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A Novel Formation of 3,4-Disubstituted Isothiazoles from 5-Amino-6-methylpyrimidinones

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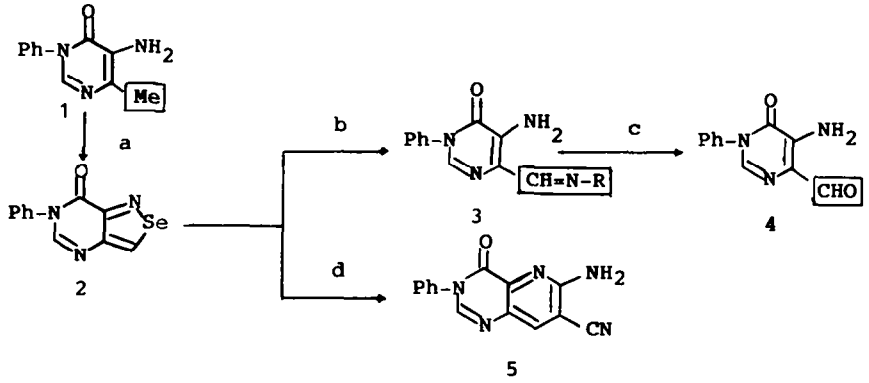
Abstract 3,4-Disubstituted isothiazoles (**8a,b, 9a,b, 10, 11, 14a,b**) were synthesized from 5-amino-6-methyl-4(3H)-pyrimidinone (**1**) or 1,3-disubstituted 5-amino-6-methyluracils (**12a,b**) via the formation of isothiazolo[4,3-d]pyrimidines (**6, 13a,b**) followed by the reaction with alkylamines.

Pyrimidines or fused pyrimidines are important materials for the synthesis of a number of compounds which have potential biological activities, and various reactions have been studied.[3] Previously we reported the facile conversion of the methyl group of 5-amino-6-methyl-3-phenyl-4(3H)-pyrimidinone (**1**)[4] to the alkyliminomethyl group via the formation of 7-oxo-6-phenyl-6H-isoselenazolo[4,3-d]pyrimidine (**2**)[5] followed by the reaction with primary alkylamines.[6] The alkyliminomethyl groups of **3** were easily hydrolyzed to the formyl group (**4**) by passing through a silica gel column. We also discovered the formation of 6-amino-7-cyano-3-phenyl-3H-pyrido[3,2-d]pyrimidine-4-one (**5**)[7] by the reaction of **2** with malononitrile in the presence of triethylamine (Chart 1). Such findings induced our interest to synthesize the sulfur analogue 7-oxo-6-phenyl-6H-isothiazolo[4,3-d]pyrimidine (**6**) and investigate the reaction with alkylamines. During the investigation we have found a novel formation of 3,4-disubstituted isothiazoles (**8a,b, 9a,b, 10, 11, 14a,b**) from **1** and 1,3-disubstituted 5-amino-6-methyluracils (**13a,b**)[8], as will be reported in this paper.

