Synthesis of [1,3,4]Thiadiazolo[3,2-*a*]pyrimidines in the Presence of Formic Acid

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Formic acid-phosphorus pentoxide was effective for the preparation of 5,7-dimethyl[1,3,4]thiadiazolo- and -[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium salts. Further, the pyrimidine ring transformation and the isocyanation of 5imino-6*H*-[1,3,4]thiadiazolo- and -[1,3]thiazolo[3,2-*a*]pyrimidin-7-ones were carried out in the presence of formic acid and triethyl orthoformate, respectively.

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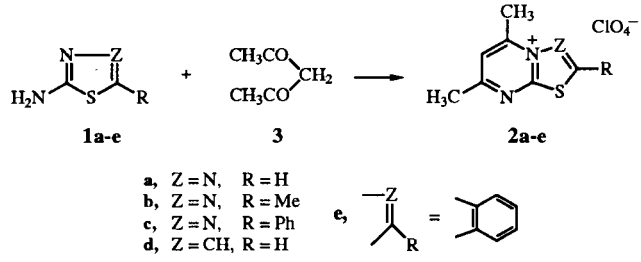
Previously, the authors reported the efficiency of methanesulfonic acid-phosphorus pentoxide as a condensation reagent for the synthesis of 7-methyl[1,3,4]thiadiazolo-[3,2-*a*]pyrimidin-5-ones from 2-amino[1,3,4]thiadiazoles **1** and β-keto esters [1]. In continuation of the work, it was revealed that the formic acid-phosphorus pentoxide was effective as well as the above reagent for the synthesis of 5,7-dimethyl[1,3,4]thiadiazolo- and -[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium salts **2** from **1** and 2,4-pentanedione **3**. In relation to this reaction, the pyrimidine ring transformation and the isocyanation of 5-imino-6*H*-[1,3,4]thiadiazolo- and -[1,3]-thiazolo[3,2-*a*]pyrimidin-7-ones **4** were found to occur by the action of formic acid and triethyl orthoformate, respectively. The present paper describes the synthesis of **2** and the related reactions.

Two [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-4-ium salts were prepared by Okabe *et al.* in polyphosphoric acid in 35-68% yields [2]. We now prepared **2a-e** by cyclization of **1a-e** with **3** at 100° for 10 hours in the presence of methanesulfonic acid-phosphorus pentoxide and formic acid-phosphorus pentoxide in yields of 29-69% and 74-98%, respectively. The formic acid-phosphorus pentoxide-mediated synthesis gave the better result in respect of yield.

Scheme 1



The ^{1}H-nmr spectra of **2** were in accordance with proposed pyrimidinium salt structures, as noted in experimental section. In the mass spectra of **2**, the intense peak of free base ion (M^+ -$HClO_4$) and three fragmentation paths i-iii were distinguished for all compounds examined, as shown in Scheme 2 and Table 1. These are shown as originating from the free base ion by a loss of $C{=}CH_2$ (path i), a NCS radical extrusion (path ii) and a retro Diels-Alder cleavage accompanying hydrogen transfer

