Syntheses and Reactions of [1,3,4]Thiadiazolo[3,2-*a*]pyrimidinone Derivatives

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Received October 10, 1990

5-Imino-6*H*-7-one, 7-amino-5-one and 5-isocyano-7-one derivatives of [1,3,4]thiadiazolo- and -[1,3]thiazolo-[3,2-*a*]pyrimidines were synthesized. 5-Isocyano-7-one derivatives were obtained by the reaction of the corresponding 5-imino-6*H*-7-ones with the Vilsmeier reagent in one step.

J. Heterocyclic Chem., **28**, 489 (1991).

In continuation of our work on the syntheses and reactions of [1,3,4]thiadiazolo[3,2-*a*]pyrimidines, [1-3], it is now revealed that 5-imino-6*H*-[1,3,4]thiazolo- and -[1,3]thiazolo-[3,2-*a*]pyrimidin-7-ones **3a-e** were directly converted to the corresponding 5-isocyanides **9a-e** under the Vilsmeier reaction conditions using *N,N*-dimethylformamide and phosphoryl chloride.

This paper describes the facile synthesis of compounds **3**, the isomeric 7-amino-5-ones **4**, 5-isocyano compounds **9** and related compounds.

Thiadiazolo- and thiazolopyrimidines **3** were prepared by the reaction of 2-amino[1,3,4]thiadiazoles **1a-c** or 2-aminothiazoles **1d-e** with ethyl cyanoacetate **2** in sodium ethoxide and ethanol or in polyphosphoric acid (PPA) (Scheme 1). During the course of the work, Santagati *et al.* have reported the synthesis of **3b** and **3c** from the reaction of **1b** and **1c** in sodium methoxide and methanol, and assigned the structures as 2-substituted 5-imino-6*H*-[1,3,4]-thiadiazolo[3,2-*a*]pyrimidin-7-ones based on the ^{1}H-nmr spectra [4]. The ir spectra of **3a-e** prepared hereof are in accordance with the imino ketone structure, since the NH, 6-CH_2 and C=O absorptions are observed at 3180-3200, 2920-2930 and 1690-1700 cm^{-1}, respectively (Table 1).

Previously, we reported the synthesis of 2,7-disubstituted [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-ones by the reaction of 5-substituted 2-amino[1,3,4]thiadiazoles with α-keto esters in the presence of phosphorus pentaoxide and methanesulfonic acid [2]. When the reaction of 5-methyl-2-amino[1,3,4]thiadiazole or 2-amino[1,3]thiazole with **2** was carried out by the use of phosphorus pentaoxide and methanesulfonic acid, 7-amino[1,3,4]thiadiazolo- and -[1,3]thiazolo[3,2-*a*]pyrimidin-5-ones, **4b** and **4d**, were yielded as isomers of **3**. The ir spectra of **4b** and **4d** are characterized by absorption at 3300-3310, 3060-3100 and 1655-1670 cm^{-1} due to the NH_2, 6-CH and C=O stretching vibrations, respectively (Table 1). The ^{1}H-nmr spectra are also consistent with the amino structure (Experimental). However, the ir and ^{1}H-nmr data of **3** and **4** gave no definitive information to distinguish between the 5-one and 7-one structures.

About the mass fragmentation modes of 2-substituted [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-ones **6** and isomeric 5-ones **7**, the following facts are known [5]. Thus the presence of intense ions corresponding to a loss of CO from the molecular ions is general for these compounds, while the difference between the fragmentation modes of these two classes of compounds is that the 7-ones undergo a retro-Diels-Alder (RDA) cleavage and a SCN radical extrusion which are absent in the 5-ones (Scheme 2). Referring to this report, Santagati *et al.* examined the mass spectra of **3** to determine the position of carbonyl group and observed the intense ions corresponding to M^+-40 or [M^+-

