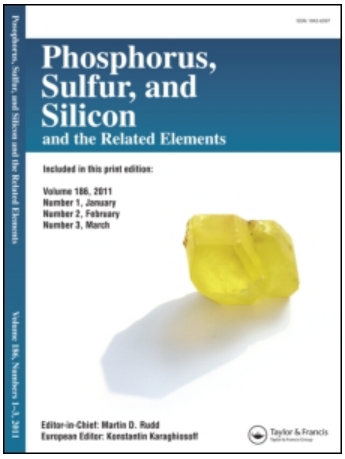

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CHEMISTRY OF 1,3-OXAZINE-6-THIONES. RING TRANSFORMATION

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CHEMISTRY OF 1,3-OXAZINE-6-THIONES. RING TRANSFORMATION

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Two 1,3-oxazine-6-thione derivatives obtained by "*S,N*-Double Rearrangement[2]" reacted with several nucleophiles to produce 1,3-diazin-6-ones, 6-imino-1,3-oxazines, 1,3,4-triazoles, 1,2,4-oxadiazoles, and 1,3-thiazol-6-ones. Their ring transformations are discussed.

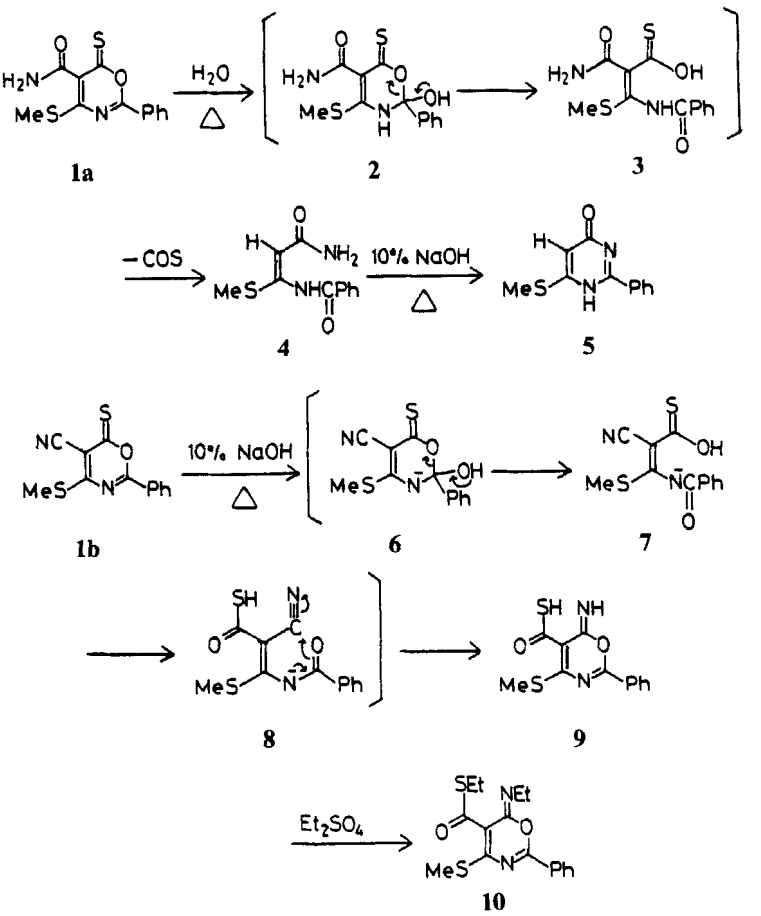
The 1,3-oxazine-6-thiones were first prepared by Lown *et al.* from diphenylcyclopropenethione and pyridinium-*N*-benzoylimine.[1] However, to our knowledge, few reports on the reactivities of these compounds have appeared. Recently, we found that 2-cyano-3-mercapto-3-alkylthioacrylamides condensed with benzoic acid in the presence of PPE (polyphosphoric ethyl ester) to form 5-carbamoyl-4-alkylthio-2-phenyl-1,3-oxazine-6-thiones in good yields.[2,3] Then, we directed our efforts to the conversion of these 1,3-oxazine-6-thiones into useful heterocycles. This paper describes the reactions of 1,3-oxazine-6-thiones with several nucleophiles and a discussion of their reaction pathways.

