A New Route to 1,2,4-Triazoles and 1,3,4-Thiadiazoles from 1-Acylbithiourea

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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.

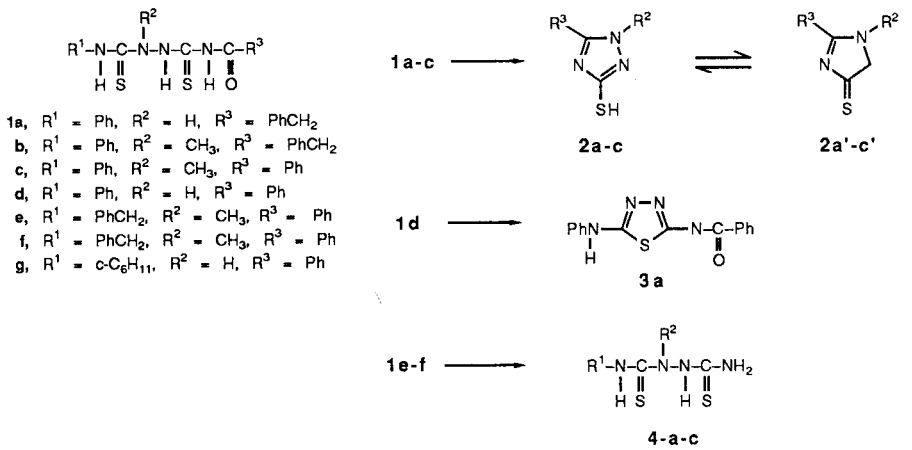
First, the intramolecular cyclization of 1-acylbithiourea **1** was examined under phase-transfer conditions and led to 1,2,4-triazoles **2**, 1,3,4-thiadiazoles **3**, and bithiourea **4**. Although many synthetic methods of 1,2,4-triazole and 1,3,4-thiadiazole have hitherto been documented, there has 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 spectra 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



