Temperature-dependent Reaction of 1,4,6-Triaminopyrimidine-2(1*H*)-thiones with Vilsmeier Reagent. Formation of [1,2,4]Triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones

Tadakazu Tsuji* and Keiko Takenaka

Department of Chemistry, Japan Women's University, 2-8-1 Mejiro-dai, Bunkyo-ku, Tokyo, Japan

Received October 6, 1989

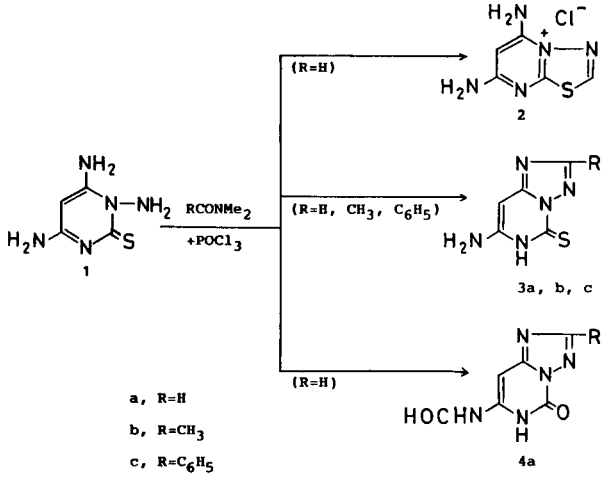
5,7-Diamino[1,3,4]thiadiazolo[3,2-*a*]pyrimidinium chloride **2**, 7-amino[1,2,4]triazolo[1,5-*c*]pyrimidine-5(6*H*)-thiones **3** and the 5(6*H*)-one derivative **4a** were synthesized by the reaction of 1,4,6-triaminopyrimidine-2(1*H*)-thione **1** with phosphoryl chloride and *N*,*N*-dimethylacylamides. Further, compounds **4** were prepared from **2**, **3** or 1,4,6-triaminopyrimidin-2(1*H*)-one **6** by the treatment with the above reagents. Compounds **3** and **4** were converted to 7-amino[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones **5**.

J. Heterocyclic Chem., **27**, 851 (1990).

1,4,6-Triaminopyrimidine-2(1*H*)-thione **1** is a polyfunctional reagent which may give fused pyrimidines. Thus it has previously been reported that the dimethylaminomethylene derivative of 5,7-diamino[1,3,4]thiadiazolo-[3,2-*a*]pyrimidinium chloride **2** forms by the reaction of **1** with a mixture of phosphoryl chloride and *N*,*N*-dimethylformamide (Vilsmeier reagent) [1]. Now it was found that the similar reaction gave either **2** or 7-amino[1,2,4]triazolo-[1,5-*c*]pyrimidine-5(6*H*)-thiones or their 5(6*H*)-ones, depending on the reaction temperature. This paper deals with the temperature-dependent Vilsmeier-type reaction of **1** and the synthesis of 7-amino[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one derivatives.

Treatment of **1** with phosphoryl chloride and *N*,*N*-dimethylformamide in a molar ratio of 1:6 at 0-5°, afforded a mixture of **2** and 7-amino[1,2,4]triazolo[1,5-*c*]pyrimidine-5(6*H*)-thione **3a** in yields of 82 and 7.2%, respectively (Scheme 1). When the same procedure was performed at 25°, a mixture of **3a** and 7-formamido[1,2,4]triazolo[1,5-*c*]-pyrimidin-5(6*H*)-one **4a** was formed in yields of 55 and 28%, respectively. On the other hand, the exclusive formation of **4a** was furnished by the treatment of **1** with the same reagent at 70°.

Scheme 1



Synthesis of 7-amino-2-methyl **3b** and -2-phenyl[1,2,4]-triazolo[1,5-*c*]pyrimidine-5(6*H*)-thiones **3c** was achieved by the reaction of **1** with phosphoryl chloride and *N*,*N*-dimethylacetamide or *N*,*N*-dimethylbenzamide. In these reactions, no thiadiazolopyrimidine derivative was obtained.

7-Amino-2-substituted[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones **5a-c** were prepared by the treatment of **3** with chloroacetic acid followed by acid hydrolysis (Scheme 2). Compounds **5a** and **5b** thus obtained were identical with those prepared by the Vilsmeier-type reaction of 1,4,6-triaminopyrimidin-2(1*H*)-one **6** followed by acid hydrolysis of the intermediates, **4a** and **4b**.