RESULTS AND DISCUSSION

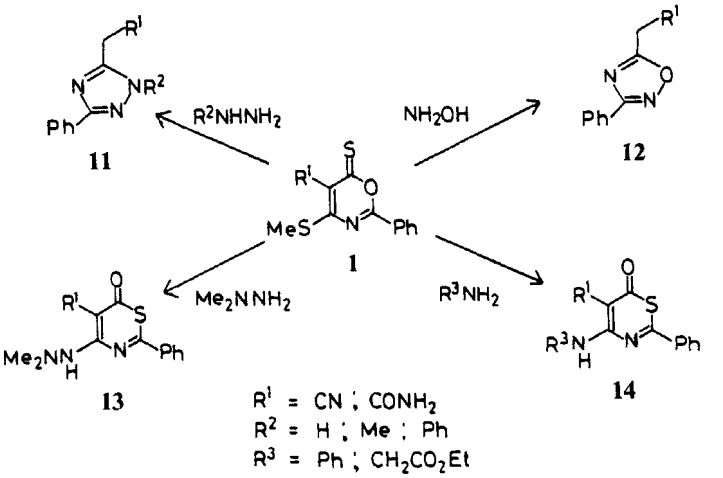
An initial experiment was conducted on the hydrolysis of 1,3-oxazine-6-thiones. The treatment of 5-carbamoyl-4-methylthio-2-phenyl-1,3-oxazine-6-thione **1a** with boiling water for 1 h afforded 3-benzoylamino-3-methylthioacrylamide **4** with loss of carbon oxysulfide. Compound **4** was then refluxed with 10% NaOH solution to give 6-methylthio-2-phenyl-1,4-dihydropyrimidin-4-one **5** in quantitative yield. On the other hand, when 5-cyano-4-methylthio-2-phenyl-1,3-oxazine-6-thione **1b** was refluxed with 10% NaOH solution, 5-thiolcarboxy-4-methylthio-2-phenyl-6-imino-1,3-oxazine **9** was obtained without elimination of carbon oxysulfide. Compound **9** was then converted into its ethyl ester **10** on treatment with diethyl sulfate. In the case of **1a**, dethiocarboxylation of an intermediate **3** is considered to take place easily due to the anchimeric assistance of the β-carbonyl group.

In a similar fashion, compounds **1** were treated with hydrazines, hydroxylamine, and amines. In these cases, some interesting ring transformations occurred and 1,3,4-triazoles **11** or 4(*N,N*-dimethylhydrazo)-1,3-thiazin-6-one **13**, 1,2,4-oxadiazoles **12**, and 4(substituted amino)-1,3-thiazin-6-one **14** were isolated, respectively. These results are shown in Scheme 2.

