Synthetic and Spectroscopic Study of 5-Amino-2-acyl-1,2,4-thiadiazolin-3-ones

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5-Amino-2-acyl-1,2,4-thiadiazolin-3-ones **2-1** can be synthesized from 5-amino-2*H*-1,2,4-thiadiazolin-3-one (**1-1**) *via* a selective acylation with an acid anhydride in pyridine. The ^{1}H nmr spectral characteristics of 5-amino-2-acyl-1,2,4-thiadiazolin-3-ones **2-1** is in particular, compared with 5-amino-2*H*-1,2,4-thiadiazolin-3-one (**1-1**) and 5-amino-2-alkyl-1,2,4-thiadiazolin-3-ones **1-2, 1-3**. The 5-amino group of **2-1** appeared as two peaks in its ^{1}H nmr spectrum, which merged to a single peak at a higher temperature, while those of compound **1-1, 1-2** and **1-3** appear only as a single peak. The restricted rotation of the C(5)-N(5) (at amino) bond of 5-amino-2-acetyl-1,2,4-thiadiazolin-3-one (**2a-1**) is about 14.5 Kcal/mol.

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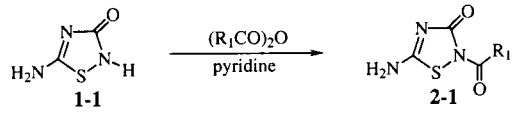
Within the framework of our systematic studies to obtain new analogs of pyrimidines and their derivatives, we have reported the synthesis and reactivity of 5-amino-2*H*-1,2,4-thiadiazolin-3-one (**1-1**) [1-5]. We are interested in **1-1** as it is an analog of cytosine in which the carbon-carbon double bond of cytosine is replaced by a divalent sulfur. While the 2-acyl-5-amino-1,2,4-thiadiazolin-3-ones **2-1** were synthesized as potential biologically active compounds, **2-1** exhibited interesting spectroscopic characteristics. The results described detail the structural phenomena of **2-1**.



1-1 **2-1**

R_1, **a** = CH_3 **b** = $CH_2CH_2CH_3$ **c** = $CH(CH_3)_2$ **d** = $C(CH_3)_3$

Results and Discussion.

The hydrogen at the 2-position of compound **1-1** is more acidic than the 5-amino group. The ^{1}H nmr peak of the 2-NH is more downfield than that of the 5-amino group. The new 2-acyl-5-amino-1,2,4-thiadiazolin-3-ones **2-1** could be prepared with an acid anhydride in pyridine similar to the alkylation of the 2-NH by strong bases such as sodium hydride, sodium methoxide or sodium hydroxide [2,3]. However, acylation is directly influenced by the steric effect of the acid anhydride. When compound **1-1** was allowed to react with trimethylacetic anhydride, acylation surprisingly took place at the 5-NH_2 group forming 5-trimethylacetylamino-2*H*-1,2,4-thiadiazolin-3-one (**3d-1**), instead of the expected 5-amino-2-trimethylacetyl-1,2,4-thiadiazolin-3-one (**2d-1**). The formation of **3d-1** was verified by comparison with an authentic sample prepared by the oxidative cyclization [4,5] of 1-trimethylacetyl-2-thiobiuret (**5d-1**). Its formation can be postulated due to the steric hindrance of the *t*-butyl group. In the case of the secondary alkyl acid anhydride, isobutyric anhydride, the steric effect is only shown as a retardation of acylation at N(2) in comparison with the primary alkyl acid anhydride, *n*-butyric anhydride (see Table I).