Scheme 2

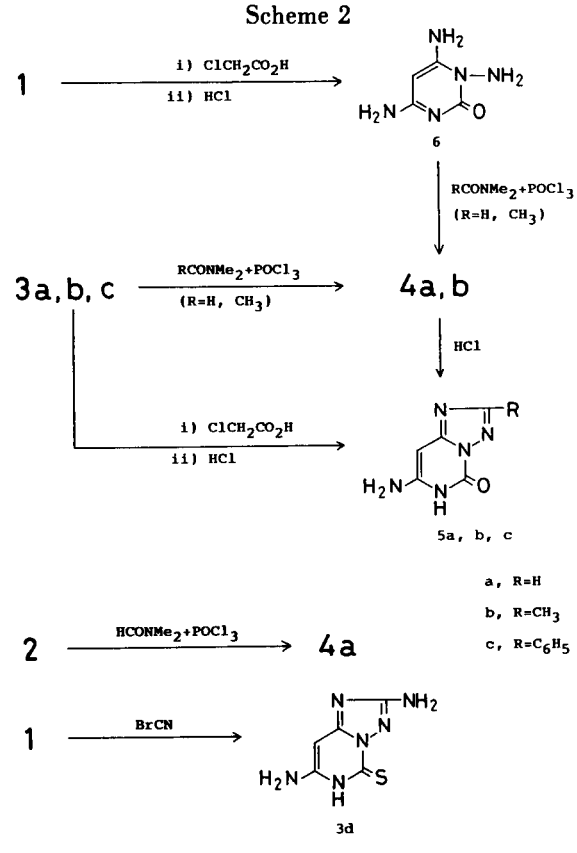
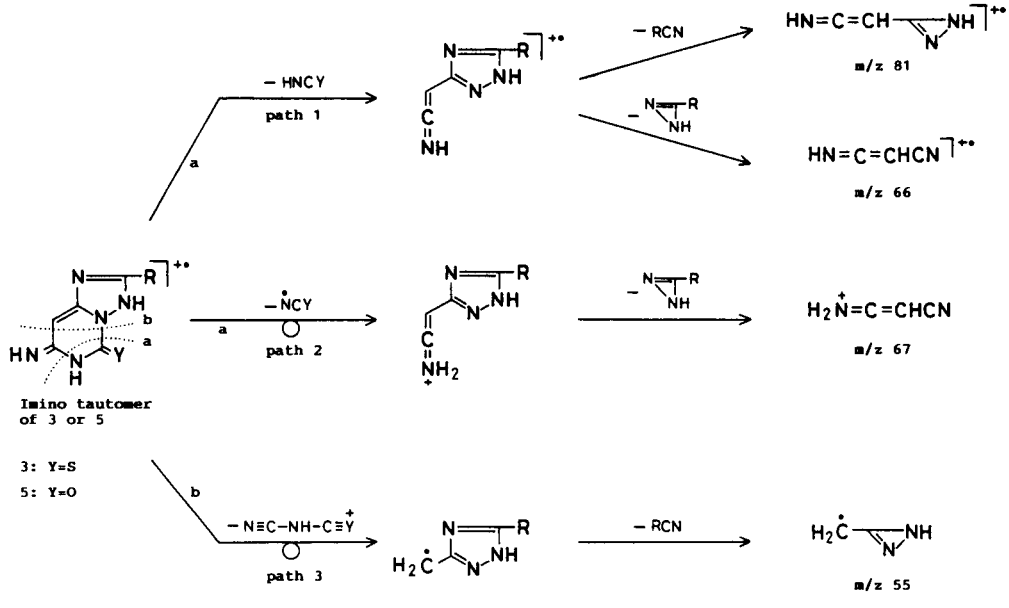


