Synthesis of 5-(Aroylamino)-2-methyl-2*H*-1,2,4-thiadiazol-3-ones by Oxidative Cyclization of 1-Aroyl-5-methyl-2-thiobiurets

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5-Aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **3** have been synthesized by oxidative cyclization of 1-aroyl-5-methyl-2-thiobiurets **2** with hydrogen peroxide in an alkaline solution. The needed 1-aroyl-5-methyl-2-thiobiurets **2** have been obtained through the addition of methylurea to the corresponding aroyl isothiocyanates.

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Introduction.

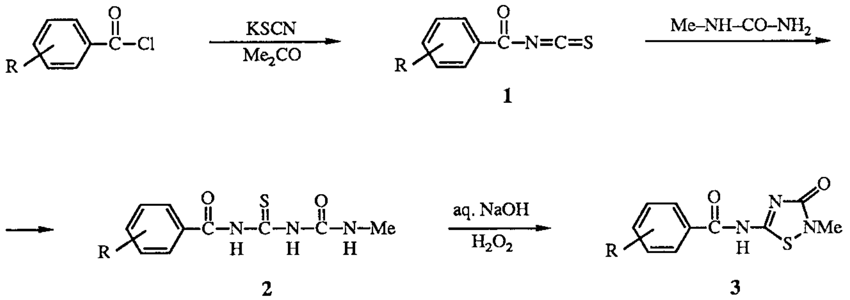
Within the framework of our systematic efforts to obtain new analogs of purine and pyrimidine bases and their nucleosides as potential anticancer, antiviral, and anti-AIDS agents, we have recently reported the synthesis of the acyclonucleosides of 5-amino-2*H*-1,2,4-thiadiazol-3-one and 5-amino-3*H*-1,3,4-thiadiazol-2-one [1]. Also, it has been demonstrated that the cyclic nucleosides of 5-amino-2*H*-1,2,4-thiadiazol-3-one exhibit antimicrobial activity [2]. On the basis of the well-known analogy between a -CH = CH- group in benzenoid hydrocarbons and the bivalent sulfur, -S-, in their heterocyclic analogs, the above compound is the analog of cytosine [3].

Because 5-amino-2*H*-1,2,4-thiadiazol-3-one is biologically active, it seems of interest to investigate the various derivatives of this compound from the point of view of their potential biological activity. Until now, only a few compounds of this type have been synthesized [1,2,4-9].

Acylation of 5-*N,N*-dimethyl-2*H*-1,2,4-thiadiazol-3-one with *N,N*-dimethylcarbamyl chloride was reported to give a mixture of *O*-acyl and *N*-acyl derivatives [4]. Similarly, methylation of 5-phenyl-2*H*-1,3,4-thiadiazol-3-one with dimethyl sulfate also leads to *O*-methyl and *N*-methyl products [5]. These reactions seem to indicate that the 2*H*-1,2,4-thiadiazol-3-one ring exists in two forms - a keto form and an enol form.

Thus, in reactions of the above type, one can always expect a mixture of *O*-substituted and *N*-substituted products. To avoid mixtures, we have decided to prepare the derivatives *via* an oxidative cyclization of 2-thiobiurets (formation of an N-S bond). No 2-thiobiuret derivatives have been prepared in this fashion so far. Only the oxidative cyclization of 2-thiobiuret itself was studied [2,6-8]. Thus, the goal of our work was to investigate the oxidative cyclization of 1-aroyl-5-methyl-2-thiobiurets **2** leading to 5-aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **3**.

Scheme 1



R,
a = H
b = *o*-Me
c = *o*-Cl
d = *m*-NO_2
e = *m*-OMe
f = *p*-OMe
g = *p*-Me
h = *p*-Cl

Results and Discussion.

The new 5-aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **3** were synthesized as shown in Scheme 1.

