

Tadashi Okawara, Yoshihiro Tateyama, Tetsuo Yamasaki, and Mitsuru Furukawa*

Faculty of Pharmaceutical Sciences, Kumamoto University Oe-hon-machi,
Kumamoto 862, Japan

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The intramolecular cyclization of 1-acylbithiourea **1** gave 1,2,4-triazole **2** and 1,3,4-thiadiazole **3**. The reaction of **1** with *p*-toluenesulfonyl chloride in the presence of triethylamine afforded **3**. Treatment of **1** with methyl iodide in the absence of any base yielded 2-methylthio-1,3,4-thiadiazole **10** and 2-imino-1,3,4-thiadiazoline **12**.

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Since triazoles and thiadiazoles have a variety of potential biological activities and utilities as technologically useful materials, a number of methods [1-3] for the preparation have been developed.

As a continuation of our study on a new synthesis of heterocycles from a compound with a thioamide group, we applied 1-acylbithiourea to the preparation of heterocycles.

First, the intramolecular cyclization of 1-acylbithiourea **1** was examined under phase-transfer conditions and led to 1,2,4-triazoles **2**, 1,3,4-thiadiazoles **3**, and bithiourea **4**. Although many synthetic methods of 1,2,4-triazole and 1,3,4-thiadiazole have hitherto been documented, there has been no report of a method from bithiourea.

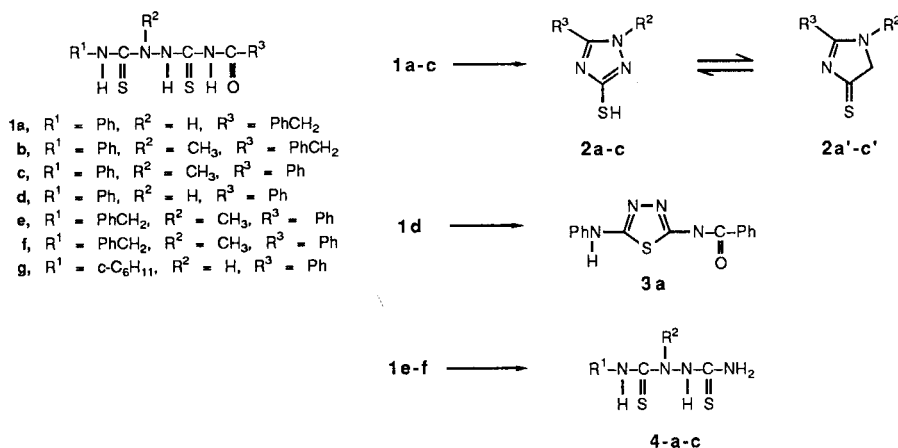
When **1a-c** was treated in aqueous 5% sodium hydroxide-methylene chloride in the presence of a phase-transfer catalyst, benzyltriethylammonium chloride (BTEAC), at room temperature, the cyclization product **2** was provided in moderate yields. Aniline was also isolated by treatment of the reaction mixture with water. The structure of **2** was assigned by spectral data and elemental analysis. The ir spectra showed no carbonyl absorption, and the mass spec-

tra exhibited the molecular ion peak corresponding to the elimination of phenylisocyanate and hydrogen sulfide from **1a-c**.

The ^{13}C -nmr spectrum of the product from **1c** in DMSO-d_6 showed the complicated signals due to the equilibrium mixture of the tautomeric isomers **2c** and **2'c** as seen in Figure a. When a drop of *N* sodium hydroxide was added to the DMSO-d_6 solution, the ^{13}C -nmr spectrum changed to the eight peaks of **2c** in Figure b. Consequently, it is apparent that the product exists in a mixture of the thiol **2** and the thione **2'** in the solution. In Figure a, the carbon at position 3 of 3-mercaptotriazole **2c** and triazoline-3-thione **2c'** were exhibited at 156 and 168 ppm, respectively.

