.63 d C-5 $^1J = 161.0$	−199.9 N-4
	7.1 dd H-5′	124.91 d C-5′ $^1J = 165.1$	−245.6 NH
	$^3J = 8.0$ $^3J = 4.9$	134.22 dd C-6′ $^1J = 161.7$	–
	7.66 ddd H-6′	$^2J = 4.7$	–
	$^3J = 7.8$ $^4J = 2.2$	137.49 t C-1′ $^2J = 6.7$	–
	$^4J = 1.2$	146.10 d C-2 $^2J = 4.7$	–
	8.44 d H-2′	147.01 d C-2′ $^1J = 178.5$	–
	$^4J = 2.2$	149.87 d C-4′ $^1J = 180.2$	–
	8.47 dd H-′	169.06 q C═O $^2J = 6.7$	–
	$^3J = 4.9$ $^4J = 1.2$	170.82 q C═O (NH) $^2J = 6.4$	–
	11.8 br s NH	–	–
 **3d**	2.03 s CH_3	21.88 q CH_3 $^1J = 129.0$	−72.2 Npyr
	2.21 s CH_3(NH)	22.54 q CH_3(NH) $^1J = 129.0$	−113.6 N-3
	6.78 s H-5	65.07 d C-5 $^1J = 160.3$	−201.1 N-4
	7.25 d H-6	119.61 dd C-6′ $^1J = 164.0$ $^2J = 5.7$	−246.3 NH
	$^3J = 8.1$	123.26 dt C-4′ $^1J = 165.1$ $^2J = 7.1$	$^1J_{N-H} = 91.1$
	7.30 dd H-4′	137.61 dd C-5′ $^1J = 164.4$ $^2J = 6.1$	–
	$^3J = 7.6$ and 4.9	145.55 d C-2 $^2J = 4.0$	–
	7.79 ddd H-5′	149.85 ddd C-3′ $^1J = 179.5$ $^2J = 7.1$	–
	$^3J = 8.1$ and 7.6	$^2J = 3.7$	–
	$^4J = 1.5$	158.82 dd C-1′ $^2J = 10.8$, $^2J = 9.1$	–
	8.52 d H-3′	168.10 q C═O $^2J = 6.4$	–
	$^3J = 4.9$	169.85 m C═O (NH)	–
	11.75 NH	–	–
 **3e**	2.06 CH_3	21.71 CH_3	−117.1 N-3
	2.16 CH_3 (NH)	22.48 CH_3 (NH)	−199.0 N-4
	6.94 dd H-4′	61.46 C-5	−243.0 NH
	$^3J = 5.0$ and 3.6	125.23 C-5′	–
	7.07d H-3′	126.11 C-4′	–
	$^3J = 3.6$	126.74 C-3′	–
	7.11 H-5	144.54 C-2′	–
	7.44 d H-3′	146.12 C-2	–
	$^3J = 5.0$	167.22 C═O	–
	11.76 NH	169.43 C═O (NH)	–

(*continued overleaf*)

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Spectral Assignments and Reference Data

Table 1. (*Continued*)

