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Dimroth-Type Ring Transformation of 1,4,6-Trisubstituted-2(1*H*)-Pyrimidinethiones with Ammonia and Primary Alkyl Amines

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1,4,6-Trisubstituted 2(1*H*)-pyrimidinethiones (Ia—k) underwent Dimroth-type ring transformation with ammonia and primary alkyl amines in the presence of silver perchlorate to afford 2-(*N*-substituted)aminopyrimidines (IIa, c, d, f, j, k) and pyrimidinium perchlorates (IIIa—c, e—j), respectively.

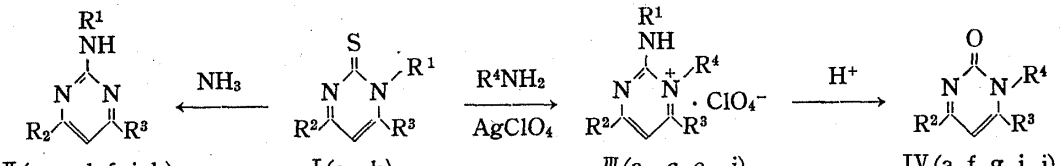
Furthermore, pyrimidinium perchlorates (III) were converted into 2(1*H*)-pyrimidinones (IV) in high yields by hydrolysis with concentrated hydrochloric acid.

Keywords——Dimroth-type ring transformation reaction; ammonia; primary alkyl amines; 2-(*N*-substituted)aminopyrimidines; silver perchlorate; 2-(*N*-substituted)aminopyrimidinium perchlorates; hydrolysis; concentrated hydrochloric acid

In the preceding paper[1], we reported that 1,4,6-trisubstituted 2(1*H*)-pyrimidinethiones underwent Dimroth-type ring transformation with hydroxylamine as a nucleophile to give a new type of 2-(*N*-substituted)aminopyrimidine 1-oxides. As a part of an extensive study on nucleophilic reactions and ring transformation reactions, we investigated the reaction of 2(1*H*)-pyrimidinethiones with ammonia and primary amines.

Results and Discussion

When 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinethione (Ia) was heated with ammonia for 20 h at 85°C in a sealed tube, Dimroth-type ring transformation occurred to give 2-anilino-4,6-dimethylpyrimidine (IIa) in 36% yield. This compound IIa was found to be identical with an authentic sample prepared from 2-chloro-4,6-dimethylpyrimidine and aniline[2]. The similar ring transformation of other 2(1*H*)-pyrimidinethiones (Ic, d, f, j, k) was examined, and the results are summarized in Table I.



	R^1	R^2	R^3	R^4
a	C_6H_5–	CH_3–	CH_3–	CH_3–
b	C_6H_5–	CH_3–	CH_3–	CH_3CH_2–
c	*p*-$CH_3C_6H_4$–	CH_3–	CH_3–	CH_3–
d	*p*-$CH_3OC_6H_4$–	CH_3–	CH_3–	—
e	*o*-$CH_3OC_5H_4$–	CH_3–	CH_3–	CH_3–
f	C_6H_5–	CH_3–	C_6H_5–	CH_3–
g	C_6H_5–	CH_3–	C_6H_5–	CH_3CH_2–
h	C_6H_5–	CH_3–	*p*-$CH_3C_6H_4$–	CH_3–
i	C_6H_5–	CH_3–	*p*-$CH_3OC_6H_4$–	CH_3–
j	C_6H_5–	CH_3–	*p*-ClC_6H_4–	CH_3–
k	CH_3–	CH_3–	C_6H_5–	—