The structures of the new 2-acyl-5-amino-1,2,4-thiadiazolin-3-ones **2-1** were established on the basis of ^{1}H NMR, ^{13}C nmr and ir spectral data (Table II). In the case of 2-acetyl-5-amino-1,2,4-thiadiazolin-3-one (**2a-1**), the spectra were identified as shown in Scheme 1. The disappearance of the 2-NH group in the ^{1}H nmr spectrum present in the original 5-amino-2*H*-1,2,4-thiadiazolin-3-one (**1-1**) and subsequent appearance of an acetyl group can serve as supporting evidence for the structure of **2a-1**. The acetyl group of **2a-1** appeared more downfield than that of 5-acetylamino-2*H*-1,2,4-thiadiazolin-3-one (**3a-1**). The chemical shifts of the acetyl groups attached directly to the ring usually occur at higher chemical shifts than those outside the ring [6]. In the ir spectra, the amide and lactam

Table 1

Acylated Products of 5-Amino-2*H*-1,2,4-thiadiazolin-3-one

Compound No.	Rexation Temperature	Rexation Time, hours	Mp (°C)	Yield (%)	Molecular Formula	HRMS m/z, Calcd./Found
2a-1	-5-0	6.0	192-194 (dec.)	74 (40) [a]	$C_4H_5N_3O_2S$	159.0102/159.0103
2b-1	-3--5	5.5	175-176 (dec.)	74 (60) [b]	$C_6H_9N_3O_2S$	187.0415/187.0417
2c-1	18-20	17.5	243-247 (dec.)	68 (57) [b]	$C_6H_9N_3O_2S$	187.0415/187.0416
3d-1	18-20	192	284	55 (2) [c]	$C_7H_{11}N_3O_2S$	201.0572/201.0572

[a] Yield recrystallized from dimethylformamide-methanol (1:10). [b] Yields recrystallized from dimethylformamide-methanol (2:1). [c] Yield recrystallized from ethanol. The balance is starting material.