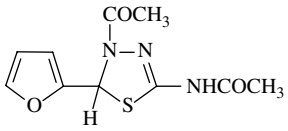
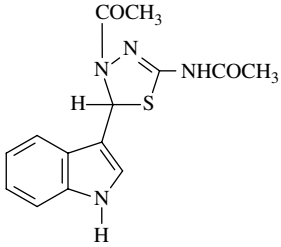
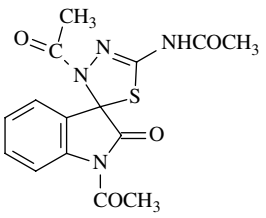
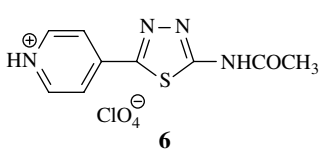
Compound 1	δ^1H 2	δ^{13}C 3	δ^{15}N 4
 **3f**	2.06 CH_3 2.21 CH_3 (NH) 6.31 d H-3′ $^3J = 3.0$ 6.39 dd H-4′ $^3J = 3.0$ and 1.7 6.90 H-5 7.59 H-5′ $^3J = 1.7$ 11.73 NH	21.86 q CH_3 $^1J = 129.4$ 22.56 q CH_3 (NH) $^1J = 129.4$ 59.38 d C-5 $^1J = 159.8$ 107.19 dt C-4′ $^1J = 176.6$, $^2J = 3.2$ 110.69 ddd C-3′ $^1J = 176.1$, $^{2,3}J = 13.6, 4.0$ 143.17 ddd C-5′ $^1J = 204.5$, $^{2,3}J = 11.2, 7.6$ 145.87 d C-2 $^2J = 4.8$ 151.60 dd C-2′ $^2J = 17.2$, $^2J = 7.2$ 167.42 q C═O $^2J = 6.4$ 169.55 C═O (NH) $^2J = 6.4$	−115.1 N-3 −199.2 N-4 −243.4 NH – – – – – – –
 **3g**	2.07 CH_3 (N-4) 2.15 CH_3 (NH) 7.00 t H-6′ $^3J = 8.0$ 7.11 t H-5′ $^3J = 8.0$ 7.15 H 5 7.30 d H-2 $^3J = 2.3$ 7.38 d H-4′ $^3J = 8.0$ 7.49 d H-7′ $^3J = 8.0$ 11.09 NH-indole 11.71 NH – – – –	22.02 q CH_3 (N-4) $^1J = 129.0$ 22.69 q CH_3 (NH) $^1J = 129.4$ 60.99 d C-5 $^1J = 158.2$ 111.93 dd C-7′ $^1J = 159.4$, $^2J = 7.6$ 114.94 C-3′ $^2J = 8.4$, $^2J = 6.0$ 118.80 dd C-5′ $^1J = 158.2$, $^2J = 7.6$ 119.15 dd C-6′ $^1J = 158.6$, $^2J = 7.2$ 121.49 dd C-4′ $^1J = 158.2$, $^2J = 7.6$ 123.63 dd C-2′ $^1J = 182.6$, $^2J = 5.2$ 123.99 m C-9′ 136.82 dd C-8′ $^2J = 9.2$, $^2J = 3.2$ 146.76 C-2 $^2J = 4.9$ 167.23 q C═O $^2J = 6.4$ 169.32 q C═O (NH) $^2J = 6.8$	−116.6 N-3 −192.3 N-4 −243.2 N_{ind} −245.4 NH – – – – – – – –
 **3h**	2.10 CH_3 (N-4) 2.15 CH_3 (NH) 2.56 CH_3 (N-1′) 7.27 dd H-6′ $^3J = 8.1$, $^3J = 7.3$ 7.41 dd H-5′ $^3J = 7.3$, $^3J = 7.2$ 7.47 d H-4′ $^3J = 7.2$ 8.08 d H-7′ $^3J = 8.2$ 12.01 NH – – – – –	21.86 q CH_3 (N-4) $^1J = 129.8$ 22.33 q CH_3 (NH) $^1J = 129.0$ 26.05 q CH_3 (N-1′) $^1J = 130.6$ 75.13 d C-5 $^3J = 3.2$ 115.72 dd C-7′ $^1J = 169.4$, $^2J = 7.2$ 123.96 dd C-6′ $^1J = 164.6$, $^2J = 8.8$ 125.88 dd C-5′ $^1J = 169.4$, $^2J = 7.6$ 127.75 dd C-9′ $^2J = 8.8$, $^3J = 7.2$ 130.37 dd C-4′ $^1J = 163.4$, $^2J = 8.0$ 139.11 dd C-8′ $^2J = 11.6$, $^3J = 9.2$ 143.91 s C-2 167.22 q C═O(NH) $^2J = 6.8$ 170.20 q C═O (N-1′) $^2J = 6.4$ 170.37 q C═O (N-4) $^2J = 6.8$ 172.95 s C═O	−115.9 N-3 −192.4 N-4 −200.6 N_{ind} −245.5 NH – – – – – – – –
 **6**	2.26 s CH_3 8.29 d H-2′, 6′ $^3J = 5.6$ 8.89 d H-3′, 5′ $^3J = 5.6$ 13.0 br s NH –	22.44 CH_3 122.38 C-2′, 6′ 141.69 C-1′ 146.45 C-3′, 5′ 158.19 C-5 160.73 C-2 169.16 C═O	−111.3 Npyr −241.7 NH $^1J_{N-H} = 90.0$ – – – –