On the other hand, **1d** gave 2-benzoylamino-5-anilino-1,3,4-thiadiazole **3a** in 58% yield, no anticipated compound **2** being isolated. The ir spectrum of **3a** showed NH and C=O absorptions at 3320 and 1640 cm^{-1} , respectively. The mass spectrum indicated the parent ion peak corresponding to the elimination of one molecular of hydrogen sulfide from **1d**. These data can not discriminate between **3a** and the tautomeric form **5**. However, the fact [4,5] that compound **6** similar to **3a** shows carbonyl absorption at

Scheme 1



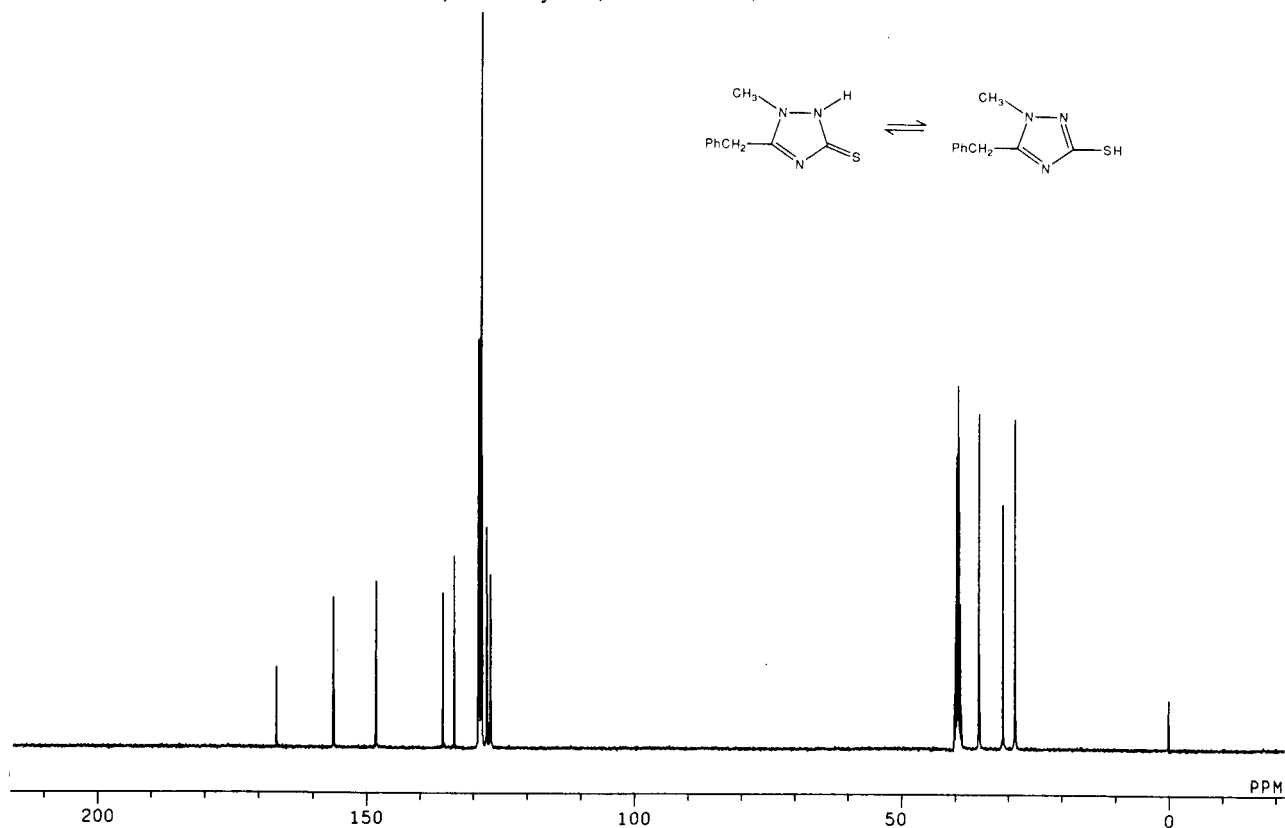
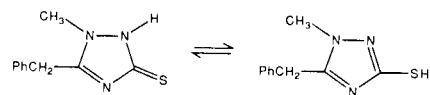