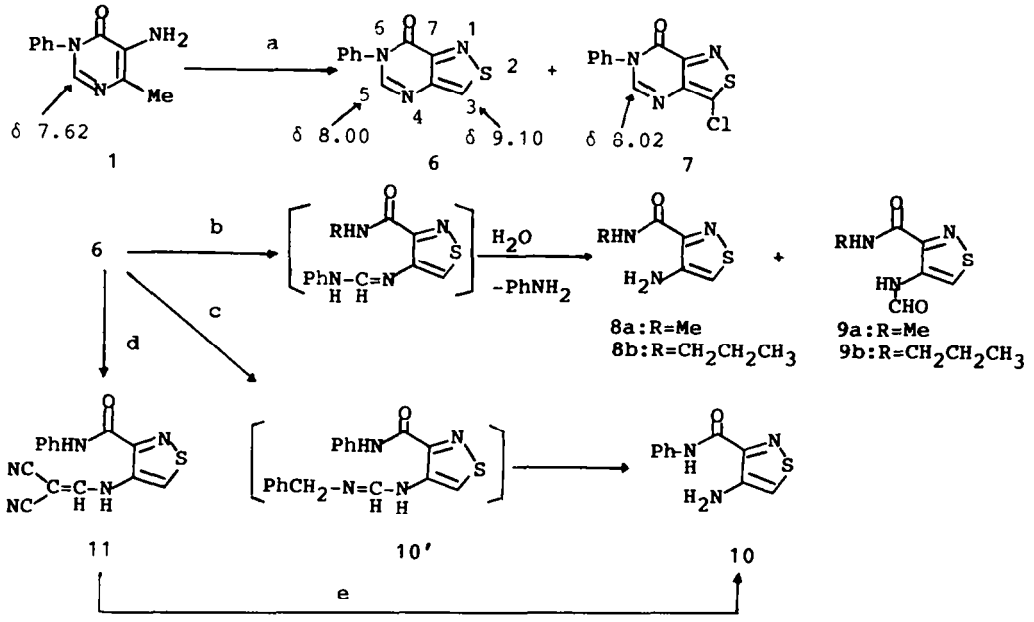


a: SeO_2/bromobenzene b: RNH_2/ethanol c: silica gel/chloroform
d: malononitrile, triethylamine/ethanol

Chart 1

Isothiazolo[4,3-d]pyrimidine **6** was readily available in 78% yield by the reaction of **1** with thionyl chloride[9] in refluxing bromobenzene[10] and was accompanied by a small amount of 3-chloro-7-oxo-6-phenyl-6H-isothiazolo[4,3-d]pyrimidine (**7**)(10%). The structures of these products **6** and **7** were established by

their infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR) and mass (MS) spectra as well as by anayltical data. The ^{1}H-NMR spectrum of **6** showed a signal of C_3-H at δ 9.10 and that of C_5-H at δ 8.00, whereas compound **7** showed a signal at δ 8.02, which was attributable to C_5-H. Thus, it was disclosed that chloro group was substituted at C_3-position. The reactivity of **6** toward alkylamines was investigated as follows. The reaction of **6** with 40% aqueous methylamine in refluxing ethanol did not proceed. However, on treatment with a large excess of 40% aqueous methylamine in a sealed tube at 100°C for 16 h, **6** underwent pyrimidine ring opening to give **8a** (47%) and **9a** (31%). The ^{1}H-NMR spectra of **8a** and **9a** disclosed pyrimidine ring opening and disappearance of the phenyl group. The absorptions of unchanged isothiazole C_3-protons of **8a** and **9a** were observed at δ 7.44 and δ 8.48, respectively. The IR spectra of these compounds showed absorptions due to amino group in the region of 3200-3400 cm^{-1}. Mass spectra and elemental analyses were consistent with the assigned structures. However, the reaction of **6** with benzylamine gave **10** in 60% yield, whose anilino group was not displaced by benzylamine. This compound was identical with that obtained by the hydrolysis of 4-(3',3'-dicyanoethenyl)amino-3-phenylcarbamoylisothiazole (**11**) which was obtained by the reaction of **6** with malononitrile in ethanol in the presence of triethylamine. Thus, it may be concluded that alkylamines such as methylamine or propylamine react towards C_7-position of **6** to give pyrimidine ring opened **8a,b** and **9a,b** and the bulky nucleophilic reagents such as benzylamine and malononitrile attack C_5-position of **6** to give **10'** or **11**, which is successively hydrolyzed to **10** (Chart 2).