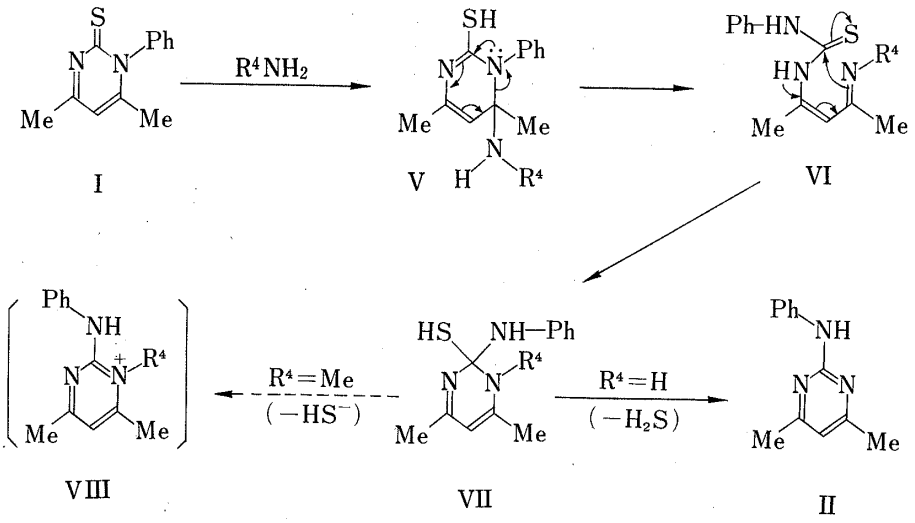
Chart 1

Table I. 2-(*N*-substituted)aminopyrimidines (IIc, d, f, j, k)

Compound No.	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IIc	39	142—153	$C_{13}H_{15}N_3$	73.20	7.08	19.70	72.94	7.08	19·75
IId	35	87—89[b]	$C_{13}H_{15}N_3O$	—	—	—	—	—	—
IIf	42	112—113.5	$C_{17}H_{15}N_3$	78.13	5.78	16.07	78.18	5.77	16.13
IIj	35	118—119	$C_{17}H_{14}ClN_3$	69.03	4.77	14.20	69.35	4.74	14.14
IIk	29	152—153 (dec.)	$C_{12}H_{13}N_3$	—	—	—	—	—	—

a) Recrystallized from benzene-hexane mixture.
b) Lit.[2] mp. 88—89°C.

Next, 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinethione (1a) was treated with methylamine as primary amine in a manner similar to that described above, but no simple product could be obtained. Therefore, Ia was treated with methylamine in a sealed tube at room temperature to afford the ring-opened product (VIa) in 53% yield. Ammonia (R^4=H) presumably attacks the C-6 carbon of 2(1*H*)-pyrimidinethione (I), and the resulting V undergoes ring-opening to form the intermediate (VI, R^4=H). By the attack of nitrogen (originated from ammonia) at the thiocarbonyl carbon and subsequent elimination of hydrogen sulfide, stable 2-anilino-4, 6-dimethylpyrimidine (II) can be obtained. The reaction of the compound I with methylamine (R^4=Me) is expected to proceed through the same reaction mechanism. However, only the ring-opened product (VI) is obtained because the intermediate VIII is unstable (Chart 2).



I V VI VIII VII II

Chart 2

Therefore, we tried to isolate the intermediate VIII as a stable salt in the presence of perchlorate ion.

When 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinethione (Ia) reacted with methylamine in the presence of barium perchlorate or sodium perchrolate, a product (mp 193—195°C) formulated as $C_{13}H_{16}ClN_3O_4$ was obtained. The proton magnetic resonance (PMR) spectrum displayed two methyl protons at δ 2.42 and δ 2.66, and one methine proton at δ 7.01 ppm. Further, a new signal was seen at δ 3.88 ppm due to *N*-methyl protons. From these data, the product was determined to be 2-anilino-1,4,6-trimethylpyrimidinium perchlorate (IIIa). However, the yield of compound IIIa was only 5%. It is supposed that the removal

of the resulting hydrogen sulfide by the precipitation as metal sulfide may raise the yield of IIIa. In fact, 2(1*H*)-pyrimidinethione (Ia) was treated with methylamine in the presence of silver perchlorate($AgClO_4$) to afford compound IIIa (48% yield) and a black precipitate. The latter was found to be silver sulfide (Ag_2S) by powder X-ray diffraction analysis. Compound IIIa was obtained by the reaction of the ring-opened product VIa and $AgClO_4$ in methanol. The ring transformation of other 2(1*H*)-pyrimidinethiones (Ib,c,e—j) with primary amines in the presence of $AgClO_4$ was examined and the results are summarized in Table II.