Scheme 1

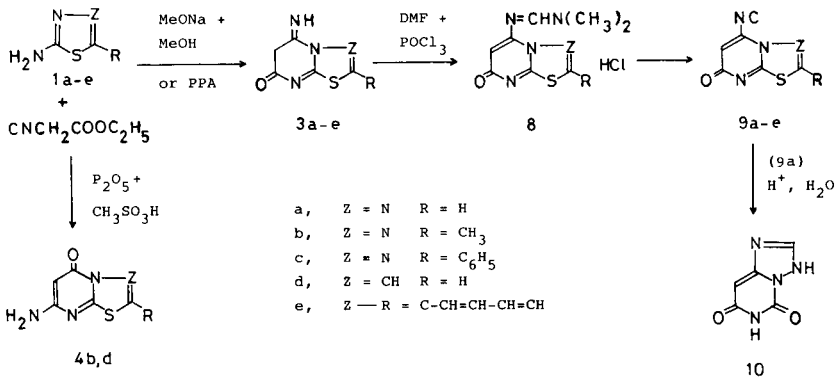


Table 1

IR and selected Ions in Mass Spectra for Compounds **3a-e**, **4b** and **4d**

Compound	IR (KBr, cm^{-1}) NH	6-CH_2	6-CH=	C=O	m/z (Relative abundance) M^+	M^+-40	HN=C=CH•	M^+-CO
3a	3200	2930	–	1700	168 (29)	128 (14)	40 (20)	–
3b	3190	2920	–	1690	182 (42)	142 (39)	40 (35)	–
3c	3180	2920	–	1700	244 (84)	204 (41)	40 (6)	–
3d	3200	2930	–	1700	167 (25)	127 (2)	40 (15)	–
3e	3190	2930	–	1690	217 (43)	177 (7)	40 (2)	–
4b	3310	–	3120	1655	182 (59)	142 (41)	40 (29)	154 (8)
4d	3300	–	3070	1670	167 (75)	127 (10)	40 (24)	139 (1)

Table 2

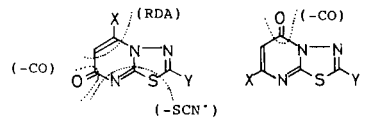
IR Data, ^{1}H-NMR Chemical Shifts and Selected Ions in Mass Spectra for Compounds **9a-e**

Compound	IR (KBr, cm^{-1}) NC	C=O	^{1}H-NMR (δ) 6-CH	H-6	Mass Spectra m/z (Relative abundance) M^+	RDA	M^+-CO	SCN•
9a•HCl	2240	1650	3060	9.44	178 (96) [a]	127 (25)	150 (100) [b]	58 (14)
9b	2200	1650	3030	8.68	192 (23)	141 (69)	164 (12)	58 (15)
9c	2200	1650	3070	8.93	254 (76)	203 (53)	226 (33)	58 (3)
9d	2200	1560	3100	8.85	177 (17)	126 (47)	149 (14)	58 (100)
9e	2210	1660	3060	[c]	227 (10)	176 (100)	199 (13)	58 (6)

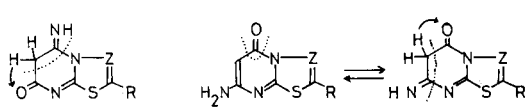
[a] M^+-HCl. [b] M^+-HCl-CO. [c] Not measured.

$(CH_2=C=NH^{\cdot})+H]$. This indicates that a RDA fragmentation does occur accompanying a concomitant hydrogen transfer to a RDA produced fragment (Scheme 2). Thus they assumed that the mass spectra of **3** are consistent with the 7-one structure, since a RDA + H fragment ion must be absent in an alternative 5-one structure [4]. In the mass spectra of **4**, however, we found the presence of intense RDA + H fragment ions which might originate in the tautomeric imino structure **5** (Scheme 2, Table 1). So it might be said that the inspection of RDA + H fragment ions is not useful for differentiating between the 5-one and 7-one structures.

Scheme 2



6 7



3 4 5

Compounds **4** were assigned to the 7-amino-5-one structure from the analysis of mass fragmentation, since a loss of CO from the molecular ions of the amino structure was observed but a loss of SCN radical was absent. These fragmentations were ascertained by high resolution mass measurement (Experimental). While, there is no confirmation that compounds **3** possess the 7-one structure because of the absence of such a fragmentation as a loss of CO, a SCN radical extrusion or a RDA process.