The intermediate 2-thiobiuret derivatives **2** were obtained by a modified procedure based on Klayman's method of the formation of 1-benzoyl-2-thiobiuret [8]. The synthesis of 1-aroyl-5-methyl-2-thiobiurets **2** is a two-step reaction. First, the reaction of an aroyl chloride with potassium thiocyanate gave a mixture of an aroyl isothiocyanate **1** and an aroyl thiocyanate, with the isothiocyanate as the main product (ir spectrum). Both the isothiocyanate and the thiocyanate possess characteristic ir bands [11]: the isothiocyanate has a broad, strong band at 2140-2040 cm^{-1}, whereas the thiocyanate possesses a sharp band at 2175-2160 cm^{-1}. In the case of the reaction of benzoyl chloride, the corresponding benzoyl isothiocyanate displays a broad, strong band at 1950 cm^{-1}, whereas the thiocyanate has a smaller shoulder at 2110 cm^{-1}. After completion of the first step, methylurea was added to the reaction mixture containing the isothiocyanate and thiocyanate, without any attempted separation. There are two possible addition products in the reaction of methylurea with an aroyl isothiocyanate. One product is a 1-aroyl-5-methyl-2-thiobiuret **2** - our desired product, the second product is a 1-aroyl-3-methyl-2-thiobiuret. The ^{1}H nmr spectra demonstrated that the isolated products are 1-aroyl-5-methyl-2-thiobiurets. Depending on the substituents, the methyl peak is a doublet at 2.6-3.0 ppm and the three NH groups appear at 12.0-13.5 ppm, 11.2-11.8 ppm, and in the aromatic proton region, respectively. The yields, melting points, ir spectra, and ^{1}H nmr spectra of the synthesized 1-aroyl-5-methyl-2-thiobiurets **2** are summarized in Table I.

1-Aroyl-5-methyl-2-thiobiurets **2** are bright yellow solids and their yields vary from 30 to 60% depending on the substituent R. Electron-withdrawing groups tend to enhance the yields. Thus, the reaction of aroyl chlorides with potassium thiocyanate could be accelerated by an electron-withdrawing substituent in the aroyl chloride.

1-Aroyl-5-methyl-2-thiobiurets **2** were then oxidatively cyclized to 5-aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **3** *via* N-S bond formation with hydrogen peroxide in an alkaline solution. We have followed a modified procedure for their synthesis, based on the method originally decribed by Revankar and Robins [2]. 1-Aroyl-5-methylthiobiurets **2** were dissolved in a sufficient amount of 2*N* sodium hydroxide (the needed amount was higher than that reported in the literature) [2]. Hydrogen peroxide (30%, 1.5 equivalents) was added dropwise to the reaction mixture while keeping the temperature at 0°. The product was separated by adjustment of the *p*H value of the solution to *p*H 4.5 with concentrated hydrochloric acid. The obtained 5-aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **3** are colorless solids.

The yields of **3** vary from 69 to 85% depending on the substituent. The structures of **3** were proven on the basis of ^{1}H nmr, ^{13}C nmr, and elemental analysis. The yields, melting points, and elemental analyses of the synthesized **3** are presented in Table II. Table III contains the ir, ^{1}H nmr, and ^{13}C nmr spectra.

To assign the ^{13}C chemical shifts in 1-toluyl-5-methyl-2-thiobiuret **(2g)**, the chemical shifts for this compound were compared with those of 2-thiobiuret which was prepared by a reported method [10]. The cyclization of 2-thiobiurets to 2*H*-1,2,4-thiadiazol-3-ones leads to changes in chemical shifts. The change from C=S to N=C-S results in a large