Table II. Pyrimidinium Perchlorates (IIIa—c, e—j)

Compound No.	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IIIa	48	193—195	$C_{13}H_{16}ClN_3O_4$	49.76	5.14	13.39	49.75	5.11	13.46
IIIb	25	201.5—202.5	$C_{14}H_{18}ClN_3O_4$	51.30	5.53	12.82	51.18	5.51	12.70
IIIc	46	218.5—219.5	$C_{14}H_{18}ClN_3O_4$	51.30	5.53	12.82	51.51	5.51	12.89
IIIe	21	207—208	$C_{14}H_{18}ClN_3O_5$	48.91	5.27	12.22	49.09	5.24	12.29
IIIf	62	253—255	$C_{18}H_{18}ClN_3O_4$	57.52	4.82	11.18	57.61	4.87	11.05
IIIg	40	225—227	$C_{19}H_{20}ClN_3O_4$	58.53	5.17	10.77	58.38	5.15	10.71
IIIh	59	203.5—205	$C_{19}H_{20}ClN_3O_4$	58.53	5.17	10.77	58.36	5.15	10.76
IIIi	72	219.5—220.5	$C_{19}H_{20}ClN_3O_5$	56.23	4.96	10.35	56.42	4.95	10.44
IIIj	39	216—216.5	$C_{18}H_{17}Cl_2N_3O_4$	56.69	4.17	10.24	52.44	4.13	10.08

a) Recrystallized from ethanol.

In the case of aromatic amines such as *p*-toluidine, pyrimidinium perchlorates could not be obtained. This could be attributed to lower nucleophilicity and to steric hindrance of aromatic amines.

Since Kröger[3] reported that 4-amino-1-methyl-2-methylaminopyrimidinium iodide was easily hydrolyzed to 1-methylcytosine, we attempted to convert pyrimidinium perchlorates (III) into 2(1*H*)-pyrimidinones (IV). Pyrimidinium perchlorate IIIa was hydrolyzed with concentrated hydrochloric acid at 160°C to afford 1,4,6-trimethyl-2(1*H*)-pyrimidinone (IVa), which was identical with an authentic sample prepared from acetylacetone and *N*-methylurea[4]. The acid hydrolysis of other 2-(*N*-substituted) aminopyrimidinium perchlorates (IIIb,f,g—j) was carried out and the results are shown in Table III.

Table III. 2(1*H*)-Pyrimidinones (IVf, g, i, j)

Compound No.	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IVf	75	185—185.5	$C_{12}H_{12}N_2O$	71.97	6.04	13.99	71.94	6.01	13.88
IVg	87	147—147.5	$C_{13}H_{14}N_2O$	72.87	6.58	13.07	72.91	6.60	13.11
IVi	39	140.5—141	$C_{13}H_{14}N_2O_2$	67.80	6.12	12.16	67.89	6.10	12.02
IVj	68	121.5—122.5	$C_{12}H_{11}ClN_2O$	61.41	4.72	11.93	61.60	4.69	11.98

a) Recrystallized from benzene–hexane mixture.

It is concluded that 1,4,6-trisubstituted 2(1*H*)-pyrimidinethiones (I) undergo Dimroth-type ring transformation with ammonia and primary alkyl amines in the presence of $AgClO_4$ to give 2-(*N*-substituted) aminopyrimidines (II) and pyrimidinium perchlorates (III), respectively. Moreover, pyrimidinium perchlorates are converted into 2(1*H*)-pyrimidinones (IV) in high yields by acid hydrolysis.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were obtained on a Jasco ITA-1 infrared spectrometer. PMR spectra were recorded on a Hitachi-24 spectrometer with tetramethylsilane as an internal standard. 2(1*H*)-Pyrimidinethiones (I) were prepared by the literature method.[5,6]

General Procedure for the Reaction of 2(1*H*)-Pyrimidinethiones (Ia, c, d, f, j, k) with Ammonia——2(1*H*)-Pyrimidinethione (I, 2 mmol) was added to a solution of absolute ethanol (10 ml) saturated with ammonia. The mixture was heated at 85°C for 20 h in a sealed tube. The reaction mixture was poured into water, and extracted with dichloromethane. Then the extract was dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. The crude products were chromatographed on silica gel with benzene–ethyl acetate (5: 1) mixture.

4,6-Dimethyl-2-(*p*-toluidino)pyrimidine (IIc)——IR ν_{max}^{KBr} cm^{-1}: 3230, 1605, 1580; PMR ($CDCl_3$) δ: 2.31 (3H, s), 2.34 (6H, s), 6.49 (1H, s), 7.0—7.7 (4H, m).

2-Anilino-4-methyl-6-phenylpyrimidine (IIf)——IR ν_{max}^{KBr} cm^{-1}: 3370, 1610, 1600, 1580; PMR ($CDCl_3$) δ: 2.45 (3H, s), 7.01 (1H, s), 7.1—8.2 (11H, m).