Scheme 2

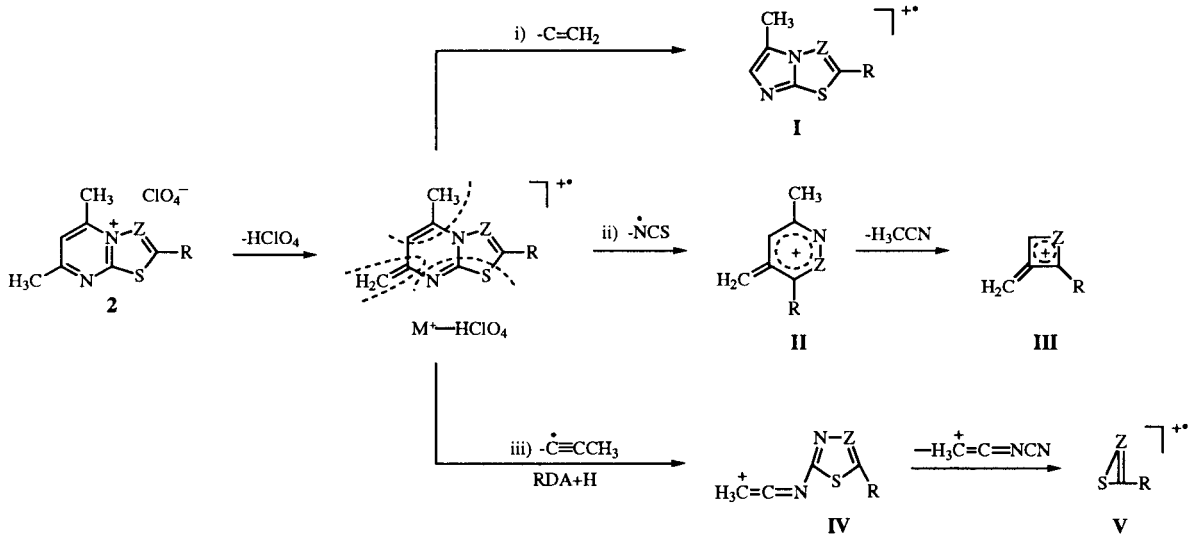


Table 1
Selected Fragments in Mass Spectra of Compounds **2a-e**

Fragment		Compounds 2a	2b	2c	2d	2e
M^+-HClO_4	m/z (Rel Int)	165 (100)	179 (75)	241 (71)	164 (46)	214 (100)
$C=CH_2$	m/z (Rel Int)	26 (1)	26 (8)	26 (2)	26 (5)	26 (1)
I	m/z (Rel Int)	139 (1)	153 (4)	215 (3)	138 (6)	188 (3)
•NCS	m/z (Rel Int)	58 (2)	58 (16)	58 (2)	—	58 (1)
II	m/z (Rel Int)	107 (95)	—	183 (1)	106 (3)	156 (1)
H_3CCN	m/z (Rel Int)	41 (2)	41 (24)	41 (2)	41 (8)	41 (4)
III	m/z (Rel Int)	66 (22)	80 (21)	142 (1)	65 (13)	115 (1)
$•C\equiv CCH_3$	m/z (Rel Int)	39 (22)	39 (48)	39 (18)	39 (42)	39 (11)
IV	m/z (Rel Int)	126 (1)	140 (5)	202 (1)	125 (39)	175 (19)
$H_3C^+=C=NCN$	m/z (Rel Int)	67 (83)	67 (14)	67 (18)	67 (27)	67 (9)
V	m/z (Rel Int)	59 (5)	73 (8)	135 (11)	58 (45)	108 (9)

(RDA+H) (path iii). The fragments were ascertained by high resolution mass measurement for **2a** and **2d** (Experimental).

In Fotis' work [3] on some 5-methyl[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-ones **5** and isomeric 7-methyl-5-ones **6**, they reported that the characteristic mass fragmentations of **5** were a CO elimination, a NCS radical extrusion and a retro Diels-Alder (RDA) process, while the characteristic fragmentation of **6** was only a CO elimination. In the fragmentation of free base ion (M^+-HClO_4) of **2**, a loss of $C=CH_2$ and a NCS radical extrusion were observed, and further a hydrogen transfer accompanying retro Diels-Alder (RDA+H) process instead of RDA process was observed. The RDA+H process is a well recognized one in the mass spectra of 5-imino-6*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-ones **4** [4]. Taking into account these three fragmentation paths, the structure of free base ion of **2** was deduced as 5-methyl-7-methylidene derivative.

In relation to the usefulness of methanesulfonic acid-phosphorus pentoxide and formic acid-phosphorus pentoxide in the synthesis of **2**, we found that the treatment of 5-imino-6*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-ones **4a-c** with these reagents at 100° for 10 hours furnished 7-amino-5-ones **7a-c**. The sole use of formic acid was effective in the present novel pyrimidine ring conversion.