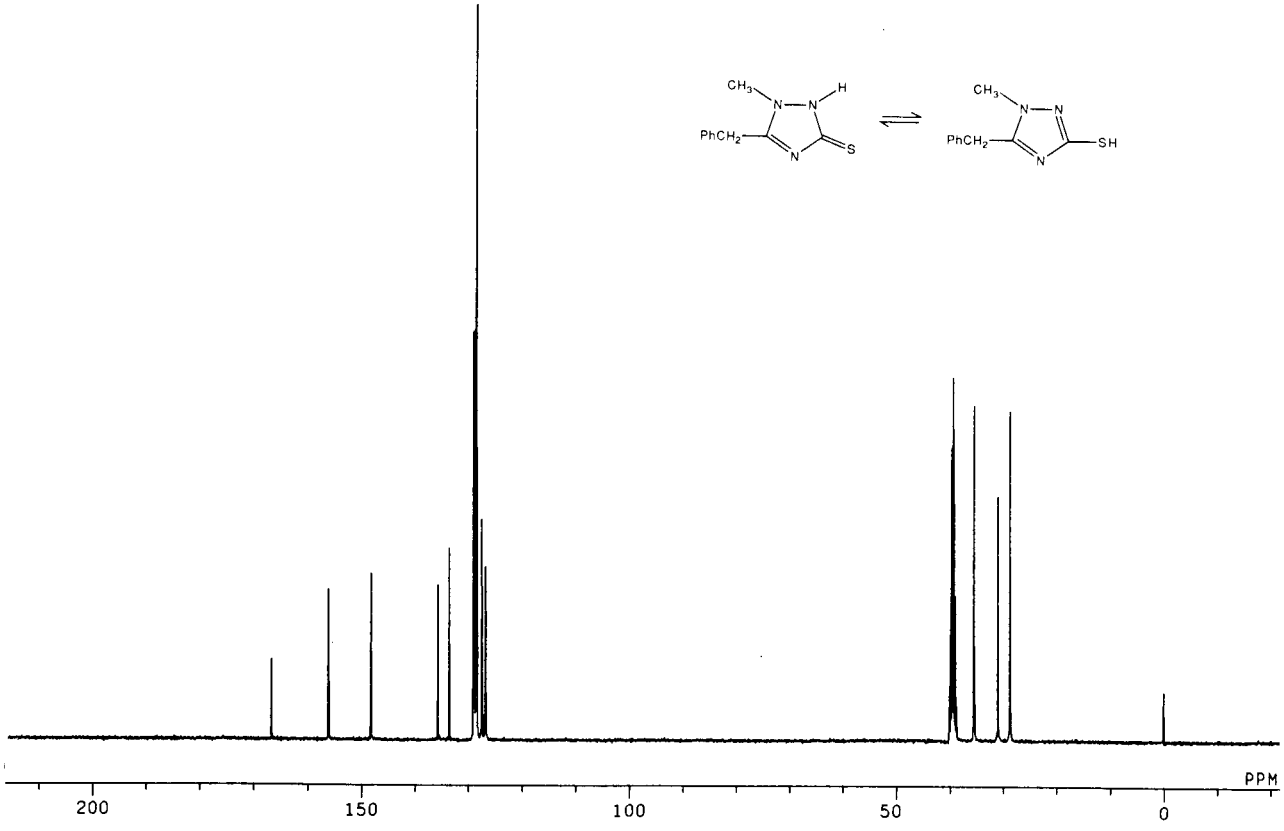


Figure a

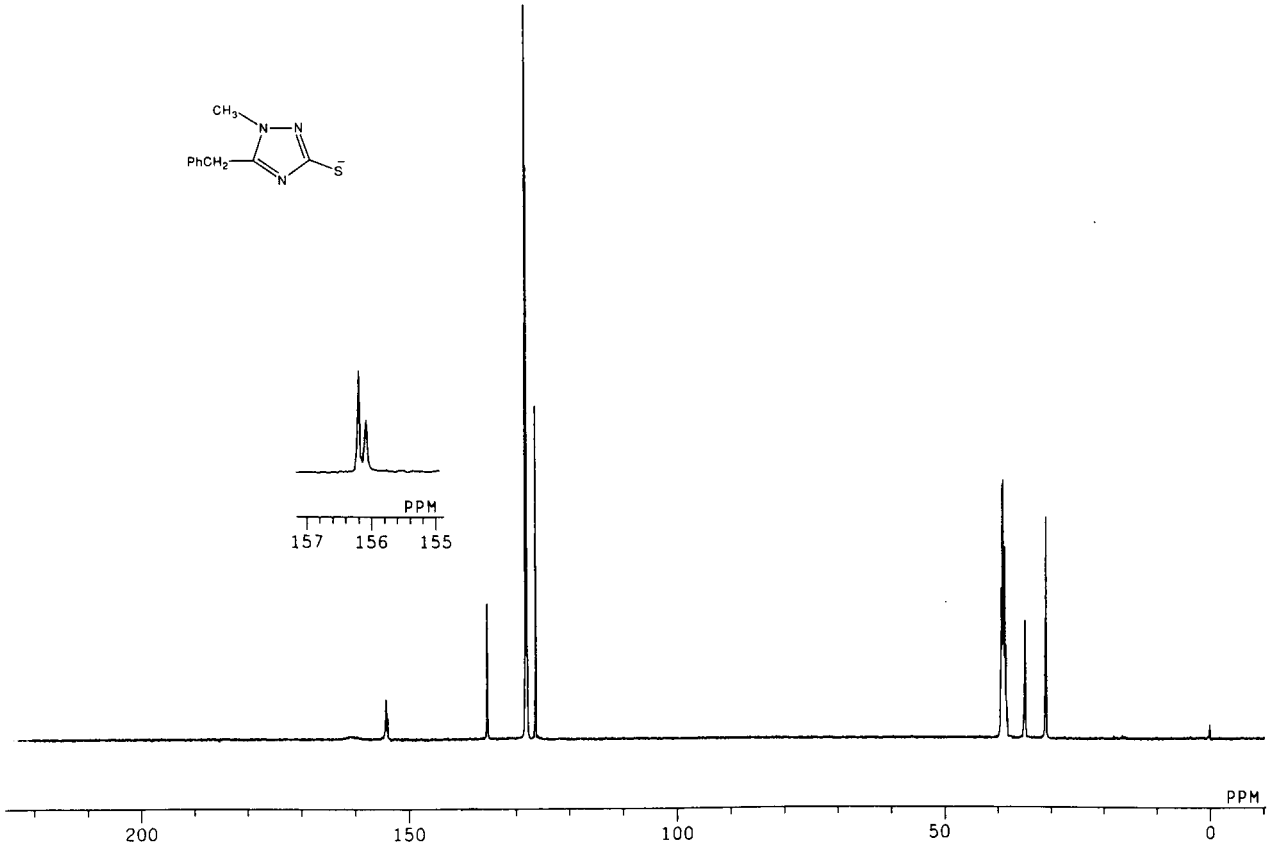


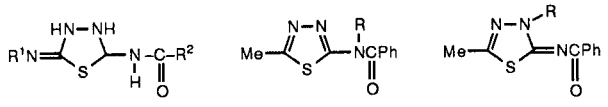
Figure b

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

	mp (°C)	Yield (%)	IR (cm^{-1})	Mass (M^+)	^{1}H–HMR (ppm)	Anaylsis (%) Calcd. (Found) C	H	N
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)
			S		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)
			S		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	(56.80)	(4.78)	(21.92)
			S		and NH, 6H)			

3-Mercaptotriazole **2a'** had ^{13}C-nmr (deuteriodimethylsulfoxide-sodium hydroxide): δ 0.80 (Me), 34.77 (CH_2), 126.19, 127.88, 128.03, 135.15 (Ph), 153.89 (C-5), 154.2 (C-2).