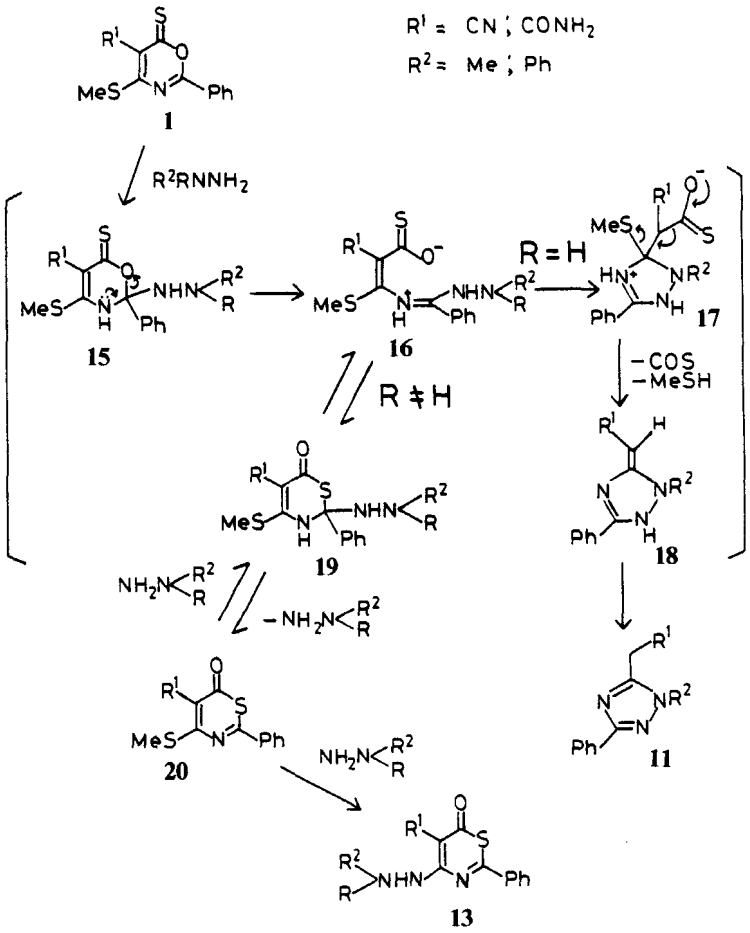
The transformation mechanism is shown by the following representative example, i.e., the reaction of **1** with hydrazines (see Scheme 3).



SCHEME 1



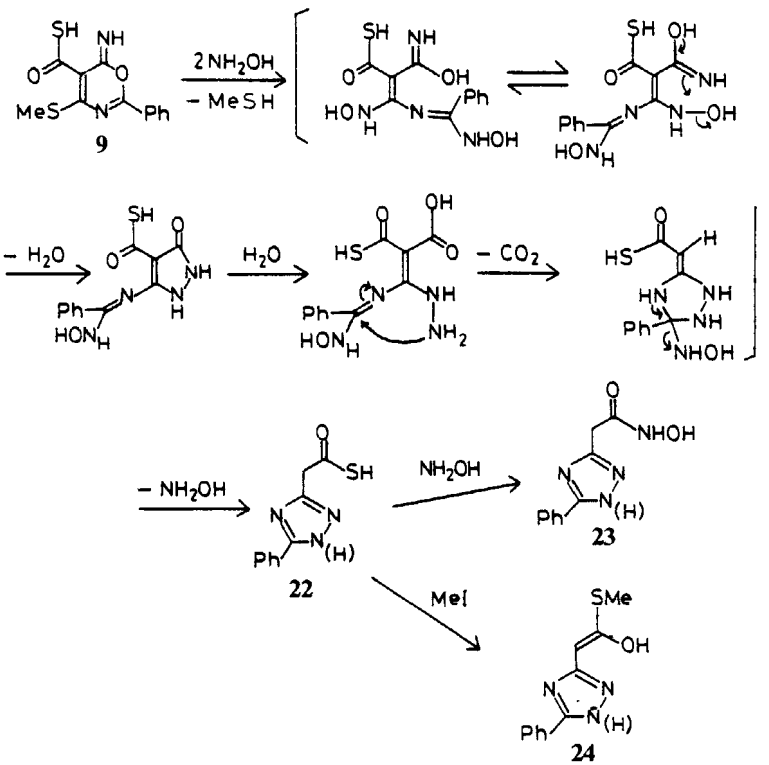
SCHEME 2



SCHEME 3

In the case of R = H of hydrazines, **1** is converted into **11** by the pathway **15** → **16** → **17** → **18**. In the case of R ≠ H, **1** can be changed to **20** via **19** and then **20** to **13**. When **20a** ($R^1 = CONH_2$)[4] was allowed to react with phenylhydrazine under the same conditions, 2-carbamoylmethyl-3,5-diphenyl-1,3,4-triazole **11f** ($R^1 = CONH_2$; R^2 = Ph) and 5-carbamoyl-2-phenyl-4(β-phenylhydrazino)-1,3-thiazin-6-one **21**[5] analogous to **13** were obtained in 60% and 40% yields, respectively. No **11f** was obtained by refluxing a solution of **21** in chloroform. These facts also can be explained quite well by the reversible processes (**16** ⇌ **19** ⇌ **20**).