Table 2

Spectral Data of Acylated Products from 5-Amino-2*H*-1,2,4-thiadiazolin-3-one

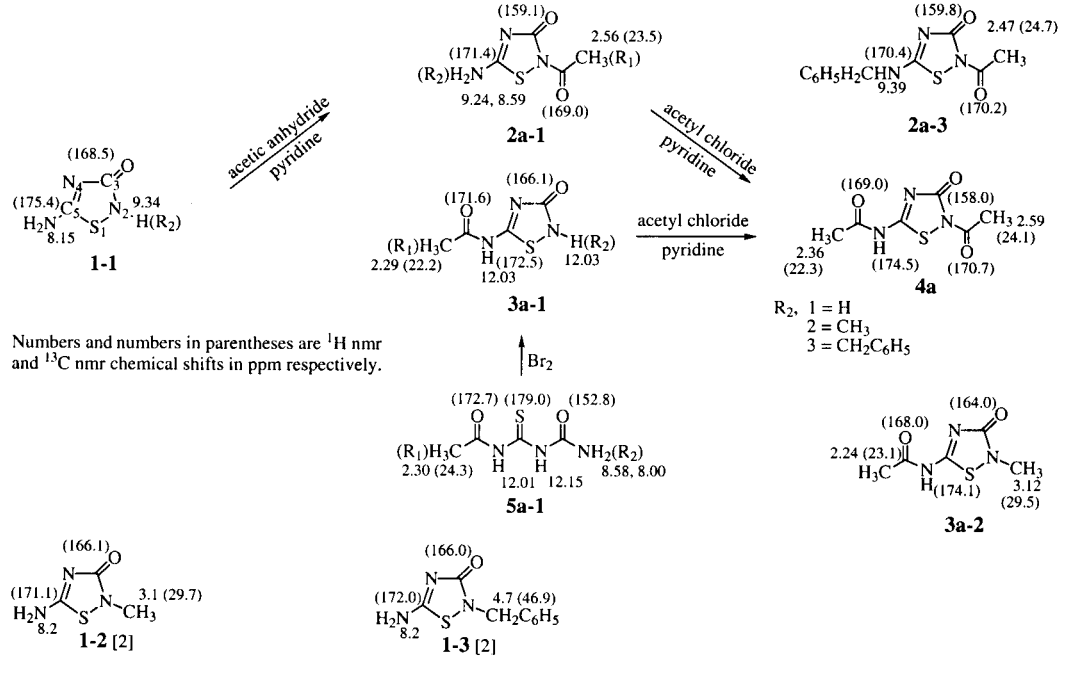
Compound No.	R_1	R_2	Infraed spectrum (potassium bromide): cm^{-1} ^1H NMR (ppm; dimethyl-d_6 sulfoxide): ^{13}C NMR (ppm; dimethyl-d_6 sulfoxide):
2a-1	Me	H	3260 (NH), 3050 (CH), 1700, 1640 (C=O), 1530 (C=N) 9.24, 8.59 (2H, b, NH_2), 2.56 (3H, s, Me), 171.4 (C=N), 169.0 (amide), 159.1 (C=O), 23.5 (Me)
2a-3	Me	Bn	3200 (NH), 3010 (CH), 1680 (C=O),1590, 1580 (C=N) 9.39 (1H, t, NH), 7.25-7.40 (5H, m, Ph), 4.64 (2H, d, CH_2), 2.47 (3H, s, Me), 170.4 (C=N), 170.2 (amide), 159.8 (C=O), 138.3, 129.8, 128.8, 128.7 (Ph), 47.9 (CH_2), 24.7 (Me)
2b-1	Pr	H	3280, 3100 (NH), 2990 (CH), 1690, 1660 (C=O), 1520 (C=N) 9.21, 8.57 (2H, b, NH_2), 2.98 (2H, t, CH_2), 1.66 (2H, m, CH_2), 0.99 (3H, t, Me) 171.8 (C=N), 171.5 (amide), 159.0 (C=O), 37.1 (CH_2), 17.4 (CH_2), 13.5 (Me)
2c-1	*i*-Pr	H	3270 (NH), 3080 (CH), 1690, 1660 (C=O), 1520 (C=N) 9.22, 8.58 (2H, b, NH_2), 3.88 (1H, septet, CH), 1.18 (6H, d, 2Me) 176.0 (amide), 171.6 (C=N), 158.5 (C=O), 32.7 (CH), 18.7 (Me)
3d-1	*t*-Bu	H	3450 (NH), 2990 (CH), 2940 (CH), 1710, 1680, 1650 (C=O), 1580 (C=N), 11.78 (2H, b, 2NH), 1.33 (9H, s, 3Me) 180.8 (amide), 173.1 (C=N), 165.0 (C=O), 39.0 (*C*Me_3), 26.4 (Me)

carbonyl stretching bands are present at 1700 and 1640 cm^{-1} respectively, along with the C=N stretching band at 1530 cm^{-1}. Furthermore, the high resolution mass spectra of the new compounds **2-1** were in good agreement with the proposed structures (Table II). The structure of **2a-1** was acetylated further to 5-acetylamino-2-acetyl-1,2,4-thiadiazolin-3-one (**4a**), as is **3a-1.**

The 5-amino group of compound **2-1** surprisingly exhibited two peaks in its ^1H nmr, which were temperature dependent. At elevated temperature, they appeared as one peak like amide hydrogens (see Figure 1). However, for 5-amino-2*H*-1,2,4-thiadiazolin-3-one (**1-1**) and 2-alkyl-5-amino-1,2,4-thiadiazolin-3-ones **1-2, 1-3**, the peak separation of the amino group could not be observed. When electron donating substituents or hydrogen are attached at position (2), the carbonyl at (3) is conjugated with N(2). In contrast, when an electron withdrawing group is attached at position (2), the carbonyl at (3) draws electron density from the C(4)=N(5) double bond and the 5-amino group. Consequently, rotation of the C(5)-N(5) (at amino) becomes restricted and the hydrogens of the amino group become non-degenerate. The two peaks of **2a-1** (δ_A = 9.12

Scheme 1

Spectral Data of Derivatives of 5-Amino-2*H*-1,2,4-thiadiazolin-3-one



ppm, β_B = 8.50 ppm at T= 22°) broaden and coalesce at 8.65 ppm (T = 44°). On the basis of the coalescence temperature and $\Delta\delta$, the energy barrier for the restricted rotation of the C(5)-N(5) bond, calculated using the method of Caldler and Garratt [7], was ascertained to be $\Delta G^* = 14.5$ Kcal/mol. This rotational energy barrier is similar to that of an amide bond [8].