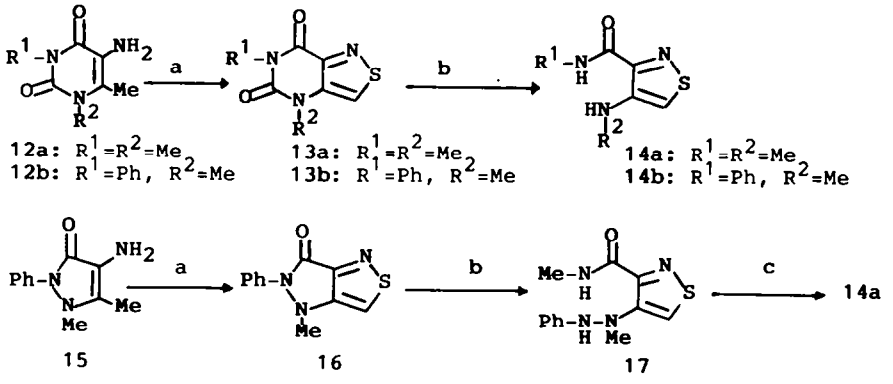


a: $SOCl_2$/bromobenzene b: 40% aqueous methylamine or propylamine
c: benzylamine d: malononitrile, triethylamine/ethanol e: HCl-EtOH (1:1)

Chart 2

We further examined the reaction of 4,6-disubstituted 5,7-dioxo-4,5,6,7-tetrahydroisothiazolo[4,3-d]pyrimidines (**13a,b**)[9] with alkylamines (Chart 3). The reaction of **13a** with 40% aqueous methylamine in a sealed tube at 100°C for 6 h gave 4-methylamino-3-methylcarbamoylisothiazole (**14a**) in 53% yield. However, this compound was also obtained by the reaction of **13a** with 70% aqueous

ethylamine or 10% ethanolic KOH in 40% or 46% yield. This fact indicates that nucleophilic reagents attack C_5-position of **13a**. Similar reaction of **13b** with 40% aqueous methylamine gave **14b** in 86% yield. Compound **14a** was also derived from 4-aminoantipyrine (**15**) via the formation of pyrazolo[4,3-c]isothiazole (**16**)[11] followed by the reaction with 40% aqueous methylamine and the reductive cleavage of N-N bond.



a: $SOCl_2$/bromobenzene b: 40% aqueous methylamine
c: H_2 (120 kg/cm^2), Raney nickel/MeOH

Chart 3

Table I. Yields (%) of 3,4-Disubstituted Isothiazoles (**8a,b**, **9a,b**, **10**, **11**, **14a,b**)

Starting Material	Reagents	Reaction Temp. (C°)	Reaction Time (h)	Product (Yield (%))
6	40% $MeNH_2$	100 (in sealed tube)	16	**8a** (47)
6	n-$C_3H_7NH_2$	100 (in sealed tube)	16	**8b** (42)
6	40% $MeNH_2$	100 (in sealed tube)	16	**9a** (31)
6	n-$C_3H_7NH_2$	100 (in sealed tube)	16	**9b** (27)
6	$PhCH_2NH_2$	90 (in sealed tube)	3	**10** (60)
6	$CH_2(CN)_2$,tri-ethylamine/EtOH	reflux	1	**11** (78)
13a	40% $MeNH_2$	100 (in sealed tube)	6	**14a** (58)
13b	70% $EtNH_2$	100 (in sealed tube)	6	**14b** (40)
13a	10% ethanoic KOH	reflux	3	**14a** (46)
13b	40% $MeNH_2$	100 (in sealed tube)	10	**14b** (86)
13b	50% Me_2NH	60 (in sealed tube)	10	**14b** (70)

As described in the beginning, reactions of isoselenazolo[4,3-d]pyrimidine **2** with nucleophilic reagents gave rise to isoselenazole ring opening along with deselenation. On the other hand, the reactions of isothiazolo[4,3-d]pyrimidines **6** and **13** with alkylamines gave isothiazoles by pyrimidine ring opening. This reaction will be useful as a novel synthesis of isothiazoles from pyrimidines.

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Experimental

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra were measured with JASCO IR-810 spectrophotometer. Mass spectra were measured with a JEOL JMS-DX 300 spectrometer. Proton nuclear magnetic resonance spectra were recorded with a JEOL JNM-MH-100 or JNM-FX-100 spectrometer using tetramethylsilane as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; q, quartet; br, broad; m, multiplet.