Figure a

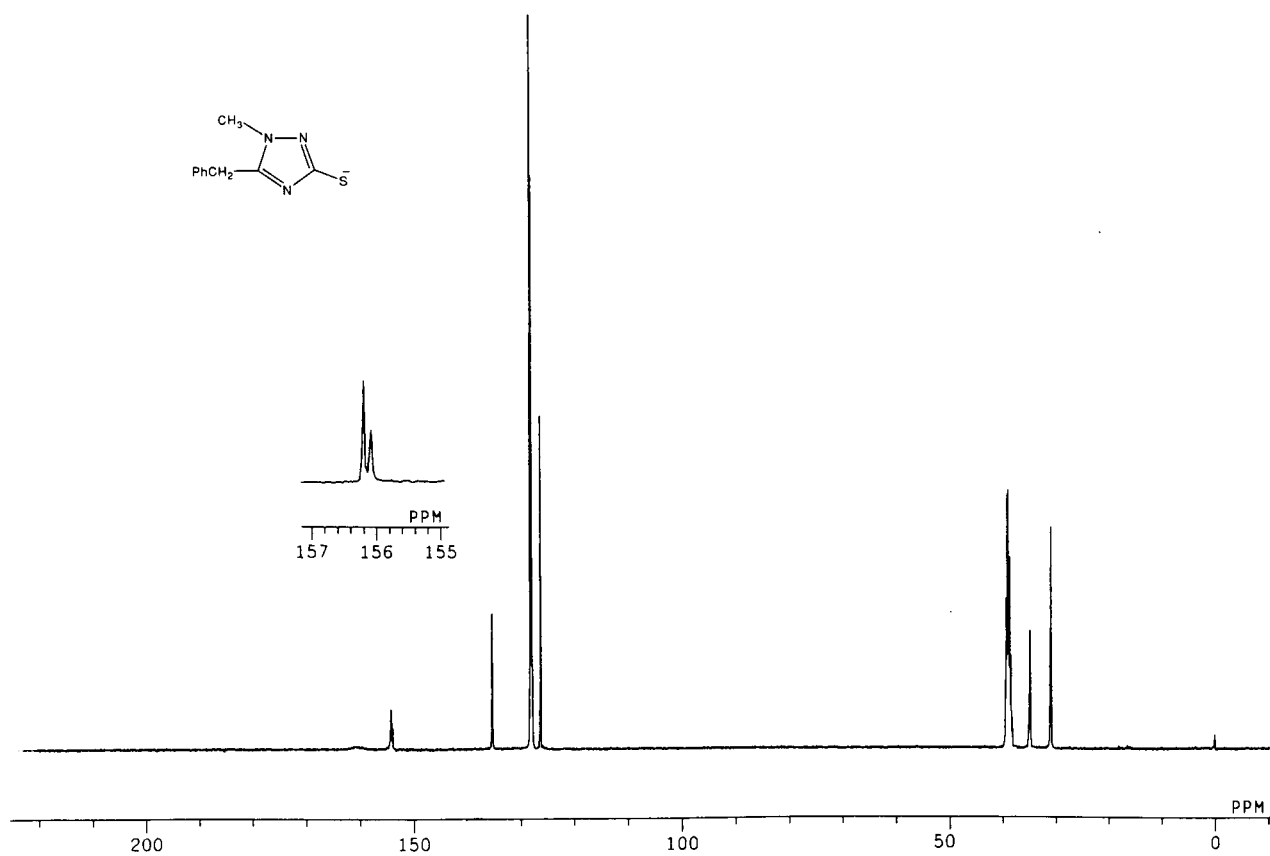
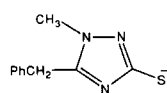