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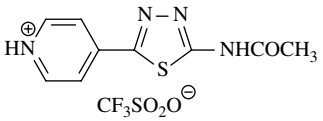
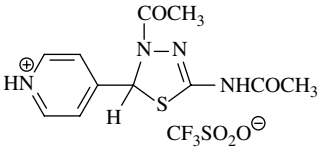
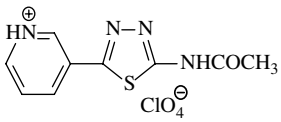
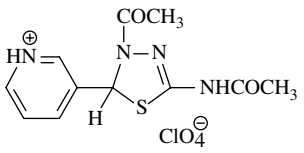
Table 1. (*Continued*)

Compound 1	δ^1H 2	δ^{13}C 3	δ^{15}N 4
 **7**	2.24 s CH_3 8.21 d H-2′, 6′ $^3J = 5.9$ 8.87 d H-3′, 5′ $^3J = 5.9$ 12.93 br s NH – –	22.65 CH_3 120.60 CF_3 $^1J_{C-F} = 321.7$[a] 122.86 C-2′, 6′ 142.61 C-1′ 145.97 C-3′, 5′ 158.21 C-5 161.14 C-2 169.47 C=O	−112.3 Npyr −242.3 NH $^1J_{N-H} = 90.9$ – – – – –
 **8**	2.04 CH_3 2.08 CH_3(NH) 7.03 s H-5 7.88 d H-2′, 6′ $^3J = 6.1$ 8.80 d H-3′, 5′ $^3J = 6.1$ 11.9 br s NH – – –	21.90 CH_3 22.53 CH_3 (NH) 65.60 C-5 120.58 CF_3 $^1J_{C-F} = 320.3$[b] 122.92 C-2′, 6′ 144.12 C-1′ 145.97 C-2 146.43 C-3′, 5′ 161.40 C-2 166.30 C=O 168.85 C=O (NH)	−117.1 Npyr −241.9 NH $^1J_{N-H} = 90.9$ – – – – – – – –
 **9**	2.24 CH_3 7.90 dd H-5′ $^3J = 7.3$, $^3J = 5.0$ 8.75 d H-6′ $^3J = 7.3$ 8.85 d H-4′ $^3J = 5.0$ 9.33 s H-2′ 12.8 br s NH	22.51 CH_3 126.20 C-5′ 128.34 C-1′ 139.22 C-6′ 143.66 C-4′ 146.77 C-5 157.49 C-2 159.77 C-2′ 169.10 C=O	−171.8 Npyr −241.7 NH – – – – – – –
 **10**	2.06 CH_3 2.21 CH_3(NH) 7.00 s H-5 8.01 dd H-5′ $^3J = 7.8$, $^3J = 5.4$ 8.41 d H-6′ $^3J = 7.8$ 8.82 d H-4′ $^3J = 5.4$ 8.86 s H-2′ 12.9 br s NH	21.91 CH_3 22.58 CH_3 (NH) 63.11 C-5 127.29 C-5′ 140.24 C-6′ 140.79 C-1′ 142.07 C-2′ 142.95 C-4′ 145.80 C-2 168.13 C=O 169.84 C=O (NH)	−115.2 N-3 −160.8 Npyr −199.2 N-4 −243.1 NH – – – – – – –