Table I

Synthesized 1-Aroyl-5-methyl-2-thiobiurets 2 and Their IR and NMR Spectral Data

Compound No.	R	Mp (°)	Yield (%)	IR Spectrum (cm^{-1}, KBr); ^{1}H NMR Spectrum (ppm, DMSO-d_6)
2a	H	170-172	53.0	3400 (NH), 3100, 2900 (CH), 1690 (C=O); 12.5 (1H, b, NH), 11.2 (1H, b, NH), 9.3 (1H, b, NH), 7.5-8.3 (5H, m,Ph), 3.0 (3H, d, HNMe)
2b	*o*-Me	168-169	48.6	3400, 3200 (NH), 2800 (CH), 1710, 1670 (C=O); 12.5 (1H, b, NH), 11.6 (1H, b, NH), 8.3 (1H, b, NH), 7.5-8.3 (4H, m, Ph), 2.8 (3H, d, HNMe), 2.4 (3H, s, PhMe)
2c	*o*-Cl	158-160	33.9	3400 (NH), 2950, 2800 (CH), 1730, 1660 (C=O); 11.7 (1H, b, NH), 10.8 (1H, b, NH), 7.3-7.6 (4H, m, Ph), 2.9 (3H, d, NHMe)
2d	*m*-NO_2	194-196	60.0	3400, 3250 (NH), 3050, 2800 (CH), 1670 (C=O); 12.5 (1H, b, NH), 11.5 (1H, b, NH), 7.3-8.8 (5H, m, Ph + NH), 2.8 (3H, d,HNMe)
2e	*m*-OMe	164-166	56.2	3250 (NH), 1950, 3050 (NH), 1670 (C=O); 13.3 (1H, b, NH), 11.5 (1H, b, NH), 7.0-8.3 (5H, m, Ph + NH), 3.8 (3H, s, OMe), 2.8 (3H, d, HNMe)
2f	*p*-OMe	198-200	54.0	3250 (NH), 2900, 3010 (CH), 1690, 1660 (C=O); 13.0 (1H, b, NH), 11.5 (1H, b, NH), 8.5 (1H, b, NH), 7.0-8.8 (5H, dd, Ph), 3.9 (3H, s, OMe), 2.8 (3H, d, HNMe)
2g	*p*-Me	199-200	34.5	3400, 3250 (NH), 2900 (CH), 1690, 1670 (C=O); 13.0 (1H, b, NH), 11.5 (1H, b, NH), 7.3-8.5 (5H, dd, Ph + NH), 2.8 (3H, d, HNMe), 2.6 (3H, s, PhMe)
2h	*p*-Cl	199-201	30.8	3400, 3250 (NH), 2900 (CH), 1730 (C=O); 13.5 (1H, b, NH), 11.5 (1H, b, NH), 7.5-8.6 (5H, dd, Ph + NH), 2.8 (3H, d, HNMe)

Table II

Synthesized 5-Aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones 3

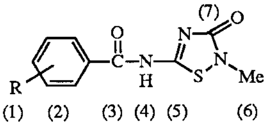
Compound No.	R	Mp (°)	Yield (%)	Molecular Formula (mol wt)	Analysis Calcd. (Found)		
					C%	H%	N%
3a	H	267-268	81.0	$C_{10}H_9N_3O_2S$ (235.27)	51.05 (51.10)	3.86 (3.82)	17.86 (17.60)
3b	*o*-Me	226-228	85.2	$C_{11}H_{11}N_3O_2S$ (249.29)	53.00 (52.51)	4.45 (4.36)	16.86 (17.25)
3c	*o*-Cl	237-239	79.0	$C_{10}H_8ClN_3O_2S$ (269.71)	44.53 (44.50)	2.99 (2.98)	15.58 (16.08)
3d	*m*-NO_2	290-293	69.4	$C_{10}H_8N_4O_4S$ (280.26)	42.86 (42.94)	2.88 (2.81)	19.99 (20.37)
3e	*m*-OMe	228-229	71.9	$C_{11}H_{11}N_3O_3S$ (265.29)	49.80 (49.82)	4.18 (4.14)	15.84 (16.08)
3f	*p*-OMe	275-277	80.4	$C_{11}H_{11}N_3O_3S$ (265.29)	49.80 (49.82)	4.18 (4.16)	15.84 (15.98)
3g	*p*-Me	278-280	74.9	$C_{11}H_{11}N_3O_2S$ (249.29)	53.00 (51.88)	4.45 (4.51)	16.86 (16.77)
3h	*p*-Cl	276-278	75.6	$C_{10}H_8ClN_3O_2S$ (269.71)	44.53 (44.40)	2.99 (2.80)	15.58 (15.60)