Figure b

Table 1
 Triazolin-3-thione **2a-c**

	mp (°C)	Yield (%)	IR (cm ⁻¹)	Mass (M ⁺)	¹ H-NMR (ppm)	Analysis (%)		
						Calcd. (Found)	C	H
2a	220	54	3050 (NH)	191	3.48 (s, NH, 1H)	56.52	4.75	21.98
			1480 (NCN) 		3.86 (s, CH ₂ , 2H)	(56.39)	(4.69)	(21.67)
					7.32 (s, Ph, 5H)			
					7.75 (br, NH, 1H)	58.56		
2b	194	55	3050 (NH)	205	3.71 (s, Me, 3H)		5.40	20.48
			1520 (NCN) 		4.19 (s, CH ₂ , 2H)	(58.76)	(5.38)	(20.46)
					7.30 (s, Ph, 5H)			
					7.75 (br, NH, 1H)			
2c	216	89	3100 (NH)	191	3.80 (s, Me, 3H)	56.52	4.75	21.98
			1480 (NCN) 		7.55-8.01 (m, Ph and NH, 6H)	(56.80)	(4.78)	(21.92)

3-Mercaptotriazole **2a'** had ¹³C-nmr (deuteriodimethylsulfoxide-sodium hydroxide): δ 0.80 (Me), 34.77 (CH₂), 126.19, 127.88, 128.03, 135.15 (Ph), 153.89 (C-5), 154.2 (C-2).

Scheme 2

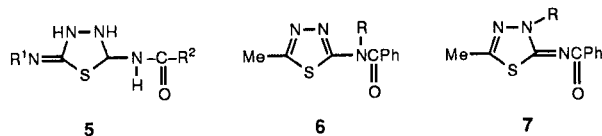


Table 2

2-Acylamino-5-aminothiadiazole **3**

	mp (°C)	Yield (%)	IR (cm ⁻¹)	Mass (M ⁺)	¹ H-NMR (ppm)	Analysis (%)		
						Calcd. (Found)	C	H
3a	293	93	3320 (NH), 3120 (NH), 1640 (C=O)	296	7.05-7.80 (m, Ph × 2, 10H), 8.20 (br, NH, 1H)	60.79 (61.14)	4.08 (4.21)	18.91 (19.00)
3b	241	89	3380 (NH), 3100 (NH), 1660 (C=O)	324	2.03 (s, NH, 1H), 3.66 (s, CH ₂ , 2H), 4.51 (d, CH ₂ , 2H), 7.36 (s, Ph, 5H), 7.38 (s, Ph, 5H), 7.75 (br, NH, 1H)	62.94 (62.80)	4.97 (5.26)	17.27 (17.07)
3c	262	84	3330 (NH), 3140 (NH), 1640 (C=O)	310	2.05 (s, NH, 1H), 4.42 (d, CH ₂ , 2H), 7.32-7.70 (m, Ph, 5H), 7.40 (s, Ph, 5H), 8.05 (br, NH, 1H)	61.92 (61.92)	4.55 (4.53)	18.05 (17.98)

1675-1660 cm^{-1} and the endo compound **7** at 1620-1610 cm^{-1} seems to support the assigned structure **3a**. The ^{13}C -nmr spectrum of **3a** showed carbons at positions 2 and 5 at 164.0 and 163.5 ppm, respectively. These data are coincident with the corresponding value of **6** [4]. Contrary to expectation, **1e-g** merely underwent alkaline hydrolysis to afford only bithioureas **4a-c** in 69-93% yields. These differences in behavior of **1a-g** are not clear at the present time.

When **1c, d, and f** were allowed to react with *p*-toluenesulfonyl chloride in the presence of triethylamine, 2-acylamino-5-amino-1,3,4-thiadiazoles **3a-c** were provided in 84-93% yields, probably through the intermediate **8** in Scheme 3.

Compounds **3a-c** were also formed by treatment of **1c, d, and f** with brominating reagents (bromine, *N*-bromosuccinimide) in a protic solvent (ethanol) in 48-49% yield.