Next, **9** was allowed to react with hydroxylamine to give 2-thiolcarboxy-5-phenyl-1,3,4-triazole **22** in 70% yield. Compound **22** was changed by an additional treatment of hydroxylamine or alkylation to the corresponding derivatives **23** or **24**, respectively. The formation of **22** can be explained by a double-ring transformation mechanism as shown in Scheme 4.



SCHEME 4

Table I shows the physical data for the products synthesized. The structures of isolated compounds were determined on the basis of elemental analyses and spectroscopic evidence including ^{13}C-nmr[6] (see Table II).

EXPERIMENTAL SECTION

3-Benzoylamino-3-methylthioacrylamide **4**. The mixture of **1a**[3] (500 mg, 1.8 mmol), water (30 ml), and tetrahydrofuran (20 ml) was refluxed for 1 h, and then the solvent was evaporated to afford a yellow material (255 mg). Recrystallization from acetic acid–water using activated charcoal gave white crystals. Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.94%; H, 5.08; N, 11.86; S, 13.57. Found: C, 55.90%; H, 4.98; N, 11.82; S, 13.43.

6-Methylthio-2-phenyl-1,3-diazin-4-one **5**. The mixture of **4** (100 mg, 0.42 mmol) and 10% NaOH (20 ml) was refluxed for 2 h. The reaction mixture was neutralized with 10% HCl to give a crude material, which was recrystallized from acetic acid–water to give light-orange crystals. Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.55%; H, 4.58; N, 12.83; S, 14.69. Found: C, 60.43%; H, 4.60; N, 12.88; S, 14.73.

General Procedure for **11**, **12**, **13**, *and* **14**. Preparation of **11e** is representative; the mixture of **1a** (200 mg, 0.7 mmol), methylhydrazine (0.1 ml), and chloroform (7 ml) was refluxed for 20 min. The colorless material was collected and recrystallized from ethanol to give colorless needles (150 mg). Refluxing times varied from 20–40 min in some instances to as much as 1–2 h in others.

11a: Anal. Calcd. for $C_{10}H_8N_4$: C, 65.20%; H, 4.38; N, 30.42. Found: C, 65.18%; H, 4.20; N, 30.48.
11b: Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39%; H, 4.98; N, 27.71. Found: C, 59.44%; H, 4.88; N, 27.55.
11c: Anal. Calcd. for $C_{11}H_{10}N_4$: C, 66.65%; H, 5.09; N, 28.27. Found: C, 66.44%; H, 4.99; N, 28.35.
11d: Anal. Calcd. for $C_{16}H_{12}N_4$: C, 73.83%; H, 4.65; N, 21.53. Found: C, 73.62%; H, 4.64; N, 21.62.

TABLE I

Physical data of products obtained by reaction of 1,3-Oxazine-6-thiones with nucleophiles