7-Oxo-6-phenyl-6H-isothiazolo[4,3-d]pyrimidine (6) and 3-Chloro-7-oxo-6-phenyl-6H-isothiazolo[4,3-d]pyrimidine (7) Thionyl chloride (12 g, 98 mmol) was added gradually to a solution of **1** (3 g, 15 mmol) in bromobenzene (70 ml). The mixture was heated at 150-160°C for 2 h. The solvent was distilled off. The residue was subjected to column chromatography on silica gel. The first chloroform eluate was collected and the solvent was distilled off. The residue was crystallized from ethanol to give **7**: Yield 0.34 g (10%), mp 169-170°C. ^{1}H-NMR ($CDCl_3$) δ: 7.20-7.70 (5H, m, Ar), 8.02 (1H, s, C_5-H). IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). MS m/z: 263 (M^+). Anal. Calcd for $C_{11}H_6ClN_3OS$: C, 50.10; H, 2.29; N, 15.93. Found: C, 50.15; H, 2.38; N, 15.94.

The second chloroform eluate was collected and the solvent was distilled off. The residue was crystallized from ethanol to give **6**: Yield 2.7 g (78%), mp 160-162°C . ^{1}H-NMR ($CDCl_3$) δ: 7.20-7.72 (5H, m, Ar), 8.00 (1H, s, C_5-H), 9.10 (1H, s, C_3-H). IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O). MS m/z: 229 (M^+). Anal. Calcd for $C_{11}H_7N_3OS$: C, 57.60; H, 3.06; N, 18.32. Found: C, 57.64; H, 3.06; N, 18.41.

4-Amino-3-(N-methyl)carbamoylisothiazole (8a) and 4-Formamido-3-(N-methyl)carbamoylisothiazole (9a) A mixture of **6** (1 g, 4.3 mmol) and excess 40% aqueous methylamine (30 ml) was heated in a sealed stainless steel tube at 100°C for 16 h. The excess methylamine was distilled off. The residue was neutralized with 5% aqueous HCl and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was subjected to column chromatography on silica gel.

The first chloroform eluate was collected and the solvent was distilled off. The residue was crystallized from ethanol to give **8a**: Yield 322 mg (47%), mp 80-82°C. ^{1}H-NMR ($CDCl_3$) δ: 2.94 (3H, d, J = 1.4 Hz, NH-CH_3), 5.14 (2H, b, NH_2), 7.28 (1H, m, CONH), 7.44 (1H, s, C_5-H). IR ν_{max}^{KBr} cm^{-1}: 3330, 3260 (NH_2), 3200 (CONH), 1660 (C=O). MS m/z: 157 (M^+). Anal. Calcd for $C_5H_7N_3OS$: C, 38.21; H, 4.49; N, 26.73. Found: C, 38.12; H, 4.12; N, 26.80.

The second chloroform eluate was collected and the solvent was distilled off. The residue was crystallized from ethanol to give **9a**: Yield 250 mg (31%), mp 160-162°C. ^{1}H-NMR ($CDCl_3$) δ: 2.87 (3H, d, J = 1.4 Hz, $NHCH_3$), 8.48 (1H, s, C_5-H), 8.82 (1H, br, -NH-CO-), 9.37 (1H, s, CHO), 10.80 (1H, br, NHCHO). IR ν_{max}^{KBr} cm^{-1}: 3290 (NH), 3240 (NHCHO), 1680 (C=O). MS m/z: 185 (M^+). Anal. Calcd for $C_6H_7N_3O_2S$: C, 38.91; H, 3.81; N, 22.69. Found: C, 39.22; H, 3.92; N, 22.79.