Table III

The IR, ^{1}H NMR and ^{13}C NMR Spectral Data for 5-Aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones 3

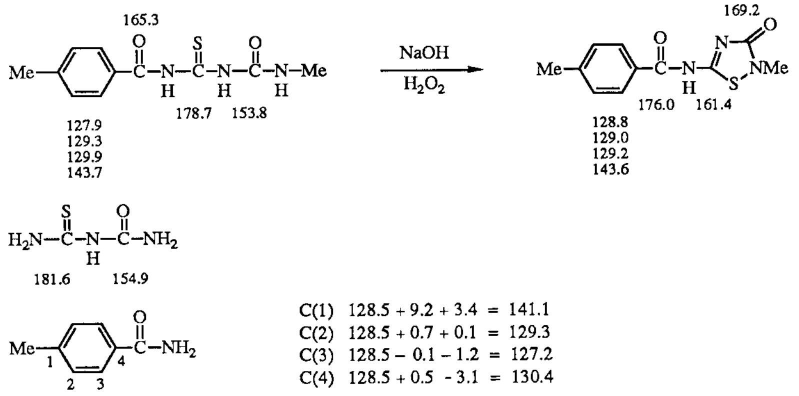
Compound No.	R	IR Spectrum (cm^{-1}, KBr); ^{1}H NMR Spectrum (ppm, DMSO-d_6) [a] ; ^{13}C NMR Spectrum (ppm, DMSO-d_6) [a]
3a	H	3300 (NH), 3050, 2900 (CH), 1680 (C=O); (2) 7.5-8.2 (5H, m, Ph), (6) 3.1 (3H, s, NMe); (2) 128.6-133.2, (3) 174.0, (5) 156.0, (6) 28.9, (7) 169.5
3b	*o*-Me	3400 (NH), 2900, 3150 (CH), 1700 (C=O); (1) 2.5 (3H, s, PhMe), (2) 7.2-7.9 (4H, m, Ph), (6) 3.1 (3H, s, NMe); (1) 20.6, (2) 125.7-138.4, (3) 175.2, (5) 157.7, (6) 28.9, (7) 168.4
3c	*o*-Cl	3400 (NH), 2900, 3050 (CH), 1670, 1640 (C=O); (2) 7.4-7.9 (4H, m, Ph), (6) 3.1 (3H, s, NMe); (2) 127.2-132.8, (3) 172.9, (5) 157.5, (6) 29.0, (7) 168.6
3d	*m*-NO_2	3400 (NH), 2900, 3050 (CH), 1690, 1640 (C=O); (2) 7.7-8.9 (4H, m, Ph), (6) 3.1 (3H, s, NMe); (2) 123.7-148.4, (3) 174.0, (5) 154.0, (6) 29.6, (7) 171.5
3e	*m*-OMe	3400 (NH), 2920, 3040 (CH), 1670, 1640 (C=O); (1) 3.8 (3H, s, OMe), (2) 7.1-7.8 (4H, m, Ph), (4) 11.5 (1H, b, NH), (6) 3.3 (3H, s, NMe); (1) 55.3, (2) 113.2-159.3, (3) 174.1, (5) 159.3, (6) 30.5, (7) 174.1
3f	*p*-OMe	3400 (NH), 2900, 3100 (CH), 1730 (C=O); (1) 3.8 (3H, s, OMe), (2) 7.0-8.1 (4H, dd, Ph), (4) 13.5 (1H, b, NH), (6) 3.1 (1H, b, NMe); (1) 55.5, (2) 114.0-163.3, (3) 179.7, (5) 163.3, (6) 28.8, (7) 169.0
3g	*p*-Me	3400 (NH), 2900, 3050 (CH), 1720 (C=O); (1) 2.5 (3H, s, PhMe), (2) 7.2-8.3 (4H, dd, Ph), (4) 13.2 (1H, b, NH), (6) 3.1 (1H, s, NMe); (1) 21.3, (2) 128.8-143.6, (3) 176.0, (5) 161.4, (6) 28.9, (7) 169.2
3h	*p*-Cl	3400 (NH), 2900, 3100 (CH), 1680 (C=O); (2) 7.4-8.1 (4H, dd, Ph), (6) 3.1 (3H, s, NMe); (2) 127.9-135.6, (3) 175.7, (5) 165.4, (6) 28.5, (7) 173.7