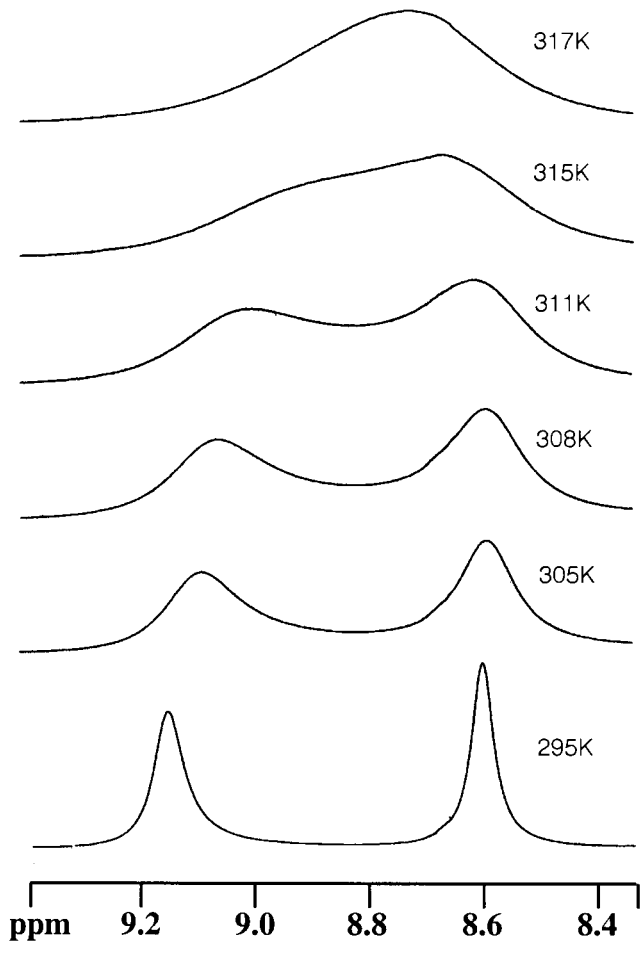


Figure 1. The proton magnetic resonance spectrum of amino group in 2-acetyl-5-amino-1,2,4-thiadiazol-3-(**2a-1**).

To reconfirm the structure of **2a-1**, the ^{13}C chemical shifts were assigned *via* an HMBC experiment. The acetyl carbonyl chemical shift at (2) could directly be assigned as 169.0 ppm. However, the chemical shifts of C(3) and C(5) could not be distinguished because these carbons are not coupled to any hydrogens. To be able to determine the chemical shifts of the ring carbons using the HMBC experiment, 5-benzylamino-2-acetyl-1,2,4-thiadiazolin-3-one (**2a-3**) was prepared. A benzyl (or methyl) substituent is not expected to influence the chemical shifts of the ring carbons greatly and 2-methyl-5-amino-1,2,4-thiadiazolin-3-one (**1-2**) [2], 2-benzyl-5-amino-1,2,4-thiadiazolin-3-one (**1-3**) [2] and 5-amino-2*H*-1,2,4-thiadiazolin-3-one (**1-1**) have almost the same ring carbon chemical shifts. Another similar example is shown in the relationship between **3a-1** and **3a-2**. The chemical shifts of C(3) and C(5) for **2a-3** could be designated as 159.8 ppm and 170.4 ppm, respectively. Consequently, the chemical shifts of C(3) and C(5) for **2a-1** could be inferred as 159.1 ppm and 171.4 ppm, respectively. Comparing the ring carbon chemical shifts of compounds **1**, **2** and **3**, carbon (5) is more or less the same but carbon (3) of **2** has a lower chemical shift than those of **1** and **3**. This can be explained as a conjugation effect of the C(4)=N(5) bond shown as the separation of 5-amino group into two peaks in their ^1H nmr spectra. The ^{13}C chemical shifts of diacetylated **4a** are also additively matched with **2a-1** and **3a-1** as shown in Scheme 1.