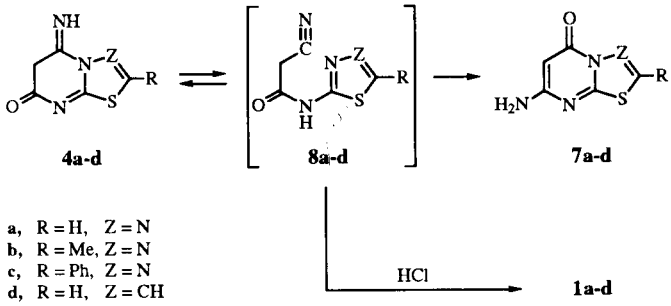
5-Imino-6*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-7-one **4d** was also convertible to **7d** by the same reaction. This indicates that the ring conversion of **4** occurred in pyrimidine moiety, but not in thiadiazole or thiazole moiety. Compounds **7b** and **7d** were identical with those [5] obtained from the reaction of **1b** and **1d** with ethyl cyanoacetate in methanesulfonic acid-phosphorus pentoxide.

On hydrolysis of **4** with 5% hydrochloric acid furnished **1**, suggesting the intermediative occurrence of the ring opened isomer, 2-cyanoacetylamino[1,3,4]thiadiazoles and -[1,3]thiazole **8**, prior to hydrolysis (Scheme 3).

When referred Lauers' work [6] on the *p*-toluenesulfonic acid-catalyzed cyclization of 2-acetoacetylamino[1,3,4]thiadiazole into **6**, wherein **6** formed by 1,3-carbonyl rearrangement of the acetoacetyl group followed by cyclization, the present reaction course of transformation of **4** to **7** might be explained by assuming the 1,3-shift of cyanoacetyl group in the ring opened isomer **8** followed by recyclization (Scheme 3).

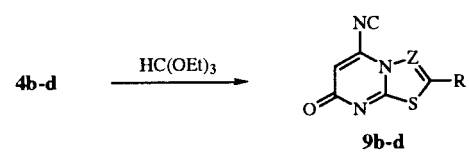
Since the *N*-formylation of 5-imino group of **4** did not occur by the treatment with formic acid, we examined the reaction of **4b-d** with triethyl orthoformate, and yielded the unexpected isocyanates **9b-d**, which were identical with the compounds [5] derived from the Vilsmeier-Haack reaction of **4b-d**.

Scheme 3



a, R = H, Z = N
b, R = Me, Z = N
c, R = Ph, Z = N
d, R = H, Z = CH

Scheme 4



b, R = Me, Z = N
c, R = Ph, Z = N
d, R = H, Z = CH

EXPERIMENTAL

The mass spectra were performed on a Jeol JMX-DX 300 spectrometer by direct insertion at 70 eV. The ^{1}H-nmr spectra were obtained using a Bruker AMX 400 spectrometer and a Jeol

JNM 60 spectrometer in DMSO-d_6. TMS was used as an internal standard. The ir spectra were recorded on a Hitachi 260-10 spectrometer.

Synthesis of 5,7-Dimethyl[1,3,4]thiadiazolo- and -[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium Perchlorates **2**.

Procedure A.

A mixture of **1** (0.01 mole), **3** (0.011 mole), methanesulfonic acid (0.05 mole) and phosphorus pentoxide (0.01 mole) was heated at 100° for 10 hours. The reaction mixture was diluted with water, and mixed with 70% perchloric acid. The precipitate was collected, washed with water and recrystallized from methanol.

Compound **2a** was obtained in 29% yield, mp 249.5° dec; hrms: m/z 165.0365 (M^+-$HClO_4$ for $C_7H_7N_3S$: Calcd. 165.0360), 139.0185 (I), 126.0171 (IV), 107.0627 (II), 67.0298 (H_3C^+=C=NCN), 66.0329 (III), 58.9815 (V), 57.9756 (•NCS), 41.0307 (H_3CCN), 39.0238 (•C≡CCH_3).

Anal. Calcd. for $C_7H_8O_4N_3SCl$: C, 31.64; H, 3.03; N, 15.82. Found: C, 31.43; H, 2.98; N, 15.64.

Compound **2b** was obtained in 46% yield, mp 208-209° (from methanol). The product **2b** was identical with the authentic sample (mp 207°) [2] in comparison with their mp and spectra.