(*continued overleaf*)

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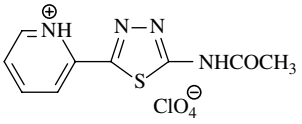
Spectral Assignments and Reference Data

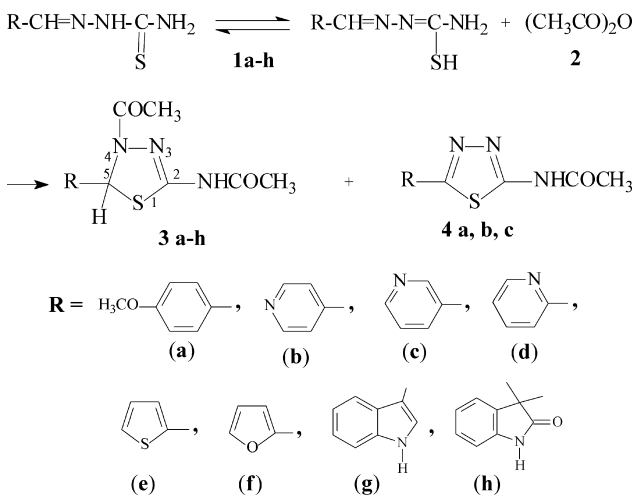
Table 1. (*Continued*)

Compound	δ^1H	δ^{13}C	δ^{15}N
1	2	3	4
 **11**	2.20 CH_3	22.80 CH_3	−188.4 Npyr
	7.25–7.30 m	117.26 C-6′	−243.6 NH
	H-4′, H-6′	118.46 C-4′	–
	8.28 dd H-5′ $^3J = 5.9$, $^3J = 4.3$	119.21 C-1′	–
	8.62 d H-3′	121.98 C-5′	–
	$^3J = 5.9$	123.07 C-3′	–
	13.4 br s NH	124.81 C-5	–
	–	162.44 C-2	–
	–	171.22 C=O	

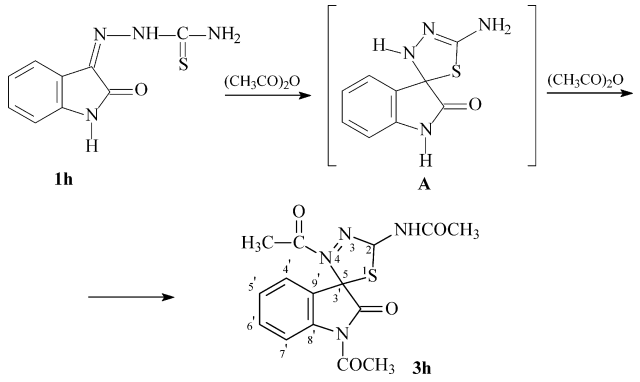
[a] $\delta\ ^9F = -77.7$ ppm was refered to $CFCl_3$.
[b] $\delta\ ^9F = -77.3$ ppm was refered to $CFCl_3$.

assignment of ^{15}N NMR signals in the thiadiazoles and thiadiazolines was made on the basics of 2D HMBC ^{1}H–^{15}N method, literature data[13] or our NMR data of azoles and hydrazones.[14,15] We had some problems with the ^{15}N NMR measurements in thiadiazoles:

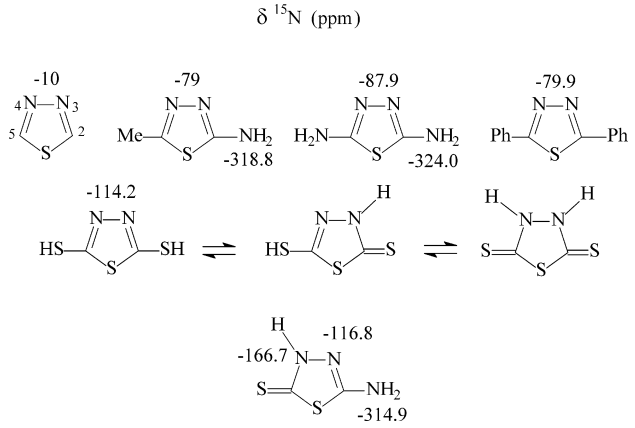
1. low solubility of thiadiazole derivatives does not allow the measurement of the ^{15}N chemical shifts by direct 1D ^{15}N method.



Scheme 1. Synthesis of 2-acetylamino-4-acetyl-5-aryl(heteryl)-1,3,4-thiazolines and 2-acetylamino-5-aryl(heteryl)-1,3,4-thiadiazoles.



Scheme 2. Synthesis of spiro[2-acetylamino-4-acetyl-1,3,4-thiadiazole-5,3′-*N*-acetylindol-2-one].



Scheme 3. ^{15}N NMR chemical shifts of 1,3,4-thiadiazoles.

2. application of 2D HMBC ^{1}H–^{15}N method is of no success either, because the method is optimized with the coupling constant values through two or three bonds, whereas the cyclic nitrogen atoms are remote from the nearest protons: at a distance of four bonds or more.

Thus, we have taken recourse to quantum-chemical calculations to determinate the ^{15}N NMR chemical shifts of cyclic nitrogen atoms of thiadiazoles. Thiadiazoles **5,** and also **4a** and **4b** for which experimental spectra could not be determined because of their poor solubility have been chosen as subjects for the calculations. B3LYP calculations of ^{15}N chemical shifts of nitrogen atoms have been carried out in the 6–311G+ basis set (Table 2).

It should be noted that the results of the B3LYP/6–311G+ calculations are satisfactorily correlated with the experimental data for **5** and **4**. Probably, quantum-chemical calculations of molecules containing the sulfur atom should be carried out in a somewhat different basis set.

The salts **6–11** (Table 1) were obtained by heating 2-,3- or 4-pyridinaldehyde thiosemicarbazone perchlorates in acetic anhydride at 107–120 °C for 5 h or by heating 4-pyridinealdehyde thiosemicarbazone (**4b**) with acetic acid followed by the addition of trifluorosulfoacid. High temperature (120 °C) leads to thiadiazole derivatives (**6, 7, 9, 11**) in high yields, whereas at lower temperatures (107–110 °C) a mixture of thiadiazoles and thiadiazolines (**8, 10**) is formed.

It is pertinent to note that 1,3,4-thiadiazoles, 1,3,4-thiadiazolines and thiosemicarbazones containing pyridine ring have at last three or four potential reactivity centers, i.e. nitrogen atoms able to protonate, for example, N-3, N-4, N_{pyr}, NH, =N–, NH_2.

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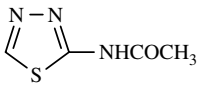
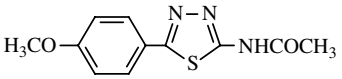
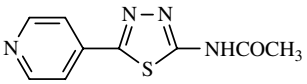
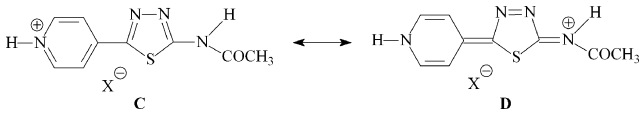
Table 2. Calculated ^{15}N chemical shifts of N-3 and N-4 nitrogen atoms of thiadiazoles **5**, **4a** and **4b** by B3LYP/6-311G+ method

Compound	$\delta^{15}N$, ppm N-3	N-4
 **5**	−85.2	−9.6
 **4a**	−82.7	−12.3
 **4b**	−80.7	−10.8



Scheme 4. Resonance structures of 2-acetylamino-1,3,4-thiadiazole-2-(4-pyridinium) salts.