This study shows experimentally that 5-amino-2*H*-1,2,4-thiadiazolin-3-one reacts as a lactam form and that the lactam carbonyl of compound **2** is conjugated with the C(4)=N(5) and 5-amino group. However, the carbonyl group of compounds **1** and **3** is conjugated with NH(2). Hence, the 5-amino group of **2-1** is separated into two peaks in its low temperature ^1H nmr spectrum.

EXPERIMENTAL

All melting points were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and were uncorrected. The ir spectra were measured on a Jasco Report-100 spectrophotometer. The ^1H and ^{13}C nmr spectra were obtained on either a 80 MHz Bruker AC-80 or a 400 MHz ARX-400. The mass spectra were recorded on a Varian MAT 212 mass spectrophotometer and exact mass measurement was obtained from a Spectra System MAT 188 data system. Elemental analyses were carried out on an Elementar Analysensysteme GmbH Vario EL at the Korea Basic Science Institute, Seoul, Korea. The thin layer chromatography was used to detect completion of the reactions and the purity of all compounds on the precoated glass plates with silica gel 60 F-254 (purchased from Whatman Catalog No. 4861110). The eluent for tlc was a mixture of *n*-hexane, ethyl acetate and acetic acid (4:8:1, v/v). Most of the commercially available starting materials and solvents were purchased from Aldrich Chemical Company.

5-Amino-2*H*-1,2,4-thiadiazolin-3-one.

It followed a pattern that we have described in the literature [2,3].

2-Acetyl-5-amino-1,2,4-thiadiazolin-3-one (**2a-1**) from **1-1**.

5-Amino-2*H*-1,2,4-thiadiazolin-3-one (**1-1**) (0.3 g, 2.56 mmoles) was suspended in anhydrous pyridine (50 ml) at -5-0°. Acetic anhydride (0.24 ml, 2.58 mmoles) in pyridine (20 ml) was added dropwise to a stirred mixture during the course of one and half hour maintaining the temperature of -5-0°. The mixture was stirred for four and half hours at the same temperature. Thin layer chromatography was followed during the reaction for the determination of the end point of the reaction *via* the disappearance of starting compound **1-1**. After the reaction, the solvent was evaporated under reduced pressure and the residue was washed with

water and ether respectively to give 2-acetyl-5-amino-1,2,4-thiadiazolin-3-one (0.30 g, 74%). To afford an analytical sample, the precipitate was recrystallized from *N,N*-dimethylformamide: methanol (1:10, v/v), mp 192-194° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 9.24 (b, 1H, NH), 8.59 (b, 1H, NH), 2.56 (s, 3H, Me); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 171.4 (C=N), 169.0 (amide), 159.1 (C=O), 23.5 (Me); ir (potassium bromide, ν cm^{-1}): 3260 (NH), 3050 (CH), 1700 (C=O), 1640, 1530 (C=N); hrms: m/z, Calcd. for $C_4H_5N_3O_2S$: 159.0102. Found: 159.0103.

All other 2-acyl-5-amino-1,2,4-thiadiazolin-3-ones **2-1** were obtained by the same procedure described above. Various reaction temperatures and reaction times depending on the acid anhydride are shown in Table I with melting points and yields of products. Table II contains spectral data.