[a] Numbers preceding the chemical shift values in the ^{1}H and ^{13}C nmr spectra indicate the type of H or C, respectively, as shown in the formula below.



upfield shift [12], whereas the transformation of the C = O group in urea to the ring C = N-C = O(NH) should lead to a downfield shift [13]. The chemical shift for the amide carbonyl group shows the smallest change among the three carbons. In the case of 5-toluylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-one (**3g**), the chemical shifts were identified as follows. The chemical shifts of carbon atoms in the phenyl ring (Table IV) were very satisfactorily correlated with the calculated values obtained using the substituent parameters [14] of monosubstituted benzenes, with the C = O(NH) group approximated as C = O(NH_2) (Scheme 2).

Scheme 2



C(1) 128.5 + 9.2 + 3.4 = 141.1
C(2) 128.5 + 0.7 + 0.1 = 129.3
C(3) 128.5 − 0.1 − 1.2 = 127.2
C(4) 128.5 + 0.5 − 3.1 = 130.4

Table IV

The Chemical Shifts of Phenyl Ring Carbon Atoms in 5-Aroyl-2-methyl-2*H*-1,2,4-thiadiazol-3-ones (3)

Compound No.	R	Chemical shifts in DMSO-d_6 (ppm) (Calcd.) [14]					
3a	H	128.6	128.7	132.2	133.2		
		(127.6)	(128.2)	(133.5)	(133.9)		
3b	*o*-Me	125.8	129.6	131.4	131.7	131.9	138.4
		(124.5)	(128.2)	(128.2)	(133.5)	(134.5)	(137.5)
3c	*o*-Cl	127.2	130.5	130.7	131.5	132.3	132.8
		(125.6)	(127.8)	(129.2)	(134.1)	(134.5)	(134.6)
3d	*m*-NO_2	123.7	127.7	131.0	134.9	135.2	148.4
		(117.0)	(120.8)	(122.3)	(128.5)	(134.8)	(144.5)
3e	*m*-OMe	113.2	119.4	121.1	129.8	133.4	159.3
		(133.5)	(118.8)	(120.1)	(128.5)	(134.8)	(157.8)
3f	*p*-OMe	114.0	124.3	130.9	163.3		
		(112.9)	(125.8)	(129.1)	(163.7)		
3g	*p*-Me	128.8	129.0	129.2	143.6		
		(128.2)	(128.2)	(130.8)	(142.8)		
3h	*p*-Cl	127.9	129.9	135.4	135.6		
		(127.8)	(129.2)	(131.9)	(139.9)		

Also, the formation of the 2*H*-1,2,4-thiadiazol-3-one ring can be supported by the disappearance of the two NH groups from the 2-thiobiurets **2**, and the change of the methyl group signal from a doublet in the ^{1}H nmr spectrum to a singlet (Tables I and III). Furthermore, elemental analyses of the new compounds **3** were in a good agreement with the proposed structures (Table II).