Table 1
Selected Fragments in Mass Spectra of Compounds **3a-d** and **5a-c**

Fragment		Compound Number						
		3a	**3b**	**3c**	**3d**	**5a**	**5b**	**5c**
M^+	m/z	167	181	243	182	151	165	227
	Rel Int	80	100	100	37	23	67	30
M^+–HNCY	m/z	108	122	184	123	108	122	184
	Rel Int	100	88	78	100	100	100	100
HNCY	m/z	59	59	59	59	43	43	43
	Rel Int	3	6	2	100	47	12	19
M^+–NCY	m/z	109	123	185	124	109	123	185
	Rel Int	24	47	65	16	9	16	19
HNCY	m/z	58	58	58	58	42	42	42
	Rel Int	2	4	1	13	50	17	5
M^+–NCNHCY	m/z	82	96	158	97	82	96	158
	Rel Int	28	23	5	7	5	6	1
$NCNHCY^+$	m/z	85	85	85	85	69	69	69
	Rel Int	5	5	5	1	6	4	3
RNC	m/z	27	41	103	42	27	41	103
	Rel Int	2	12	9	11	6	9	11
$RCHN_2$	m/z	42	56	118	57	42	56	118
	Rel Int	1	5	4	23	50	11	27
m/z 55	Rel Int	9	12	8	4	6	3	5
m/z 66	Rel Int	4	8	3	7	4	8	1
m/z 67	Rel Int	9	12	7	26	9	7	2
m/z 81	Rel Int	5	12	6	11	42	18	13

Scheme 3



Treatment of **3a** and **3b** under Vilsmeier condition at 50-70° furnished the exclusive formation of **4a** and **4b**, respectively, as a result of the replacement of the thiocarbonyl group of **3** into the carbonyl group. Interestingly, compound **4a** was obtained by the ring transformation of **2** with phosphoryl chloride and *N*,*N*-dimethylformamide at 50-70°, whereas no formation of **3a** was detected in the reaction mixture (reaction temperature, 20-70°). Thus it is likely that the treatment of **1** with phosphoryl chloride and *N*,*N*-dimethylformamide at a low temperature gives a mixture of **2** and **3a**, those are transformed to **4a** at elevated reaction temperature.

Compound **3d** was prepared by the reaction of **1** with cyanogen bromide.

Assignment of structures of **3** and **5** was based on elementary analysis and spectral data. Partial mass spec-

tral data of **3** and **5** are presented (Table 1). In mass spectra of **3** and **5**, molecular ions were observed, and three distinct fragmentation paths to form 1,2,4-triazole species were distinguished for all compounds (Scheme 3). These are shown as originated from molecular ions of the imino tautomers of **3** and **5** by loss of HNCY (path 1), NCY radical (path 2) and $N \equiv C\text{-}NH\text{-}C \equiv Y^+$ (path 3), respectively. Paths 1 and 2 which form the first two 1,2,4-triazole ions, M^+-HNCY and M^+-NCY, where Y = S or O, are characteristic for the fragmentation of cytosine and its analogs [2]. Expel of $N \equiv C\text{-}NH\text{-}C \equiv Y^+$ from M^+ forming 1,2,4-triazole radical in path 3 involves a hydrogen transfer from the nitrogen atom at 7-position to the carbon atom at 8-position. There seems to be no report which concerns such a pathway as path 3 among the fragmentation of cytosine and its analogs.

Loss of RCN and $RCHN_2$ from the initially occurred three fragments is characteristic of 1,2,4-triazole species [3]. The compositions of all these fragments listed in Table 1 were ascertained by high resolution mass measurement of **3b** and **5b**, as shown in the Experimental.

In triazolopyrimidine chemistry, only a few method are known for the preparation of [1,2,4]triazolo[1,5-*c*]pyrimidines [4,5], those were now synthesized by one step employing readily available **1** as a starting material.

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained using a JEOL JNM-PMX 60 spectrometer (60 MHz). TMS was used as an internal standard. Mass spectra were performed on a JEOL JMX-DX 300 spectrometer by direct insertion at 70 eV.

Vilsmeier-type Reaction of 1,4,6-Triaminopyrimidine-2(1*H*)-thione **1**.

Procedure A. Formation of a Mixture of **2** and **3a**.