Compound **2c** was obtained in 54% yield, mp 237.5°.

Anal. Calcd. for $C_{13}H_{12}O_4N_3SCl$: C, 45.68; H, 3.54; N, 12.30. Found: C, 45.43; H, 3.30; N, 12.14.

Compound **2d** was obtained in 69% yield, mp 230°; hrms: m/z 164.0412 (M^+-$HClO_4$ for $C_8H_8N_2S$: Calcd. 164.0408), 138.0240 (I), 125.0167 (IV), 106.0691 (II), 67.0272 (H_3C^+=C=NCN), 65.0353 (III), 57.9860 (V), 41.0299 (H_3CCN), 39.0236 (•C≡CCH_3). This was identical with the sample prepared by Procedure B.

Procedure B.

To a solution of phosphorus pentoxide (3 mmoles) in formic acid (10 ml), 2-amino[1,3,4]thiadiazole or -[1,3]thiazole **1** (3 mmoles) and 2,4-pentanedione **3** (3.3 mmoles) were added, and the whole was heated at 100° for 10 hours. The reaction mixture was evaporated to dryness under reduced pressure and the residue was diluted with water (10 ml). The solution was mixed with 70% perchloric acid, and the resultant precipitate was collected and recrystallized to give **2**.

Compound **2a** was obtained in 98%, mp 248° (from water); ^{1}H-nmr: 2.84 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 8.15 (s, 1H, H-6), 10.05 (s, 1H, H-2); hrms: m/z 165.0356 (M^+-$HClO_4$ for $C_7H_7N_3S$: Calcd. 165.0360).

Compound **2b** was obtained in 80% mp 211-211.5° (from methanol); ^{1}H-nmr: 2.81 (s, 3H, CH_3), 2.94 (s, 3H, CH_3), 3.02 (s, 3H, 2-CH_3), 8.12 (s, 1H, H-6); hrms: m/z 179.0529 (M^+-$HClO_4$ for $C_8H_9N_3S$: Calcd. 179.0517).

Compound **2c** was obtained in 93%, mp 233° (from methanol); ^{1}H-nmr: 2.86 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 8.20 (s, 1H, H-6), 7.80 (m, 3H, arom), 8.25 (d, 2H, arom); hrms: m/z 241.0655 (M^+-$HClO_4$ for $C_{13}H_{11}N_3S$: Calcd. 241.0673).

Compound **2d** was obtained in 74% yield, mp 230-230.5° (from methanol); ^{1}H-nmr: 2.77 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 7.95 (s, 1H, H-6), 8.50 and 8.77 (ABq, J = 4.69 Hz, 2H, CH=CH); hrms: m/z 164.0388 (M^+-$HClO_4$ for $C_8H_8N_2S$: Calcd. 164.0408).

Compound **2e** was obtained in 77% yield, mp 258-260° (from methanol); ^{1}H-nmr: 2.83 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 8.08 (s, 1H, H-6), 7.91 (m, 2H, arom), 8.65 (m, 2H, arom); hrms: m/z 214.0550 (M^+-$HClO_4$ for $C_{12}H_{10}N_2S$: Calcd. 214.0564).

Ring Transformation of 5-imino-6*H*-[1,3,4]thiadiazolo- and -[1,3]thiazolo[3,2-*a*]pyrimidin-7-ones **4** into 7-Amino[1,3,4]-thiadiazolo- and -[1,3]thiazolo[3,2-*a*]pyrimidin-5-ones **7**.

Procedure A.

A mixture of compounds **4** (5 mmoles), methanesulfonic acid (25 mmoles) and phosphorus pentoxide (5 mmoles) was heated at 100° for 10 hours. The solution was concentrated in diminished pressure and added water. The mixture was neutralized with 10% ammonium hydroxide. The resulted precipitate was collected, washed with water and recrystallized to give **7**.

Compound **7a** was obtained in 54% yield, mp >300° (from water); the compound obtained hereof was identical with the sample obtained by Procedure C.

Compound **7b** was obtained in 72% yield, mp 288° dec (from methanol). The product was identical with an authentic sample [5].