The nitrogen chemical shifts of the pyridine fragment both in thiadiazoles **4b, 4c** and thiadiazolines **3b**–**3d** changed in the region from −52 to −72 ppm, while in their salts they are located in the region from −160 to −188 ppm (**9**–**11**) or in the region from −112 to −117 ppm (**6**–**8**). This means that we are dealing with the protonated pyridine nitrogen atom, and the nitrogen atom signals shift to high field ∼50 or ∼100 ppm. An analogous picture has been observed by us in the alkylation of pyridine hydrazones.[15] The chemical shifts of ^{15}N pyridine nitrogen atom of hydrazone pyridinium salts have been increased by ∼100 ppm, (−70 ÷ −80 → −170 ÷ −190 ppm)[15] i.e. screening of ^{15}N nuclei of quaternary nitrogen atom considerably increases. As far as the proton spectra (Table 1) are concerned, they are not characteristic to reveal the protonated forms of compounds. NH-proton of quaternary nitrogen atom practically does not manifest in proton spectra because it takes part in the exchange process with water present in the solvent (DMSO). The only indirect evidence for the formation of salts (i.e. the presence of the protonated form) is the shift of the resonance signals of pyridine ring protons to low field by ∼0.5 ppm.

The low value of $\delta^{15}N$ pyridine nitrogen atom in **6**–**8** (−112 to −117 ppm) in comparison with ones in **9**–**11** (−160 to −188) can be caused by the contribution of quinoid structure of type **D** (Scheme 4).

In conclusion, it should be noted that a global shielding of ^{15}N nuclei in going from the neutral molecule to its salt can be a test for quaternization of the pyridine nitrogen atom, and ^{15}N NMR spectroscopy is a unique method for the identification of pyridinium salts.

EXPERIMENTAL

^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectra of the studied compounds were recorded in DMSO-d_6 at room temperature on Bruker DPX-400 and AV-400 spectrometers (400.13, 100.61, 40.56 and 376.46 MHz, respectively). ^{1}H, ^{13}C and ^{15}N, ^{19}F Chemical shift (δ in ppm) were measured with an accuracy of 0.01, 0.02, and 0.1 ppm, respectively, and referred to TMS (^{1}H, ^{13}C), nitromethane (^{15}N), and trichlorofluoromethane (^{19}F). Coupling constants (J in Hz) ^{1}H–^{1}H, ^{1}H–^{13}C, and ^{1}H–^{15}N values approach 0.1 Hz. Some proton signals were assigned using ^{1}H–^{1}H two-dimensional spectra NOESY, whereas the ^{13}C and ^{15}N NMR signal assignment was made by using 2D NMR methods HSQC-GP, and HMBC-GP (^{1}H–^{13}C), HSQC-GP and HMBC-GP (^{1}H–^{15}N) and also with account data reported in the literature.[13,14,16] Two-dimensional inverse proton-detected heteronuclear shift-correlation spectra were obtained with standard pulse sequences.[17] The HMBC spectra were recorded with an acquisition time of 0.2 s, a spectral width of 6000 Hz, 1024 points in the ^{1}H dimension, and 17 and 20 KHz spectral width for ^{15}N and ^{13}C dimension, 512 increments, and, aiming at long-range coupling constant of 5 and 10 Hz for ^{15}N and ^{13}C, respectively, with a relaxation delay of 2 s.

The B3LYP/6–311G+ calculations were carried out with using the Gaussian-98 program.[18] IR Spectra were run a Specord 75-IR spectrophotometer (thin layer).

The synthetic part is given as 'Supplementary Material'.

Supplementary material

Supplementary electronic material for this paper is available in Wiley InterScience at: http://www.interscience.wiley.com/jpages/0749-1581/suppmat/

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