EXPERIMENTAL

All melting points were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were measured on a Jasco A-1 spectrophotometer. The ^{1}H and ^{13}C nmr spectra were obtained on a 80 MHz Bruker AC-80 nmr spectrometer. The elemental analyses were carried out on a Perkin-Elmer apparatus, model 240, at the Korea Research Institute of Chemical Technology, Dae Jeon, Korea. Most of the commercially available starting materials and solvents were purchased from Aldrich Chemical Company, Milwaukee, WI.

1-(*p*-Toluyl)-5-methyl-2-thiobiuret (**2g**).

Potassium thiocyanate (2.1 g, 2.16 x 10^{-2} mole) was dissolved in anhydrous acetone (50 ml) at 45-50°. *p*-Toluyl chloride (2.8 ml, 3.27 g, 2.12 x 10^{-2} mole) was added dropwise to the above solution in the course of 1.5 hours. The reaction mixture was stirred for 30 minutes, and then it was left to cool down to room temperature. The precipitated potassium chloride and excess potassium thiocyanate were filtered off with suction. Methylurea (1.6 g, 2.16 x 10^{-2} mole) was added to the filtrate and the mixture was refluxed for 2 hours. The reaction mixture was then cooled to room temperature and then evaporated under reduced pressure to dryness. The yellow residue was stirred with ice water for 10 minutes to remove the inorganic salts and excess methylurea. The resulting bright yellow precipitate was filtered off to give 1-(*p*-toluyl)-5-methyl-2-thiobiuret (1.75 g, 35%). Recrystallization from ethanol afforded the pure product **2g**, mp 199-200°; ir (potassium bromide): ν 3400, 3250 (NH), 2900 (CH), 1690, 1670 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 13.0 (1H, b, NH) (b = broad), 11.5 (1H, b, NH), 7.3-8.5 (5H, AB pattern, Ph + NH), 2.8 (3H, d, HNMe), 2.6 ppm (3H, s, PhMe); ^{13}C nmr (DMSO-d_6): δ 21.0 (PhMe), 26.0 (HNMe), 127.9, 129.3, 129.9, 143.7 (Ph), 153.8 (O=CNH$_2$), 178.7 (C=S), 165.3 ppm (PhC=O).

All other 2-thiobiurets **2** were synthesized in the same fashion (Table I).

5-(*p*-Toluylamino)-2-methyl-2*H*-1,2,4-thiadiazol-3-one (**3g**).

1-(*p*-Toluyl)-5-methyl-2-thiobiuret (**2g**, 1.0 g, 4.18 x 10^{-3} mole) was completely dissolved in aqueous sodium hydroxide (2*N*, 20 ml, 4 x 10^{-2} mole) at 0°. Hydrogen peroxide (30%, 0.13 ml, 0.19 g, 5.51 x 10^{-3} mole) was then added dropwise to the reaction mixture. The mixture was stirred for 50 minutes at the same temperature and then it was acidified to *p*H 4.5 with concentrated hydrochloric acid. The resulting colorless solid, 5-(*p*-toluylamino)-2-methyl-2*H*-1,2,4-thiadiazol-3-one (**3g**), was separated and collected with suction (0.78 g, 75%). It was recrystallized from ethanol to give the pure compound **3g** (0.57 g, 55%), mp 278-280°; ir (potassium bromide): ν 3400 (NH), 2900, 3050 (CH), 1720 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 13.2 (1H, b, NH), 7.2-8.3 (4H, dd, Ph), 3.1 (3H, s, NMe), 2.5 ppm (3H, s, PhMe); ^{13}C nmr (DMSO-d_6): δ 21.3 (PhMe), 28.9 (NMe), 128.8, 129.0, 129.2, 143.6 (Ph), 161.4 (C=N), 169.2 (PhC=O), 176.0 ppm (NC=O).

For elemental analysis, see Table II.

All other substituted 2*H*-1,2,4-thiadiazol-3-ones **3** were obtained by the same procedure (Table II).

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