4-Amino-3-[N-(propyl)carbamoyl]isothiazole (8b) and 4-Formamido-3-[N-(propyl)carbamoyl]isothiazole (9b) A mixture of **6** (1 g, 4.3 mmol) and excess propylamine was heated in a sealed tube at 100°C for 16 h. The resulting mixture was worked up by the same manner as described above for **8a** and **9a**. **8b**: Yield 340 mg (42%), mp 77-79°C (from ethanol). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J = 6 Hz, N-$CH_2CH_2CH_3$), 1.62 (2H, m, N-$CH_2CH_2CH_3$), 3.34 (2H, m, N-$CH_2CH_2CH_3$), 5.12 (2H, br, NH_2), 7.27 (1H, br, CONH), 7.44 (1H, s, C_5-H). IR ν_{max}^{KBr} cm^{-1}: 3290 (NH), 3240 (NHCHO), 1680 (C=O). MS m/z: 185 (M^+). Anal. Calcd for $C_7H_{11}N_3OS$: C, 45.41; H, 5.95; N, 22.70. Found: C, 45.32; H, 5.85; N, 22.52. **9b**: Yield 250 mg (27%), mp 168-169°C (from ethanol). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 6 Hz, N-$CH_2CH_2CH_3$), 1.54 (2H, m, NHCH$_2$$CH_2CH_3$), 3.27 (2H, m, N-$CH_2CH_2CH_3$), 5.07 (1H, b, NH), 7.20 (1H, b, CONH), 7.44 (1H, s, C_5-H). IR ν_{max}^{KBr} cm^{-1}: 3260 (CONH), 3200 (NHCHO), 1670 (C=O). MS m/z: 213 (M^+). Anal. Calcd for $C_8H_{11}N_3O_2S$: C, 45.07; H, 5.16; N, 19.72. Found: C, 45.01; H, 5.02; N, 19.59.

4-Amino-3-(N-phenyl)carbamoylisothiazole (10) A mixture of **6** (230 mg, 1 mmol) and benzylamine (30 ml) was heated in a sealed tube at 90°C for 3 h. The reaction mixture was neutralized with 10% aqueous HCl and extracted with chloroform. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography on silica gel. The chloroform eluate was collected and the solvent was distilled off to give a crystalline residue, whih was recrystallized from ethanol to furnish colorless prisms of mp 108-110°C. Yield 140 mg (60%). ^{1}H-NMR ($CDCl_3$) δ: 5.10 (2H, b, NH_2), 7.00-7.80 (5H, m, Ar), 7.50 (1H, s, C_5-H), 9.10 (1H, b, NH). IR ν_{max}^{KBr} cm^{-1}: 3420, 3330, 3270 (NH_2, NH), 1660 (C=O). MS m/z: 219 (M^+). Anal. Calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 55.02; H, 4.10; N, 18.92.

4-(3',3'-Dicyanoethenyl)amino-3-(N-phenyl)carbamoylisothiazole (11) A mixture of **6** (2.6 g, 11 mmol), malononitrile (2.6 g, 40 mmol), and a catalytic amount of triethylamine in 80 ml of ethanol was refluxed for 1 h. The resulting crystals were collected and recrystallized from acetone. Yield 2.61 g (78%), mp 263-264°C. ^{1}H-NMR ($CDCl_3$) δ: 7.10-8.00 (5H, m, Ar), 8.80 (1H, d, J = 15 Hz, -C=CH-NH), 9.20 (1H, s, C_5-H), 10.80 (1H, b, NHCO), 11.10 (1H, d, J = 15 Hz, -C=CH-NH). IR ν_{max}^{KBr} cm^{-1}: 1620 (C=O), 2200 (CN). MS m/z: 295 (M^+). Anal. Calcd for $C_{14}H_9N_5OS$: C, 56.94; H, 3.07; N, 23.71. Found: C, 57.13; H, 2.94; N, 23.91.

Synthesis of 10 by the Hydrolysis of 11 A mixture of **11** (295 mg, 1 mmol), conc. aqueous HCl (5 ml), and ethanol (5 ml) was refluxed for 1.5 h. After cooling, the reaction mixture was neutralized with 5% aqueous NaOH. The resulting crystals were collected by filtration and recrystallized from hexane-benzene (7:3). Yield 171 mg (78%). This compound was identical with that obtained by the reaction of **6** with benzylamine.

4-(N-Methyl)amino-3-methylcarbamoylisothiazole (14a) A mixture of 4,6-dimethyl-5,7-dioxo-4,5,6,7-tetrahydroisothiazolo[4,3-d]pyrimidine (**13a**)[9] (394 mg, 2 mmol) and 40% aqueous methylamine (20 ml) was heated in a sealed stainless steel tube at 100°C for 6 h. The excess aqueous methylamine was distilled off.