In the foregoing paper, we described the ring transformation of 5,7-diamino[1,2,4]thiadiazolo[3,2-*a*]pyrimidinium salts into 7-amino-6*H*-[1,2,4]triazolo[1,5-*c*]pyrimidine derivatives. In order to obtain unambiguous evidence of the 5-amino-7-one structure, the Vilsmeier reaction of **3** was attempted.

The treatment of **3c** and **3e** with *N,N*-dimethylformamide and phosphoryl chloride gave the 5-dimethylaminomethyleneamino derivatives **8c** and **8e**, and further treatment of them with the same reagents gave the 5-isocyanides **9c** and **9e** as a result of α-elimination of dimethylamine from the dimethylaminomethyleneamino group. Compounds **9a-e** were alternatively prepared in one step by the Vilsmeier reaction of **3a-e** in 21-71% yields (Scheme 2). In contrast, the Vilsmeier reaction of **4b** and **4e** resulted in the recovery of starting materials.

The ir spectra of **9** are characterized by the absorption of isonitrile group at 2200 cm^{-1}. The mass spectra of **9** in-

dicated that there exists three fragmentation paths represented by the appearance of M^+-CO, SCN· and the RDA fragment ions, those which are characteristic for 5-substituted [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-ones [5] (Table 2).

On heating the aqueous solution of the hydrochlorides of **9a-e** at 100° for 20-35 hours, the isonitrile group was hydrolyzed to the amino group forming **3a-e**. While, the treatment of **9a** with 10% hydrochloric acid at 100° for 25 minutes afforded 3*H*,6*H*-[1,2,4]triazolo[1,5-*c*]pyrimidin-5,7-dione **10** along with **3a** (Scheme 2). The structure of **10** was deduced from the ir and ^{1}H-nmr spectra (Experimental). Thus, the 5-amino-7-one structure of **3** was established unequivocally by combining the spectral data of **9** with the formation of **10** from **3**.

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained using a JEOL JNM-PMX 60 spectrometer (60 MHz) in DMSO-d_6. TMS was used as an internal standard. Mass spectra were performed on a JEOL JMX-DX 300 spectrometer by direct insertion at 70 eV.

Synthesis of 5-Imino-6*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-ones **3a-c** and 5-Imino-6*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-7-ones **3d-e**.

Method A.

To a solution of sodium (1.15 g) in anhydrous ethanol (170 ml), **1a-e** (0.05 mole) and ethyl cyanoacetate **2** (0.05 mole) were added and the resulting solution was refluxed for 8 hours. The solution was poured into ice water (300 ml) and acidified with acetic acid. The precipitate was collected, washed with water and recrystallized from methanol to afford **3a-e** in 73-90% yields as colorless microcrystals.

Method B.

A mixture of 2-amino-5-methyl[1,3,4]thiadiazole **1b** or 2-aminothiazole **1d** (0.03 mole), ethyl cyanoacetate **2** (0.03 mole) and polyphosphoric acid (15.45 g) was heated in an oil bath at 70° for 32 hours. The cooled reaction mixture was treated with ice water. The precipitate was collected, washed with water and recrystallized to give **3b** and **3d** in 26 and 30% yields, respectively.

Compound **3a** had mp >300°.

Anal. Calcd. for $C_5H_4ON_4S$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.76; H, 2.37; N, 33.51.

Compound **3d** had mp 221-221.5°.

Anal. Calcd. for $C_6H_5ON_3S$: C, 43.10; H, 3.01; N, 25.14. Found: C, 43.29; H, 3.35; N, 25.23.

Compound **3e** had mp 239-240°.

Anal. Calcd. for $C_{10}H_7ON_3S$: C, 55.28; H, 3.25; N, 19.34. Found: C, 55.05; H, 3.42; N, 19.60.

Compounds **3b** and **3c** are identical with the authentic samples [4] in comparison with mp and spectra.

Synthesis of 7-Amino-5-methyl[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one **4b** and 7-Amino[1,3]thiazolo[3,2-*a*]pyrimidin-5-one **4d**.