Product	Mp, Bp °C/0.3 Torr	Yield, %	Appearance (recry. solv.)
4	mp 159–161	60	white crystals ($AcOH–H_2O$)
5	mp 256–7	100	light orange crystals ($AcOH–H_2O$)
9	mp 172–3	60	light yellow needles (EtOH)
10	mp 89–90	65	yellow plates ($CHCl_3$–hexane)
11a (R^1 = CN; R^2 = H)	mp 156–7	71	light yellow plates ($CHCl_3$–hexane)
11b (R^1 = $CONH_2$; R^2 = H)	mp 182–4	98	light yellow prisms (EtOH–hexane)
11c (R^1 = CN; R^2 = Me)	mp 57–8 bp 175	98	colorless needles (distil.)
11d (R^1 = CN; R^2 = Ph)	bp 200	94	light yellow oil (distil.)
11e (R^1 = $CONH_2$; R^2 = Me)	mp 207–8	99	colorless needles (EtOH)
11f (R^1 = $CONH_2$; R^2 = Ph)	mp 224–5	85	colorless needles (EtOH)
12a (R^1 = CN)	mp 77–8 bp 150	56	light yellow needles (distil.)
12b (R^1 = $CONH_2$)	mp 161–2	70	colorless needles (EtOH)
13a (R^1 = $CONH_2$)	mp 183–4	50	yellow needles (EtOH)
14a (R^1 = $CONH_2$; R^3 = Ph)	mp 213–4	91	yellow needles ($CHCl_3$)
14b (R^1 = $CONH_2$; R^3 = CH_2CO_2Et)	mp 228–9	99	colorless needles ($AcOH–H_2O$)
22	mp 128–9	72	light yellow needles ($CHCl_3$–hexane)
23	mp 141–3	71	light yellow needles (AcOEt–hexane)
24	mp 103–4	92	light yellow prisms (EtOH)

11e: Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.09%; H, 5.59; N, 25.91. Found: C, 61.12%; H, 5.62; N, 25.98.
11f: Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.05%; H, 5.07; N, 20.13. Found: C, 68.99%; H, 5.12; N, 20.13.
12a: Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86%; H, 3.81; N, 22.69. Found: C, 64.78%; H, 3.77; N, 22.75.
12b: Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11%; H, 4.46; N, 20.68. Found: C, 59.15%; H, 4.62; N, 20.73.
13a: Anal. Calcd. for $C_{13}H_{14}N_4SO_2$: C, 53.78%; H, 4.86; N, 19.30. Found: C, 53.92%; H, 4.95; N, 19.28.
14a: Anal. Calcd. for $C_{17}H_{13}N_3SO_2$: C, 63.14%; H, 4.05; N, 13.00. Found: C, 63.22%; H, 4.12; N, 13.12.
14b: Anal. Calcd. for $C_{15}H_{15}N_3SO_4$: C, 54.04%; H, 4.54; N, 12.61. Found: C, 54.08%; H, 4.60; N, 12.72.

TABLE II

Spectral data of products obtained by reaction of 1,3-oxazine-6-thiones with nucleophiles