1-Acetyl-2-thiobiuret (**5a-1**) [5].

Potassium thiocyanate (KSCN) (30 g, 0.3 mole) was dissolved in 300 ml of acetone at 40-50°. and acetyl chloride (20 ml, 0.3 mole) was added to the potassium thiocyanate solution. After refluxing for one hour, the reaction mixture was cooled to room temperature in an ice bath. The by-product potassium chloride was filtered and urea (15 g, 0.25 mole) was added to the filtrate. Again the reaction mixture was refluxed for three hours. The solvent was distilled under the reduced pressure and the residue was washed with water and *n*-hexane respectively, to obtain 1-acetyl-2-thiobiuret (16.9 g, 42%). To afford an analytical sample, the product was recrystallized from methanol, mp 198-199°; ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 12.01 (b, 1H, (C=O)NH(C=O)), 12.15 (b, 1H, (C=S)NH(C=S)), 8.58 (b, 1H, (C=O)NH), 8.00 (b, 1H, (C=O)NH), 2.30 (s, 3H, Me); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 179.0 (C=S), 172.7 (C=O), 152.8 (NH(C=O)NH_2), 24.3 (Me); ir (potassium bromide, ν, cm^{-1}): 3240, 3230, 3150 (NH), 3000 (CH), 1710 (C=O), 1670 (C=O).

1-Acetyl-5-methyl-2-thiobiuret (**5a-2**) [4].

The yellow 1-acetyl-5-methyl-2-thiobiuret (yield, 50%) was obtained with methylurea instead of urea by the same procedure for 1-acetyl-2-thiobiuret. To afford an analytical sample, the product was recrystallized from ethanol, mp 183°; ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 12.28 (b, 1H, (C=O)NH(C=S)), 11.94 (b, 1H, (C=S)NH(C=O)), 9.02 (b, 1H, (C=O)NH), 2.83 (d, 3H, NMe), 2.24 (s, 3H, Me); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 179.1 (C=S), 172.9 (C=O), 152.5, (NH(C=O)NH_2), 26.3 (NMe), 24.3 (Me); ir (potassium bromide, ν, cm^{-1}): 3160 (NH), 3000 (CH), 1700 (C=O), 1670(C=O), 1540, 1500.

1-Trimethylacetyl-2-thiobiuret (**5d-1**) [5].

1-Trimethylacetyl-2-thiobiuret (yield, 40%) was prepared with trimethylacetyl chloride instead of acetyl chloride by the same procedure for 1-acetyl-2-thiobiuret. To afford an analytical sample, the product was recrystallized from methanol, mp 143-144°; ^{1}H nmr (deuteriochloroform, δ, ppm): 12.34 (b, 1H, (C=S)NH(C=O)), 9.08 (b, 1H, (C=O)NH), 8.69 (b, 1H, (C=O)NH), 6.44 (b, 1H, N*H*(C=O)CMe3), 1.27 (s, 9H, 3Me); ^{13}C nmr (deuteriochloroform, δ, ppm): 180.4 (C=S), 179.5 (C=O), 154.2 (NH(C=O)NH_2), 40.9 (*C*Me_3), 27.3 (Me); ir (potassium bromide, ν, cm^{-1}): 3300 (NH), 2980(CH), 1720 (C=O), 1680 (C=O).

1-Benzyl-2-thiobiuret [9].

Urea (2 g, 0.04 mole) was added to a solution of benzyl isothiocyanate (5 g, 0.03 mole, purchased from Aldrich) in dioxane (30 ml). The reaction mixture was refluxed for 32 hours. After the reaction, the solvent was removed under the reduced pressure. The resulting residue was washed with water to give 1-benzyl-2-thiobiuret (1.6 g, 22%), mp 158-160°; ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 10.87 (1H, b, NH), 9.85 (1H, b, NH), 7.59-7.31 (5H, m, Ph), 7.13 (1H, b, NH), 6.37, (1H, b, NH), 4.84 (2H, d, CH_2); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 180.6 (C=S), 155.6 (C=O), 137.8, 128.5, 127.5, 127.3 (Ph), 47.6 (CH_2); ir (potassium bromide, ν, cm^{-1}): 3560 (NH), 3250 (CH), 1680 (C=O), 1580 (C=N).