A mixture of **1b** or **1d** with ethyl cyanoacetate **2** (1.12 g, 0.01 mole), phosphorus pentoxide (0.71 g, 0.005 mole) and methanesulfonic acid (9.61 g, 0.1 mole) was heated in an oil bath at 105° for 20 hours. The cooled reaction mixture was treated with ice water and neutralized with 10% ammonium hydroxide. The precipitate was collected, washed with water and recrystallized from methanol to give **4b** and **4d**.

Compound **4b** was obtained in 71% yield, mp 280.5-281° (from methanol); ^{1}H-nmr: 2.74 (s, 3H, CH_3), 4.17 (s, 2H, NH_2), 5.00 (s, 1H, H-6); high resolution ms: m/z 182.02403 (M^+ for $C_6H_6ON_4S$ Calcd. 182.02618), 154.03606 (M^+-CO), 142.00880 [M^+-(HN=C=CH·) + H], 40.01958 (HN=C=CH·).

Anal. Calcd. for $C_6H_6ON_4S$: C, 39.55; H, 3.32; N, 30.75. Found: C, 39.36; H, 3.18; N, 30.70.

Compound **4d** was obtained in 48% yield, mp 210.5-212° dec (from water); ^{1}H-nmr: 3.16 (s, 2H, NH_2), 5.30 (s, 1H, H-6), 7.40 and 7.98 (ABq J = 5.0 Hz, 2H, CH=CH); high resolution ms: m/z 167.01677 (M^+ for $C_6H_5ON_3S$, Calcd. 167.01529); 139.02062 (M^+-CO), 126.99659 [M^+-(HN=C=CH·) + H], 40.02685 (HN=C=CH·).

Anal. Calcd. for $C_6H_5ON_3S$: C, 43.10; H, 3.01; N, 25.14. Found: C, 42.89; H, 3.36; N, 25.22.

Synthesis of 5-(*N,N*-Dimethylaminomethyleneamino) Derivatives **8c** and **8e**.

General Procedure.

To a solution of **3c** or **3e** (3 mmoles) in *N,N*-dimethylformamide (14 ml), phosphoryl chloride (6 mmoles) was added dropwise under ice cooling, and the whole was stirred at room temperature for 20 hours. The resulting precipitate was collected, treated with water. The water-insoluble substance was recrystallized from methanol to give **8c** or **8e** as colorless crystals.

Compound **8c** was obtained in 30% yield, mp 205-206.5° dec; ir: 1670 cm^{-1} (C=O); high resolution ms: m/z 299.08480 (M^+-HCl for $C_{14}H_{13}ON_5S$ Calcd. 299.08462).

Anal. Calcd. for $C_{14}H_{14}ON_5SCl$: C, 50.07; H, 4.20; N, 20.86. Found: C, 50.18; H, 4.03; N, 20.99.

Compound **8e** was obtained in 5% yield, mp 227-229°; ir: 1680 cm^{-1} (C=O); high resolution ms: m/z 272.07205 (M^+-HCl for $C_{13}H_{12}ON_4S$ Calcd. 272.07229).

Anal. Calcd. for $C_{13}H_{13}ON_4SCl$: C, 50.56; H, 4.24; N, 18.15. Found: C, 50.77; H, 4.03; N, 18.34.

Synthesis of 5-Isocyano[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-ones **9a-c** and 5-Isocyano[1,3]thiazolo[3,2-*a*]pyrimidin-7-ones **9d-e**.

Method A.

To a solution of **8c** or **8e** (0.002 mole) in *N,N*-dimethylformamide (7 ml), phosphoryl chloride (0.002 mole) was added dropwise at room temperature, and the resulting solution was stirred at 70° for 5 hours. After cooling, a solution was diluted with water (30 ml) and stood in a refrigerator for 20 hours. The resulting precipitate was collected, suspended in water, and made basic (*p*H 8) with 5% sodium hydroxide. The crystals obtained were recrystallized from methanol to give **9c** or **9e**.

Method B.