2-Anilino-6-(*p*-chlorophenyl)-4-methylpyrimidine (IIj)——IR ν_{max}^{KBr} cm^{-1}: 3360, 1590, 1520; PMR ($CDCl_3$) δ: 2.45 (3H, s), 7.0—8.2 (10H, m).

4-Methyl-2-methylamino-6-phenylpyrimidine (IIk)——IR ν_{max}^{KBr} cm^{-1}: 3280, 1630, 1600; PMR ($CDCl_3$) δ: 2.33 (3H, s), 3.02 (3H, d, J=5.0 Hz), 6.83 (1H, s), 7.2—8.2 (5H, m).

Reaction of Ia with Methylamine——A mixture of 2(1*H*)-pyrimidinethione (**Ia**, 2 mmol) and a large excess of methylamine in absolute ethanol (10 ml) was heated at 100°C in a sealed tube for 12 h, but no simple product could be obtained. This mixture was stirred at room temperature for 12 h in a sealed tube. The solvent was removed *in vacuo*, and the crude products were chromatographed on silica gel with benzene–ethyl acetate–methanol (2: 4: 1) mixture to give 2-methylimino-4-(3′-phenylthioureido)-3-pentene. IR ν_{max}^{film} cm^{-1}: 3340, 1625, 1255; PMR ($CDCl_3$) δ: 2.01 (3H, s), 2.04 (3H, d, J=0.7 Hz). 3.37 (3H, s), 5.60 (1H, q, J=0.7 Hz), 7.0—7.3 (5H, m).

General Procedure for the Reaction of 2(1*H*)-Pyrimidinethiones (Ia—c, e—j) with Primary Alkyl Amines—A small excess of silver perchlorate was added to a mixture of 2(1*H*)-pyrimidinethione (I, 3 mmol) and primary alkyl amine (18 mmol, aqueous solution) in methanol (30 ml). The mixture was stirred at room temperature overnight. The black precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The crude products were purified by recrystallization from ethanol.

2-Anilino-1,4,6-trimethylpyrimidinium Perchlorate (IIIa)——IR ν_{max}^{KBr} cm^{-1}: 3360, 1620, 1600, 1560; PMR (DMSO-d_6) δ: 2.42 (3H, s), 2.67 (3H, s), 3.88 (3H, s), 7.01 (1H, s), 7.2—7.6 (5H, m).

2-Anilino-1-ethyl-4,6-dimethylpyrimidinium Perchlorate (IIIb)——IR ν_{max}^{KBr} cm^{-1}: 3320, 1625, 1600, 1560; PMR (DMSO-d_6) δ: 1.48 (3H, t, J=7.0 Hz), 2.39 (3H, s), 2.70 (3H, s), 4.48 (2H, q, J=7.0 Hz), 7.09 (1H, s), 7.2—7.6 (5H, m).

1,4,6-Trimethyl-2-(*p*-toluidino)pyrimidinium Perchlorate (IIIc)——IR ν_{max}^{KBr} cm^{-1}: 3330, 1630, 1600, 1560; PMR (DMSO-d_6) δ: 2.38 (3H, s), 2.42 (3H, s), 2.66 (3H, s), 3.86 (3H, s), 7.03 (1H, s), 7.31 (4H, s).

2-(*o*-Anisidino)-1,4,6-trimethylpyrimidinium Perchlorate (IIIe)——IR ν_{max}^{KBr} cm^{-1}: 3260, 1600, 1580, 1540; PMR (CD_3OD) δ: 2.36 (3H, s), 2.63 (3H, s), 3.84 (3H, s), 4.69 (3H, s), 6.9—7.5 (5H, m).

2-Anilino-1,4-dimethyl-6-phenylpyrimidinium Perchlorate IIIf)——IR ν_{max}^{KBr} cm^{-1}: 3305, 1620, 1600, 1570; PMR (CD_3OD) δ: 2.51 (3H, s), 3.80 (3H, s), 6.88 (1H, s), 7.2—7.7 (10H, m).

2-Anilino-1-ethyl-4-methyl-6-phenylpyrimidinium Perchlorate (IIIg)——IR ν_{max}^{KBr} cm^{-1}: 3310, 1635, 1600, 1560; PMR (DMSO-d_6) δ: 1.30 (3H, t, J=7.0 Hz), 2.48 (3H, s), 4.28 (2H, q, J=7.0 Hz), 7.09 (1H, s), 7.3—7.8 (10H, m).