In the reactions of **1a, b, and d** with methyl iodide in the absence of base, 2-acylamino-5-methylthio-1,3,4-thiadiazole **10** and 5-acylamino-2-anilidene-3-methyl-1,3,4-thiadiazoline **12** were produced in 52-63% yield. The reaction is presumed to be initiated by *S*- and *N*-methylation to form the intermediate **9**, followed by cyclization through the attack of SH group with elimination of methylaniline to afford **10**. On the other hand, **1d** was merely methylated on the sulfur atom, followed by elimination of methylmercaptan to **12** as shown in Scheme 3.

Scheme 3

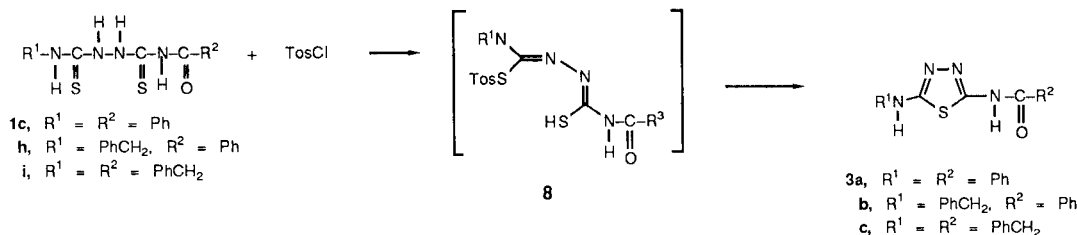


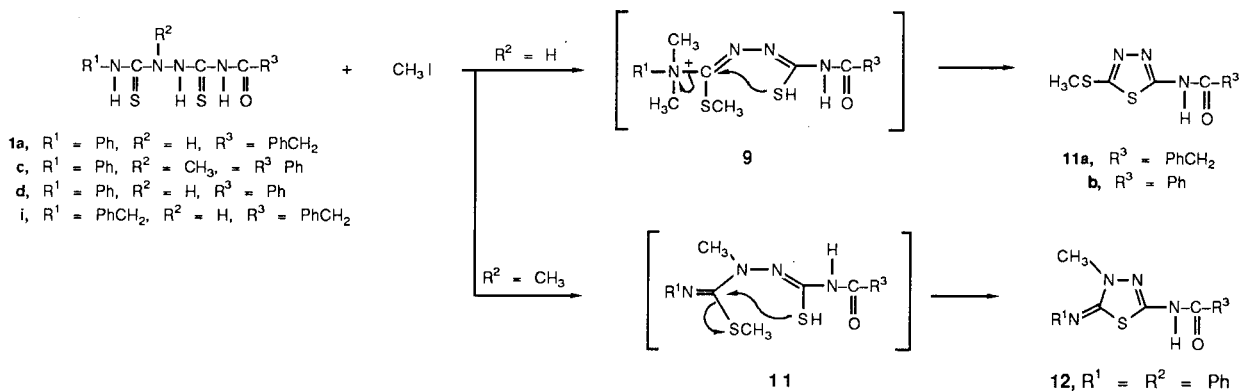
Table 3

2-Acylamino-5-methylthio-1,3,4-thiadiazole **10** and 5-Benzoylamino-2-anilidene-3-methyl-1,3,4-thiazolidine **12**

	mp (°C)	Yield (%)	IR (cm^{-1})	Mass (M^+)	$^1\text{H-NMR}$ (ppm)	Analysis (%)		
						Calcd. (Found)	C	H
10a	202	56	3130 (NH), 1660 (C=O)	251	2.80 (s, Me, 3H), 7.51-8.25 (m, Ph and NH, 6H)	47.77 (47.90)	3.61 (3.98)	16.73 (16.43)
10b	196	63	3120 (NH), 1680 (C=O)	265	2.73 (s, Me, 3H), 4.05 (s, CH_2 , 2H), 7.30-7.66 (m, Ph and NH, 6H)	49.91 (50.12)	4.18 (4.30)	15.84 (16.03)
12	261	60	3100 (NH), 1655 (C=O)	310	3.93 (s, Me, 3H), 7.51-8.32 (m, Ph and NH, 6H)	61.92 (62.23)	5.55 (5.78)	18.05 (18.36)

^{13}C -nmr (deuteriodimethylsulfoxide): δ 15.76 (Me), 41.13 (CH_2), 126.22, 127.74, 128.56, 133.75 (Ph), 157.37 (C-5), 159.50 (C-2), 168.60 (C=O).