5-Acetylamino-2*H*-1,2,4-thiadiazolin-3-one (**3a-1**) from **5a-1** [5].

1-Acetyl-2-thiobiuret (1 g, 6.2 mmoles) was dissolved in 10 ml of ethanol at 30°. A bromine-ethanol solution (1 *M*, 6.2 ml, 6.2 mmoles) was added to the above solution in the course of 10 minutes. The mixture was stirred for 30 minutes and the reaction mixture cooled in an ice bath. The resulting precipitate was filtered to collect the 5-acetylamino-2*H*-1,2,4-thiadiazolin-3-one (0.55 g, 56%). To afford an analytical sample, the product was recrystallized from water, mp 216° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 12.03 (b, 2H, 2NH), 2.29 (s, 3H, Me); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 172.5 (C=N), 171.6 (amide), 166.1 (C=O), 22.2 (Me); ir (potassium bromide, ν, cm^{-1}): 3100 (NH), 2870 (CH), 1670, 1640, 1610 (C=O), 1550 (C=N).

Anal. Calcd. for $C_4H_5N_3O_2S$: C, 30.19; H, 3.17; N, 26.40. Found: C, 30.11; H, 3.35; N, 26.62.

5-Acetylamino-2-methyl-1,2,4-thiadiazolin-3-one (**3a-2**) from **5a-2** [4].

The white 5-acetylamino-2-methyl-1,2,4-thiadiazolin-3-one (yield, 72%) was prepared by the same procedure as for **3a-1**. To afford an analytical sample, the product was recrystallized from *N,N*-dimethylformamide:ethanol (1:5, v/v), mp 230° dec; ^{1}H nmr (pyridine-d_5, δ, ppm): 3.12 (s, 3H, NMe), 2.24 (s, 3H, Me); ^{13}C nmr (pyridine-d_5, δ, ppm): 174.1 (C=N), 168.0 (amide), 164.0 (C=O), 29.5 (NMe), 23.1 (Me); ir (potassium bromide, ν, cm^{-1}): 3050 (NH), 2900 (CH), 1690 (C=O), 1660, 1560 (C=N).

5-Trimethylacetylamino-2*H*-1,2,4-thiadiazolin-3-one (**3d-1**) from **5d-1** [5].

5-Trimethylacetyl-amino-2*H*-1,2,4-thiadiazolin-3-one (**3d-1**, yield, 62%) was prepared by the identical procedure for **3a-1**. To afford an analytical sample, the product was recrystallized from ethanol, mp 284°; ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 11.78 (b, 2H, 2NH), 1.33 (s, 9H, 3Me); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 180.8 (amide), 173.1 (C=N), 165.0 (C=O), 39.0 (*C*Me_3) 26.4 (Me); ir (potassium bromide, ν, cm^{-1}): 3450 (NH), 2990, 2940 (CH), 1710 (C=O), 1680 (C=O), 1650, 1580 (C=N).

5-Benzylamino-2*H*-1,2,4-thiadiazolin-3-one [9] from 1-benzyl-2-thiobiuret.

5-Benzylamino-2*H*-1,2,4-thiadiazolin-3-one (68%) was prepared by the identical procedure for **3a-1**. To afford an analytical sample, the product was recrystallized from ethanol, mp 182-184°; ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 8.92 (2H, b, 2NH), 7.28 (5H, m, Ph), 4.54 (2H, s, CH_2); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 175.4 (C=N), 167.8 (C=O), 137.9, 128.5, 127.4, 127.3 (Ph), 47.4 (Me); ir (potassium bromide, ν, cm^{-1}): 3300 (NH), 3050, 2910 (CH), 1700 (C=O), 1510 (C=N).