To a solution of **1** (1.57 g, 0.01 mole) in *N,N*-dimethylformamide (47 ml), phosphoryl chloride (5.6 ml) was added dropwise under ice-cooling and the whole was kept for 2 hours at 0-5°. The reaction mixture was poured into ice-water (30 ml), and after storage in a refrigerator for 4 days, a mixture was separated by suction into precipitate A and filtrate B. Precipitate A was washed with water and recrystallized from water to give 5,7-diamino[1,3,4]thiadiazolo[3,2-*a*]pyrimidinium chloride **2** as colorless needles; mp 278-280° dec, yield 82%; ir (potassium bromide): 3400, 3300 (NH_2), 1630 cm^{-1} (C=N$^+$); ^{1}H-nmr (DMSO-d_6): 9.67 (s, 1H, H-2), 6.07 (s, 1H, H-6); ms: m/z (relative intensity) 167 (100) (M^+-HCl), 109 (43) (M^+-HCl-NCS), 67 (97).

Anal. Calcd. for $C_5H_6N_5SCl$: C, 29.48; H, 2.97; N, 34.39. Found: C, 29.43; H, 3.08; N, 34.12.

Filtrate B was kept in a refrigerator for additional 1 week. The resulting precipitate was collected, and recrystallized from water to give 7-amino[1,2,4]triazolo[1,5-*c*]pyrimidine-5(6*H*)-thione **3a** as colorless fine needles, mp 277° dec, yield 7.2%; ir (potassium bromide): 3400 (NH_2), 3200 cm^{-1} (NH); ^{1}H-nmr (DMSO-d_6): 5.90 (s, 1H, H-8), 8.53 (s, 1H, H-2).

Anal. Calcd. for $C_5H_5N_5S$: C, 35.93; H, 3.02; N, 41.91. Found: C, 36.18; H, 3.05; N, 41.70.

Procedure B. Formation of a Mixture of **3a** and **4a**.

A solution of **1** (157 mg, 1 mmole) in *N,N*-dimethylformamide (4.7 ml) was mixed with phosphoryl chloride (0.56 ml) at 25° with stirring and stirred at this temperature for 2 hours. The solution was poured into ice water (3 ml) and allowed to stand in a refrigerator for 4 days. The precipitate was collected by suction, and purified to give **3a** in 55% yield. The filtrate was stored in a refrigerator for additional 3 days. The resulting precipitate was collected, washed with water and recrystallized from water to give 7-formamido[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one **4a** as colorless needles in 38% yield, mp >300°; ir (potassium bromide): 3170 (NH), 1760, 1695 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): 5.90 (s, 1H, H-8), 8.43 (s, 1H, H-2), 10.20 (s, 1H, HCO).

Anal. Calcd. for $C_6H_5O_2N_5$: C, 40.23; H, 2.81; N, 39.09. Found: C, 39.91; H, 2.84; N, 38.70.

Procedure C. Formation of **4a**.

To a solution of **1** (314 mg, 2 mmoles) in *N,N*-dimethylformamide (9.4 ml), phosphoryl chloride (1.12 ml) was added dropwise at 70°, and the resulting solution was stirred at this temperature for 2 hours. After cooling, a solution was diluted with ice-water (6 ml) and stood in a refrigerator for 2 weeks. The precipitate was collected, washed with water and recrystallized from water to give **4a** in 56% yield, mp >300°; high resolution ms: m/z Calcd. for $C_6H_5O_2N_5$: 179.04432. Found: 179.04624.

7-Amino-2-methyl[1,2,4]triazolo[1,5,-*c*]pyrimidine-5(6*H*)-thione **3b**.

To a solution of **1** (187 mg, 0.87 mmole) in *N,N*-dimethylacetamide (1.4 ml) and phosphoryl chloride (0.16 ml) was added dropwise under ice-cooling. After the whole was heated at 50° for 2 hours, a mixture was treated with ice-water. The precipitate was collected, treated with 5% sodium bicarbonate, and recrystallized from water to give colorless needles; mp 251-253°; yield 86%; ir (potassium bromide): 3400, 3290 (NH_2), 3180 cm^{-1} (NH); ^{1}H-nmr (DMSO-d_6): 2.51 (s, 3H, CH_3), 5.91 (s, 1H, H-8); high resolution ms: m/z 181.03962 (M^+ for $C_6H_7N_5S$, Calcd. 181.04221), 122.05974 (M^+-HNCS), 58.97860 (HNCS), 123.06616 (M^+-NCS), 57.97171 (NCS), 96.05595 (M^+-NCNHCS), 84.98603 (NCNHCS$^+$), 41.03482 (CH_3CN), 56.03287 ($C_2H_4N_2$), 55.02533 ($C_2H_3N_2$), 66.02630 ($C_3H_2N_2^+$), 67.02927 ($C_3H_3N_2^+$), 81.03186 ($C_3H_3N_3^+$).