Product	Ir (KBr), cm^{-1}	Mass, M^+	Nmr (DMSO-d_6) ppm
4	3400, 3330, 3180 (NH_2, NH), 1660 (CO)	236	($CDCl_3$) 15.0 (br, 1 H, NH), 8.1 (m, 2 H, Ph), 7.55 (m, 3 H, Ph), 5.60 (br, 2 H, NH_2), 4.95 (s, 1 H, CH), 2.30 (s, 3 H, SCH_3)
5	3060 (NH), 1640 (CO)	218	(Py-d_5) 8.40 (m, 2 H, Ph), 7.70 (m, 3 H, Ph), 6.60 (s, 1 H, CH), 2.50 (s, 3 H, SCH_3)
9	3330, 3200,3120 (NH) 1700 (CO)	278	10.20 (br, 1 H, SH or NH) 9.65 (br, 1 H, SH or NH) 8.25 (m, 2 H, Ph), 7.75 (m, 3 H, Ph), 2.70 (s, 3 H, CH_3)
10	2980, 2900 (CH), 1700 (CO)	334	8.55 (m, 2 H, Ph), 7.55 (m, 3 H, Ph), 4.50 (q, 2 H, CH_2, J = 8 Hz), 3.35 (q, 2 H, J = 8 Hz), 2.20 (s, 3 H, CH_3), 1.48 (t, 3 H, CH_3, J = 8 Hz) 1.45 (t, 3 H, CH_3, J = 8 Hz)
11a	3050 (Ph) 2950–2800 (CH), 2250 (CN)	184	8.50 (br, 1 H, NH), 8.05 (m, 2 H, Ph), 7.40 (m, 3 H, Ph), 3.95 (s, 2 H, CH_2)
11b	3250 (NH), 1640 (CO)	202	8.50 (br, 1 H, NH), 8.00 (m, 2 H, Ph), 7.85 (br, 1 H, NH_2), 7.40 (m, 3 H, Ph), 7.20 (br, 1 H, NH_2)
11c	3050 (Ph), 2950 (CH), 2250 (CN)	198	7.55 (m, 5 H, Ph), 3.95 (s, 3 H, CH_3) 3.85 (s, 2 H, CH_2)
11d	3050 (Ph), 2920 (CH), 2250 (CN)	260	8.10 (m, 2 H, Ph), 7.80 (m, 8 H, Ph), 3.82 (s, 2 H, CH_2)
11e	3300, 3150 (NH), 1710 (CO)	216	7.95 (m, 2 H, Ph), 7.70 (br, 1 H, NH_2), 7.40 (m, 3 H, Ph), 7.20 (br, 1 H, NH_2), 3.85 (s, 3 H, CH_3), 3.80 (s, 2 H, CH_2)
11f	3350, 3150 (NH_2) 1680 (CO)	278	8.10 (m, 2 H, Ph), 7.60 (m, 9 H, Ph, NH_2), 7.20 (br, 1 H, NH_2), 3.80 (s, 2 H, CH_2)
12a	2940, 2900 (CH), 2250 (CN)	185	8.05 (m, 2 H, Ph), 7.50 (m, 3 H, Ph), 4.10 (s, 2 H, CH_2)
12b	3350, 3190 (NH_2), 1680 (CO)	203	8.00 (m, 2 H, Ph), 7.90 (br, 1 H, NH_2), 7.60 (m, 3 H, Ph), 7.35 (br, 1 H, NH_2), 4.00 (s, 2 H, CH_2)
13a	3320, 3150 (NH, NH_2), 1660, 1650 (CO)	290	8.75 (br, 1 H, NH), 8.10 (m, 2 H, Ph), 8.00 (br, 1 H, NH_2), 7.70 (m, 3 H, Ph), 7.50 (br, 1 H, NH_2)
14a	3320, 3150 (NH, NH_2), 1670, 1660 (CO)	323	14.1 (br, 1 H, NH), 8.90 (br, 1 H, NH), 8.30 (br, 1 H, NH_2), 7.95 (m, 2 H, Ph), 7.65 (m, 9 H, Ph, NH_2)
14b	3300, 3150, 3050 (NH, NH_2), 1740, 1660, 1650 (CO)	333	12.0 (br, 1 H, NH), 8.40 (br, 1 H, NH_2), 7.92 (m, 2 H, Ph), 7.70 (m, 3 H, Ph), 7.10 (br, 1 H, NH_2), 4.45 (d, 2 H, CH_2, J = 8 Hz), 4.15 (q, 2 H, CH_2, J = 8 Hz), 1.15 (t, 3 H, CH_3, J = 8 Hz)
22	3380, 3260, 3120 (NH), 1620 (CO)	219	($CDCl_3$) 8.90 (br, 1 H, NH or SH), 8.05 (br, 1 H, NH or SH), 8.03 (m, 2 H, Ph), 7.50 (m, 3 H, Ph), 4.50 (s, 2 H, CH_2)
23	3480 (OH), 3350, 3150, 3100 (NH), 1680 (CO)	218	9.25 (s, 1 H, OH), 8.02 (m, 2 H, Ph), 7.60 (m, 3 H, Ph), 5.75 (s, 2 H, NH), 3.80 (s, 2 H, CH_2)
24	3340 (OH), 3360, 3150 (NH)	233	($CDCl_3$) 8.10 (m, 2 H, Ph), 7.45 (m, 3 H, Ph), 6.60 (br, 2 H, NH, OH), 5.20 (s, 1 H, CH), 2.46 (s, 3 H, CH_3)

6-Imino-4-methylthio-2-phenyl-5-thiolcarboxy-1,3-oxazine **9**. The reaction was carried out as described for **5**. Anal. Calcd. for $C_{12}H_{10}N_2S_2O_2$: C 51.78%; H, 3.62; N, 10.06. Found: C, 51.68%; H, 3.58; N, 10.01.