Scheme 2



5 **6** **7**

Table 2

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

	mp (°C)	Yield (%)	IR (cm^{-1})	Mass (M^+)	^{1}H-NMR (ppm)	Analysis (%) Calcd. (Found) C	H	N
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)

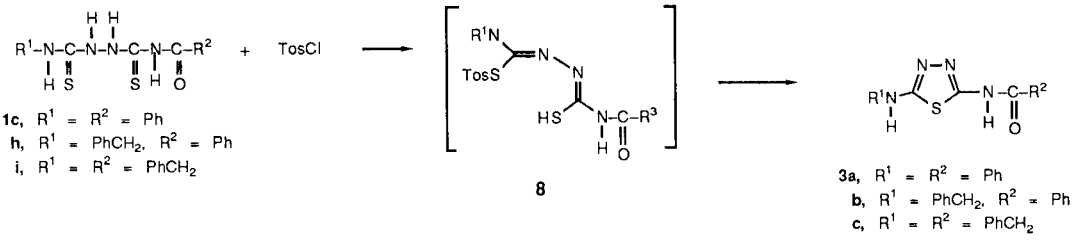
1675-1660 cm^{-1} and the endo compound **7** at 1620-1610 cm^{-1} seems to support the assigned structure **3a**. The ^{13}C-nmr spectrum of **3a** showed carbons at positions 2 and 5 at 164.0 and 163.5 ppm, respectively. These data are coincident with the corresponding value of **6** [4]. Contrary 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-anilinidene-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



1c, $R^1 = R^2 = Ph$
h, $R^1 = PhCH_2$, $R^2 = Ph$
i, $R^1 = R^2 = PhCH_2$

3a, $R^1 = R^2 = Ph$
b, $R^1 = PhCH_2$, $R^2 = Ph$
c, $R^1 = R^2 = PhCH_2$

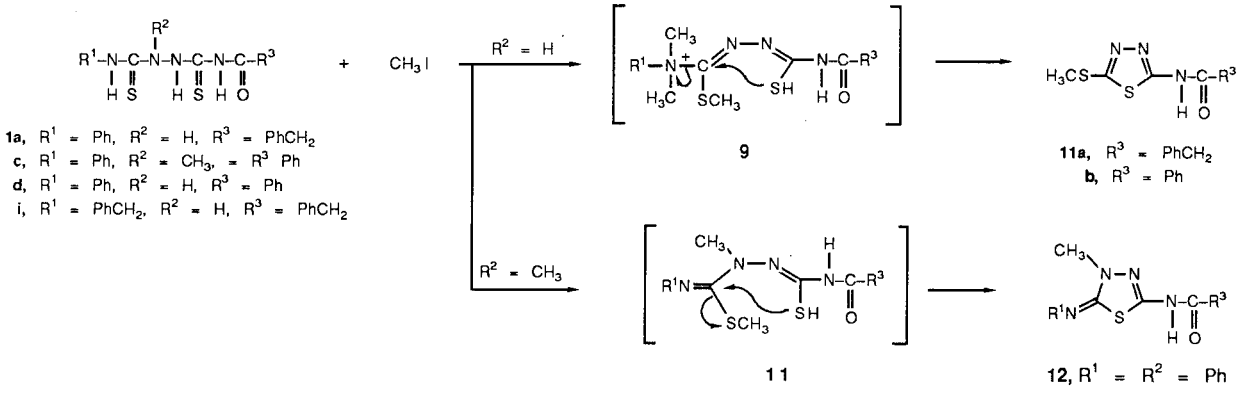
Table 3

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

	mp (°C)	Yield (%)	IR (cm^{-1})	Mass (M^+)	^1H-NMR (ppm)	Analysis (%) Calcd. (Found) C	H	N
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



1a, $R^1 = Ph$, $R^2 = H$, $R^3 = PhCH_2$
c, $R^1 = Ph$, $R^2 = CH_3$, $= R^3$ Ph
d, $R^1 = Ph$, $R^2 = H$, $R^3 = Ph$
i, $R^1 = PhCH_2$, $R^2 = H$, $R^3 = PhCH_2$

11a, $R^3 = PhCH_2$
b, $R^3 = Ph$

12, $R^1 = R^2 = Ph$

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 ^{1}H-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 × 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; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 7.02-7.75 (m, Ph × 2, 10H), 8.15 (br, NH, 1H).

Anal. Calcd. for $C_{15}H_{12}N_4OS$: 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-Anilinidene-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.

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