2-Anilino-1,4-dimethyl-6-(*p*-tolyl)pyrimidinium Perchlorate (IIIh)——IR ν_{max}^{KBr} cm^{-1}: 3280, 1620, 1560; PMR (CD_3OD) δ: 2.49 (3H, s), 2.55 (3H, s), 4.80 (3H, s), 6.90 (1H, s), 7.3—7.7 (9H, m).

2-Anilino-6-(*p*-methoxyphenyl)-1,4-dimethylpyrimidinium Perchlorate (IIIi)——IR ν_{max}^{KBr} cm^{-1}: 3285, 1620, 1605, 1560; PMR (DMSO-d_6) δ: 2.43 (3H, s), 3.72 (3H, s), 3.86 (3H, s), 6.9—7.7 (10H, m).

2-Anilino-6-(*p*-chlorophenyl)-1,4-dimethypyrimidinium Perchlorate (IIIj)——IR ν_{max}^{KBr} cm^{-1}: 3280, 1625, 1600, 1560; PMR (DMSO-d_6) δ: 2.44 (3H, s), 3.69 (3H, s), 6.83 (1H, s), 7.3—7.7 (9H, m).

Reaction of 2(1*H*)-Pyrimidinethione (Ia) with Methylamine in the Presence of Barium Perchlorate or Sodium Perchlorate——A mixture of 2(1*H*)-pyrimidinethione (**Ia**, 3 mmol), methylamine (18 mmol, 40% aqueous solution) and barium perchlorate (3 mmol) or sodium perchlorate (6 mmol) in methanol (30 ml) was stirred at room temperature for 3 days. The solution was concentrated under reduced pressure. The residue was purified by recrystallization from ethanol to give the product IIIa (yield 5%).

Reaction of Compound VIa with Silver Perchlorate——A small excess of silver perchlorate was added to a solution of 2-methylimino-4-(3′-phenylthioureido)-3-pentene (VIa, 0.66 mmol) in methanol (5 ml). The mixture was stirred at room temperature overnight. The reac ion mixture was treated according to the general procedure for the reaction of 2(1*H*)-pyrimidinethiones with primary alkyl amines to give IIIa (48% yield).

Acid Hydrolysis of Pyrimidinium Perchlorates (IIIa, f, g, i, j) with Concentrated Hydrochloric Acid——A mixture of pyrimidinium perchlorate (III, 2 mmol) and concentrated hydrochloric acid (10 ml) was heated

at 160°C in a sealed tube for 1 h. The reaction mixture was neutralized with aqueous sodium hydroxide, and extracted with dichloromethane, then the extract was dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo*, and the crude products were chromatographed on silica gel with chloroform–acetone–ethanol (100: 20: 4) mixture.

1,4-Dimethyl-6-phenyl-2(1*H*)-pyrimidinone (IVf)——IR ν_{max}^{KBr} cm^{-1}: 1645, 1600; PMR ($CDCl_3$) δ: 2.39 (3H, s), 3.38 (3H, s), 6.15 (1H, s), 7.1—7.8 (5H, m).

1-Ethyl-4-methyl-6-phenyl-2(1*H*)-pyrimidinone (IVg)——IR ν_{max}^{KBr} cm^{-1}: 1640, 1600; PMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.0 Hz), 2.37 (3H, s), 3.91 (2H, q, J=7.0 Hz), 6.09 (1H, s), 7.1—7.7 (5H, m).

6-(*p*-Methoxyphenyl)-1,4-dimethyl-2(1*H*)-pyrimidinone (IVi)——IR ν_{max}^{KBr} cm^{-1}: 1645, 1600; PMR ($CDCl_3$) δ: 2.34 (3H, s), 3.39 (3H, s), 4.82 (3H, s), 6.12 (1H, s), 6.8—7.4 (4H, m).

6-(*p*-Chlorophenyl)-1,4-dimethyl-2(1*H*)-pyrimidinone (IVj)——IR ν_{max}^{KBr} cm^{-1}: 1690, 1595; PMR ($CDCl_3$) δ: 2.39 (3H, s), 3.37 (3H, s), 6.18 (1H, s), 7.1—7.9 (4H, m).

References and Notes

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