6-Ethylimino-5-ethylthiocarboxy-4-methylthio-2-phenyl-1,3-oxazine **10**. To the mixture of **9** (232 mg, 84 mmol), KOH (4.7 g, 84 mmol), and ethanol (30 ml) was added diethyl sulfate (20 ml). The resulting mixture was stirred for 1 h at room temperature and then separated from potassium sulfate. The filtrate was neutralized with 10% HCl solution and extracted with chloroform. The extract was evaporated to afford crystals. Anal. Calcd. for $C_{16}H_{18}N_2S_2O_2$: C, 57.46%; H, 5.42; N, 8.38. Found: C, 57.33%; H, 5.42; N, 8.35.

5-Phenyl-2-thiolcarboxymethyl-1,3,4-triazole **22**. To the mixture of hydroxylamine hydrochloride (1.4 mmol), triethylamine (1.4 mmol), ethanol (5 ml), and a small amount of water was added a solution of **9** (1 mmol) in 10 ml of ethanol. The resulting solution was stirred for 2 h at room temperature and then concentrated on a rotary evaporator. The residues were extracted with AcOEt. The extract was worked up by column chromatography on silica gel using ethyl acetate/benzene (1 : 2) as eluent. Anal. Calcd. for $C_{10}H_9N_3SO$: C, 54.78%; H, 4.14; N, 19.16. Found: C, 54.77%; H, 4.14; N, 18.88.

2-Hydroxyaminocarboxymethyl-5-phenyl-1,3,4-triazole **23**. The use of hydroxylamine hydrochloride (2 mmol) in the above experiment gave **23** in 71% yield instead of **22**. Further, **22** was converted quantitatively to **23** by an additional treatment with hydroxylamine. Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04%; H, 4.62; N, 25.68. Found: C, 54.81%; H, 4.69; N, 25.53.

2(β-Hydroxy-β-methylthioethenyl)-5-phenyl-1,3,4-triazole **24**. To an ice-cold mixture of **9** (1 mmol), KOH (1 mmol), and ethanol (20 ml) was added methyl iodide (1 mmol) under stirring. The resulting solution was stirred for 2 h, concentrated on a rotary evaporator, and then extracted with ethyl acetate. The extract was worked up by column chromatography on silica gel using ethyl acetate/benzene (1 : 5) as eluent. Anal. Calcd. for $C_{11}H_{11}N_3SO$: C, 56.63%; H, 4.75; N, 18.01. Found: C, 56.60%; H, 4.73; N, 18.06.

REFERENCES AND NOTES

1. J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **50**, 584 (1972).
2. M. Yokoyama, M. Nakamura, T. Imamoto and K. Yamaguchi, *J. Chem. Soc., Chem. Commun.*, **1981**, 560.
3. M. Yokoyama, M. Nakamura, H. Ohteki, T. Imamoto and K. Yamaguchi, *J. Org. Chem.*, **47**, 1090 (1982).
4. Compound **20a** was prepared from **1a** quantitatively on treatment with refluxing ethanol (see ref. 3).
5. Compound **21**: yellow crystals; 235° dec; mass, 338 (M^+); ir (KBr) 3320, 3120 cm^{-1} (NH, NH_2), 1640 (CO); nmr (DMSO-d_6) δ 13.20 (br, 1 H, NH), 8.65 (br, 2 H, NH, NH_2), 7.9 (m, 2 H, Ph), 7.7 (br, 1 H, NH_2), 7.5 (m, 3 H, Ph), 7.15 (m, 2 H, Ph), 6.80 (m, 3 H, Ph). Anal. Calcd. for $C_{17}H_{14}N_4SO_2$: C, 60.34%; H, 4.17; N, 16.56. Found: C, 59.82%; H, 4.25; N, 16.45.
6.