Anal. Calcd. for $C_6H_7N_5S.H_2O$: C, 36.18; H, 4.55; N, 35.16. Found: C, 36.36; H, 4.87; N, 35.00.

7-Amino-2-phenyl[1,2,4]triazolo[1,5-*c*]pyrimidine-5(6*H*)-thione **3c**.

To a solution of **1** (3.14 g, 0.02 mole) and *N,N*-dimethylbenzamide (5.97 g) in hexamethylphosphorictriamide (50 ml) was added phosphoryl chloride (11.2 ml). After a solution was heated at 75° for 5 hours, the solvent was distilled off in vacuum. The residue was washed with water, neutralized with 5% sodium bicarbonate, and recrystallized from methanol to give pale yellow plates, yield 32%, mp 269-269.5°; ir (potassium bromide): 3435 (NH_2), 3210 cm^{-1} (NH); ^{1}H-nmr (DMSO-d_6): 6.10 (s, 1H, H-8), 7.67-8.20 (m, 5H, arom).

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.32; H, 3.73; N, 28.80. Found: C, 53.98; H, 3.64; N, 28.97.

Synthesis of 7-Amino **5a**, 7-Amino-2-methyl **5b** and 7-Amino-2-phenyl[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones **5c**.

Method A. From **3**.

A solution of **3a-c** (1 mmole) in 5% chloroacetic acid (3.42 ml) was refluxed for 4 hours, and evaporated to dryness. The residue was refluxed with 10% hydrochloric acid for 30 minutes, evaporated and neutralized with 5% sodium bicarbonate (8 ml). The resulting precipitate was collected and recrystallized from water.

Compound **5a**.

This compound was obtained as colorless fine needles, mp >300°, yield 25%; ir (potassium bromide): 3360 (NH_2), 3140 (NH), 1760 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): 6.45 (s, 1H, H-8), 8.10 (s, 1H, H-2).

Anal. Calcd. for $C_5H_5ON_5$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.88; H, 3.20; N, 46.51.

Compound **5b**.

This compound was obtained as colorless fine needles, mp >300°, yield, 30%; ir (potassium bromide): 3340 (NH_2), 3190 (NH), 1760 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): 2.23 (s, 3H, CH_3), 6.33 (s, 1H, H-8); high resolution ms: m/z 165.06540 (M^+ for $C_6H_7ON_5$, Calcd. 165.06505), 122.06043 (M^+-HNCO), 43.00980 (HNCO), 123.06328 (M^+-NCO), 41.99811 (NCO), 96.05692 (M^+-NCNHCO), 41.02762 (CH_3CN), 56.03601 ($C_2H_4N_2$), 55.02828 ($C_2H_3N_2$), 67.03140 ($C_3H_3N_2^+$), 81.03185 ($C_3H_3N_3^+$).

Anal. Calcd. for $C_6H_7ON_5$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.70; H, 4.12; N, 42.24.

Compound **5c**.

This compound was obtained as colorless fine needles, mp 288-289° dec, yield 7.9%; ir (potassium bromide): 3400, 3250 (NH_2), 3180 (NH), 1750 cm^{-1} (C=O); high resolution ms: m/z Calcd. for $C_{11}H_9ON_5$: 227.08070. Found: 227.07709.

Method B. From **6**.

A solution of **6** (705 mg, 5 mmoles) in *N,N*-dimethylformamide or *N,N*-dimethylacetamide (30 mmoles) was reacted with phosphoryl chloride (5 mmoles) at 70° for 2 hours or at 80° for 40 hours. The insoluble substance was filtered off from the reaction mixture and the filtrate was poured into ice water and kept in a refrigerator for 1 week. The resulting precipitate **4a** or **4b** was collected and refluxed with 10% hydrochloric acid for 1 hour. After a solution was concentrated *in vacuo* and treated with 5% sodium bicarbonate, the resulting precipitate was collected and recrystallized from water. Compounds **5a** and **5b** were obtained in yields of 38 and 42%, respectively. These were identical in all respects with the compounds obtained by Method A.

Vilsmeier-Type Reaction of **3a** and **3b**. Formation of **4a** and **4b**.