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.28; S, 15.47. Found: C, 51.94; H, 4.38; N, 21.10; S, 15.15.

2-Acetyl-5-acetylamino-1,2,4-thiadiazolin-3-one (**4a**) from **2a-1**. Method 1.

2-Acetyl-5-amino-1,2,4-thiadiazolin-3-one (**2a-1**) (0.3 g, 1.9 mmoles) was dissolved in anhydrous pyridine (10 ml). Acetyl chloride (0.13 ml, 1.9 mmoles) was added once to the stirred solution maintaining the temperature of 40-45°. The mixture was stirred for one hour at the same temperature. The resulting reaction mixture was cooled and the solvent was distilled under reduced pressure. The residue was washed with water and ether respectively to provide 2-acetyl-5-acetylamino-1,2,4-thiadiazolin-3-one (0.32 g, 87%). To afford an analytical sample, the product was recrystallized from acetic acid, mp 247-250°; ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 2.59 (s, 3H, Me), 2.36 (s, 3H, Me); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 174.5 (C=N), 170.7 (amide), 169.0 (amide), 158.0 (C=O), 24.1, (Me), 22.3 (Me); ir (potassium bromide, ν, cm^{-1}): 3450 (NH), 3140, 3050 (CH), 1720 (C=O), 1690, (C=O), 1560 (C=N).

Anal. Calcd. for $C_6H_7N_3O_3S$: C, 35.82; H, 3.51; N, 20.90. Found: C, 35.79; H, 3.63; N, 21.14.

2-Acetyl-5-acetylamino-1,2,4-thiadiazolin-3-one (**4a**) from **3a-1**.

5-Acetylamino-2*H*-1,2,4-thiadiazolin-3-one (0.5 g, 3.1 mmoles) was suspended in anhydrous pyridine (10 ml). Acetyl chloride (0.22 ml, 3.1 mmoles) was added to the stirred mixture and heated at 40-45° for one hour. The resulting reaction mixture was then cooled to room temperature and the solvent was distilled under reduced pressure. The residue was washed with water and ether respectively to afford 2-acetyl-5-acetylamino-1,2,4-thiadiazolin-3-one (0.56 g, 89%). The melting point and spectral data of the product are identical with the product synthesized by method 1.

2-Acetyl-5-benzylamino-1,2,4-thiadiazolin-3-one (**2a-3**).

5-Benzylamino-2*H*-1,2,4-thiadiazolin-3-one (0.1 g, 0.48 mmole) was dissolved in anhydrous pyridine (5 ml) at room temperature. Acetic anhydride (0.05 ml, 0.53 mmole) was added to the stirred mixture. The mixture was stirred for three hour at the same temperature. After the reaction, ice-water (50 ml) was added to the reaction mixture and stored in the refrigerator overnight. The resulting precipitate was filtered and washed with water to give 2-acetyl-5-benzylamino-1,2,4-thiadiazolin-3-one (0.04 g, 32%). To afford the analytical sample, it was recrystallized from pyridine, mp 149-151°, ^{1}H nmr (dimethyl-d_6 sulfoxide, δ, ppm): 9.39 (1H, t, NH), 7.25-7.40 (5H, m, Ph), 4.64 (2H, d, CH_2), 2.47 (3H, s, Me); ^{13}C nmr (dimethyl-d_6 sulfoxide, δ, ppm): 170.4 (C=N), 170.2 (amide), 159.8 (ring C=O), 138.3, 129.8, 128.8, 128.7 (Ph), 47.9 (CH_2), 24.7 (Me); ir (potassium bromide, ν, cm^{-1}): 3200 (NH), 3010 (CH), 1680 (C=O),1590, 1580 (C=N).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 51.84; H, 4. 48; N, 16.96; S, 12.96.

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