To a solution of **3** (0.01 mole) in *N,N*-dimethylformamide (40 ml), phosphoryl chloride (0.01 mole) was added dropwise at 50°, and the solution was stirred at 70° for 5 hours. A solution was diluted with water and the resulting precipitate of the hydrochloride salts of **9** was collected. The hydrochloride salt of **9a** (**9a.HCl**) was purified by crystallization from methanol. Other crude hydrochloride salts except **9a.HCl** were subjected to alkaline treatment and purified by crystallization from methanol

to give **9b-e**. Compound **9a** was failed to yield from **9a.HCl**, since it was readily decomposed by the alkaline treatment.

Compound **9a.HCl** was obtained in 67% yield, mp 231.5° dec; high resolution ms: m/z 177.99421 (M^+-HCl for $C_6H_2ON_4S$ Calcd. 177.9949).

Anal. Calcd. for $C_6H_3ON_4SCl$: C, 33.58; H, 1.40; N, 26.11. Found: C, 33.70; H, 1.32; N, 25.97.

Compound **9b** was obtained in 68% yield, mp 258-258.5°; high resolution ms: m/z 192.00899 (M^+ for $C_7H_4ON_4S$ Calcd. 192.01054), 164.01596 (M^+-CO), 140.99956, 57.97693 (RDA).

Anal. Calcd. for $C_7H_4ON_4S$: C, 43.74; H, 2.10; N, 29.15. Found: C, 43.61; H, 2.32; N, 29.38.

Compound **9c** was obtained in 46% yield, mp 289-291° dec; high resolution ms: m/z 254.02485 (M^+ for $C_{12}H_6ON_4S$ Calcd. 254.02618), 226.03106 (M^+-CO), 203.01661, 57.98924 (RDA).

Anal. Calcd. for $C_{12}H_6ON_4S$: C, 56.68; H, 2.38; N, 22.04. Found: C, 56.45; H, 2.58; N, 21.93.

Compound **9d** was obtained in 71% yield, mp 254-254.5° dec; high resolution ms: m/z 177.00017 (M^+ for $C_7H_3ON_3S$ Calcd. 177.99965), 149.00388 (M^+-CO), 126.99055, 57.98924 (RDA).

Anal. Calcd. for $C_7H_3ON_3S$: C, 47.45; H, 1.71; N, 23.72. Found: C, 47.68; H, 1.93; N, 23.90.

Compound **9e** was obtained in 21% yield, mp 278-278.5°; high resolution ms: m/z 227.01447 (M^+ for $C_{11}H_5ON_3S$ Calcd. for 227.01529), 199.02160 (M^+-CO), 176.00907, 67.97052 (RDA).

Anal. Calcd. for $C_{11}H_5ON_3S$: C, 58.14; H, 2.22; N, 18.49. Found: C, 58.00; H, 2.36; N, 18.71.

Acid Hydrolysis of **9b-e**.

An aqueous solution of **9b-e** was adjusted *p*H to 4.0 by adding hydrochloric acid, and heated at 100° for 20-35 hours. The solution was evaporated to dryness and the residue was recrystallized from methanol to afford **3b-e** in 63-81% yields. The products were identical with the authentic samples in all respects.

3*H*,6*H*-[1,2,4]triazolo[1,5-*c*]pyrimidin-5,7-dione **10**.

A solution of **9a.HCl** (0.002 mole) in 10% hydrochloric acid (30 ml) was refluxed for 25 minutes. After cooling, the resulting precipitate (**3a**, 15 mg) was separated from the filtrate by filtration. The filtrate was evaporated to dryness in diminished pressure, and the residue was extracted with hot methanol. After removal of the solvent from the extract, the residue was recrystallized from methanol to give **10** as colorless prisms, mp 217-218° dec, yield 35%; ir: 3340 (3-NH), 3170, 3070 (6-NH), 1680 cm^{-1} (C=O); ^{1}H-nmr: 5.73 (s, 1H, H-8), 8.75 (s, 1H, H-2); ms: m/z 152 (M^+), 109 (M^+-HNCO), 43 (HNCO); high resolution ms: m/z 152.03338 (M^+ for $C_5H_4O_2N_4$ Calcd. 152.03408).

Anal. Calcd. for $C_5H_4O_2N_4$: C, 39.48; H, 2.65; N, 36.84. Found: C, 39.66; H, 2.80; N, 36.71.

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