The residue was chromatographed on silica gel by eluting with a mixture of chloroform-methanol (25:1) to give **14a**. Yield 200 mg (58%), mp 41-42°C (from ethanol). ^{1}H-NMR ($CDCl_3$) δ: 2.85 (3H, d, J = 1.4 Hz, $NHCH_3$), 2.95 (3H, d, J = 1.4 Hz, $NHCH_3$), 6.38 (1H, b, $NHCH_3$), 7.54 (1H, s, C_5-H), 8.40 (1H, b, NHCO). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1650 (C=O). MS m/z: 171 (M^+). Anal. Calcd for $C_6H_9N_3OS$: C, 42.09; H, 5.30; N, 24.54. Found: C, 42.35; H, 5.16; N, 24.34.

3-Methylcarbamoyl-4-(N-phenyl)aminoisothiazole (14b) A mixture of 6-methyl-4-phenyl-5,7-dioxo-4,5,6,7-tetrahydroisothiazolo[4,3-d]pyrimidine (**13b**)[9] (518 mg, 2 mmol) and 40% aqueous methylamine (20 ml) was heated in a sealed stainless steel tube at 100°C for 6 h and treated in the same manner as described for **14a**. Yield 400 mg (86%), mp 232-236°C (from methanol). ^{1}H-NMR ($CDCl_3$) δ: 3.00 (3H, d, J=1.4 Hz, CH_3NHCO), 7.20 (5H, m, aromatic protons), 8.00 (1H, s, C_5-H), 9.20 (1H, b, NH). IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 1655 (C=O). MS m/z : 233 (M^+). Anal. Calcd for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.63; H, 4.68; N, 18.09.

Synthesis of 14a by the Reduction of 17 Raney nickel catalyst (W-2)(2 g) was added to a solution of 3-methylcarbamoyl-4-(N-methyl-N'-phenylhydrazino)-isothiazole (**17**)[11] (1 g, 3.8 mmol) in methanol (50 ml). The mixture was shaken in an autoclave at 100°C for 18 h under hydrogen gas (120 kg/cm^2). The catalyst was removed by filtration. The filtrate was evaporated to give an oily residue, which was purified by column chromatography on silica gel with chloroform to give **14a**. Yield 570 mg (87%), mp 41-42°C (from ethanol). This compound was identical with that obtained by the reaction of **13a** with 40% aqueous methylamine.

References and Notes

1) Present address: Uji Pharmaceutical Company, Research Institute, Uji 612, Japan.
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3) D. J. Brown, "The Pyrimidines", Interscience Publishers, New York, 1962; D. J. Brown, "Fused Pyrimidines", Part I and Part II, Interscience Publishers, New York, 1967.
4) T. Ueda, N. Oda and I. Ito, Chem. Pharm. Bull., **28**, 2144 (1980).
5) T. Ueda, Y. Shibata, J. Sakakibara, M. Inoue and T. Ishida, Chem. Pharm. Bull., **30**, 3424 (1982).
6) T. Ueda, S. Kawai and J. Sakakibara, Chem. Pharm. Bull., **35**, 398 (1987).
7) T. Ueda, Y. Shibata and J. Sakakibara, Chem. Pharm. Bull., **33**, 3065 (1985).
8) S. Senda, K. Hirota and K. Banno, J. Med. Chem., **15**, 471 (1972); S. Senda, A. Suzui, M. Honda H. Fujimura, Chem. Pharm. Bull., **6**, 482 (1958).
9) Similar ring closure by means of thionyl chloride was previously reported by us: T. Ueda, H. Yoshida and J. Sakakibara, Synthesis, 695 (1985).
10) Among the solvents such as benzene, toluene, xylene, bromobenzene and mesitylene, bromobenzene was the most suitable solvent in this reaction.
11) T. Ueda, Y. Shibata and J. Sakakibara, J. Heterocycl. Chem., **23**, 1773 (1986).