Scheme 4



The application of bithiourea to the preparation of other heterocycles is currently being investigated.

EXPERIMENTAL

All the melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were recorded with a JASCO IRA-1 grating i.r.spectrometer. The ^1H -nmr spectra were determined with a JEOL-60H spectrometer and the ^{13}C -nmr spectra were measured with a JEOL-FX-100 spectrometer using tetramethylsilan as an internal standard. Mass spectra were measured with a JEOL-01 mass spectrometer.

1-(Acylthiocarbamoyl)thiosemicarbazide **1**.

Compound **1** was prepared by stirring a mixture of thiosemicarbazide and acylisothiocyanate in ethanol at room temperature [5].

1,2-Dihydro-1*H*-1,2,4-triazole-3-thione **2'**.

A suspension of **1a-c** (1 mmole) in methylene chloride (10 ml)-5% sodium hydroxide (2 ml) was stirred for 12 hours at room temperature in the presence of BTEAC (20 mg). The methylene chloride layer was separated, washed with water (10 ml $\times$ 3) and dried over anhydrous sodium sulfate. Removal of the solvent gave crude **2'**, which was recrystallized from ethanol. The results are shown in Table 1.

2-Acylamino-5-aminothiadiazole **3**.

A. From **1d** under Phase-transfer Conditions.

This compound was prepared from **1d** (0.66 g, 5 mmoles) by the same method as described above, mp 293°, yield 0.34 g (58%); ir (potassium bromide): 3320 (NH), 1640 (C=O) cm^{-1} ; ms: (M^+) 296; ^1H -nmr (deuteriodimethylsulfoxide): δ 7.02-7.75 (m, Ph $\times$ 2, 10H), 8.15 (br, NH, 1H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{OS}$: C, 60.79; H, 4.08; N, 18.91. Found: C, 61.02; H, 4.32; N, 19.00.

B. From **1c**, **d**, and **f** in the Presence of *p*-Toluenesulfonyl Chloride and Triethylamine.

To a solution of **1c**, **d**, and **f** (1 mmole) and triethylamine (0.10 g, 1 mmole) in anhydrous methylene chloride (20 ml) was added *p*-toluenesulfonyl chloride (0.19 g, 1 mmole). The mixture was stirred for 2 hours at room temperature. The separated crystals were filtered and recrystallized from ethanol. The results are summarized in Table 2.

C. From **1c**, **d**, and **f** and Brominating Agents (Bromine and NBS).

To a solution of **1c**, **d**, and **f** (1 mmole) in ethanol (20 ml) or methylene chloride (20 ml) was added bromine (0.16 g, 1 mmole) or NBS (0.18 g, 1 mmole). The mixture was stirred for 1 hour at room temperature. The separated crystals were filtered and recrystallized from ethanol. The structure was confirmed by comparison of the ir spectra with that of **3**.

1-(Thiocarbamoyl)thiosemicarbazide **4**.

This compound was obtained from **1e-g** by the same method as mentioned in the preparation of **2**.

2-Acylamino-5-methylthio-1,3,4-thiadiazole **10** and 2-Anilindene-5-benzoylamino-4-methyl-1,3,4-thiazoline **12**.

A solution of **1a**, **c**, **d**, or **i** (5 mmoles) and methyl iodide (1.4 g, 10 mmoles) in anhydrous methylene chloride (30 ml) was stirred at room temperature for 3-4 days. The separated crystals were filtered and recrystallized from ethanol. The results are shown in Table 3.

REFERENCES AND NOTES

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