Procedure B.

A mixture of **4** (1 mmole), formic acid (3.3 ml) and phosphorus pentoxide (1 mmole) was heated at 100° for 10 hours. The solution was concentrated under diminished pressure, water was added and the mixture was neutralized with 10% ammonium hydroxide. The precipitate was collected, washed with water and recrystallized to give **7**, which were identical with the sample obtained by Procedure C.

Compound **7b** was obtained in 53% yield, mp 288-288.5° dec (from methanol).

Compound **7c** was obtained in 47% yield, mp 267.5-268° dec (from water).

Compound **7d** was obtained in 30% yield, mp 227-228° dec (from water).

Procedure C.

A solution of compounds **4** (1 mmole) in formic acid (10 ml) was refluxed for 10 hours. Thereafter, the solution was evaporated to dryness. To the residue was added water, and the mixture was neutralized with 10% ammonium hydroxide. The precipitate was collected, washed with water and purified to give **7**.

Compound **7a** was obtained in 98% yield, mp >300° (from water); ^{1}H-nmr: 5.25 (s, 1H, H-6), 7.36 (s, 2H, NH_2), 9.26 (s, 1H, H-2); hrms: m/z 168.0088 (M^+ for $C_5H_4ON_4S$: Calcd. 168.0105).

Compound **7b** was obtained in 95% yield, mp 292° dec (from water); ^{1}H-nmr 2.51 (s, 3H, CH_3), 5.04 (s, 1H, H-6), 7.03 (s, 2H, NH_2); hrms: m/z 182.0262 (M^+ for $C_6H_6ON_4S$: Calcd. 182.0262).

Compound **7b** was identical with the authentic sample [5].

Compound **7c** was obtained in 74% yield, mp 269-270° dec (from methanol); ^{1}H-nmr: 5.14 (s, 1H, H-6), 7.21 (s, 2H, NH_2), 7.62 (m, 3H, arom), 7.99 (d, 2H, arom); hrms: m/z 244.0398 (M^+ for $C_{11}H_8ON_4S$: Calcd. 244.0418).

Compound **7d** was obtained in 82% yield, mp 223-224° dec (from water); ^{1}H-nmr: 5.15 (s, 1H, H-6), 7.04 (s, 2H, NH_2), 7.29 and 7.84 (AB q, J = 5.00 Hz, 2H, CH=CH); hrms: m/z 167.0143 (M^+ for $C_6H_5ON_3S$: Calcd. 167.0153). This compound was identical with an authentic sample [5].

Acid Hydrolysis of Compounds **4**.

A solution of **4a**, **4b** or **4d** (0.5 mmole) in 10% hydrochloric acid (1 ml) was refluxed for 5 hours. After completion, the solution was evaporated to dryness in diminished pressure, and dissolved in water (1 ml). The solution was adjusted to *p*H 7 with

5% sodium hydroxide, and concentrated. After storage in a refrigerator, the resulted precipitate was collected and recrystallized from methanol to give **1a**, **1b** and **1d**, respectively, which were identical with the corresponding authentic samples in comparison with mp and spectra

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

To a solution of compounds **4** (0.55 mmole) in *N,N*-dimethylformamide (2 ml), triethyl orthoformate (6 mmoles) was added. The reaction mixture was heated at 100° for 10 hours and concentrated in vacuum. After addition of water to the solution, the resulting precipitate was collected and recrystallized from methanol to give **9**. Their ir spectra had the absorption of an isonitrile group at 2230 cm^{-1}. Compounds obtained hereof were identical with the authentic samples [5].

Compound **9b** was obtained in 69% yield, mp 258° dec; ^{1}H-nmr: 2.60 (s, 3H, CH_3), 8.68 (s, 1H, H-6).

Compound **9c** was obtained in 34% yield, mp 293° dec; ^{1}H-nmr: 7.60-7.95 (m, 5H, arom), 8.93 (s, 1H, H-6).

Compound **9d** was obtained in 49% yield, mp 256° dec; ^{1}H-nmr: 7.00 and 7.35 (AB q, 2H, CH=CH), 8.85 (s, 1H, H-6).

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