Compound **3a** (167 mg, 1 mmole) was treated with *N,N*-dimethylformamide (4.7 ml) and phosphoryl chloride (0.56 ml) at 50° for 2 hours. After addition of ice water, the precipitate **4a** was collected, treated with 5% sodium bicarbonate, and recrystallized from water to give **4a** in 43% yield. The product was identical with the sample of **4a** obtained by the above method.

Similarly, **3b** (78.3 mg, 0.43 mmole) was treated with *N,N*-dimethylformamide (5 ml) and phosphoryl chloride (0.081 ml) at 70° for 2 hours to give **4b** (28.5 mg, 34%), mp 214-216° (from methanol), colorless fine needles; ir (potassium bromide): 3280 (NH), 1760, 1670 cm^{-1} (C=O); high resolution ms: m/z Calcd. for $C_7H_7O_2N_5$: 193.05997. Found: 193.05781.

Vilsmeier-Type Reaction of **2**. Formation of **4a**.

To a suspension of **2** (1.02 mg, 0.5 mmole) in *N,N*-dimethylformamide (2.35 ml) was added phosphoryl chloride (0.28 ml) at 50° and the resulted solution was heated with stirring at 50° for 4 hours. After cooling, precipitate A was separated by filtration from filtrate B. Precipitate A was poured into ice water and the solution was allowed to stand for 5 days at room temperature. The precipitate was collected and refluxed with 10% hydrochloric acid (20 ml) for 1 hour. The solution was evaporated to dryness in vacuum, and the residue was recrystallized from water to recover **2** in 32% yield.

Filtrate B was poured into ice water and kept for 1 week in a refrigerator. The resulted precipitate was collected, treated with 5% sodium bicarbonate and recrystallized from water to give **4a** (41%), which was identical with the authentic sample in all respects.

2,7-Diamino[1,2,4]triazolo[1,5-*c*]pyrimidine-5(6*H*)-thione **3d**.

Compound **1** (100 mg) was heated with cyanogen bromide (150 mg) and water (5 ml) at 70° for 24 hours with stirring. The solution was evaporated to dryness and the residue was washed with water, dissolved in water and made basic with 1 *N* sodium hydroxide. The whole was allowed to stand for 2 weeks at 35°. The resulting precipitate was collected, washed with water and recrystallized from water to give colorless plates, mp 220-223° dec, yield 42%; ir (potassium bromide): 3320 (NH_2), 3140 cm^{-1} (NH); ^{1}H-nmr (DMSO-d_6): 5.83 (s, 1H, H-8).

Anal. Calcd. for $C_5H_6N_6S$: C, 32.97; H, 3.32; N, 46.14. Found: C, 32.88; H, 3.60; N, 46.58.

1,4,6-Triaminopyrimidin-2(1*H*)-one **6**.

A solution of **1** (943 mg) in 5% chloroacetic acid (56.7 ml) was refluxed for 11 hours. After evaporation to dryness, the residue was treated with 5% sodium bicarbonate, washed with water and recrystallized from water to give colorless plates, mp 212-213.5°, yield 78%; ir (potassium bromide): 3430, 3350, 3300 (NH_2), 1720 cm^{-1} (C=O).

Anal. Calcd. for $C_4H_7ON_5$: C, 34.04; H, 5.00; N, 49.63. Found: C, 33.89; H, 5.23; N, 49.32.

REFERENCES AND NOTES

[1] T. Tsuji and Y. Kamo, *Chem. Letters*, 641 (1972).

[2a] J. M. Rice, G. O. Dudek and M. Barker, *J. Am. Chem. Soc.*, **87**, 4569 (1965); [b] Q. N. Porter, Mass Spectrometry of Heterocyclic Compounds, 2nd Ed, John Wiley, NY, 1985, p 786.

[3a] K. T. Potts, R. Armbruster and E. Houghton, *J. Heterocyclic Chem.*, **8**, 773 (1971); [b] A. Bernardini, P. Viallefront and J. Daunis, *ibid.*, **12**, 655 (1975); [c] Y. Miyamoto, *Chem. Pharm. Bull.*, **33**, 2678 (1985).

[4] Y. Tamura, J. Kim and M. Ikeda, *J. Heterocyclic Chem.*, **12**, 107 (1975).

[5] C. Yamazaki, *J. Org. Chem.*, **46**, 3956 (1981).