Chemistry of Heterocyclic Compounds, Vol. 32, No. 5, 1996

REACTIONS OF ISOMERIC 6-METHYL-2-METHYLTHIO-4-CYANOMETHOXYPYRIMIDINE AND 6-METHYL-2-METHYLTHIO-3-CYANOMETHYLPYRIMIDINONE-4 WITH N-NUCLEOPHILES

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It was found that 6-methyl-2-methylthio-4-cyanomethoxypyrimidine (O-isomer) reacted via the cyano group with ammonia and hydroxylamine to give an amidine and an amidoxime respectively. The O-isomer did not react with either primary or secondary amines under similar conditions, but nucleophilic substitution at position 2 of the O-isomer was effected by converting the 2-methylthio group into a 2-methylsulfonyl. 6-Methyl-2-methylthio-3-cyanomethylpyrimidinone-4 (N_3-isomer) formed imidazo[1,2-a]pyrimidinones-5 with ammonia and primary amines, 2-amino-6-methyl-3-cyanomethylpyrimidinones-4 with secondary amines and either an amidoxime or an imidazo[1,2-a]-pyrimidinone-5 with hydroxylamine, depending on the reaction temperature.

In a previous communication [1] we reported the synthesis of two isomeric pyrimidinyl acetonitrile compounds, specifically the N_3- (I) and O-isomers (II), which involved the selective alkylation of 4-hydroxy-6-methyl-2-methylthiopyrimidine using chloroacetonitrile. The fact that compounds I and II have two electrophilic reaction centers (the cyano group and position 2 of the pyrimidine ring with its differing arrangement of surrounding radicals), shows them to be of interest in terms of their chemical behavior.

In this work we have examined the reaction of nitriles I and II with N-nucleophiles, specifically ammonia, hydroxylamine, and primary and secondary amines, and identified the differences caused by the structure of the isomers in equivalent reactions. At the same time, we have synthesized new pyrimidine derivatives with potential value as biologically active substances.

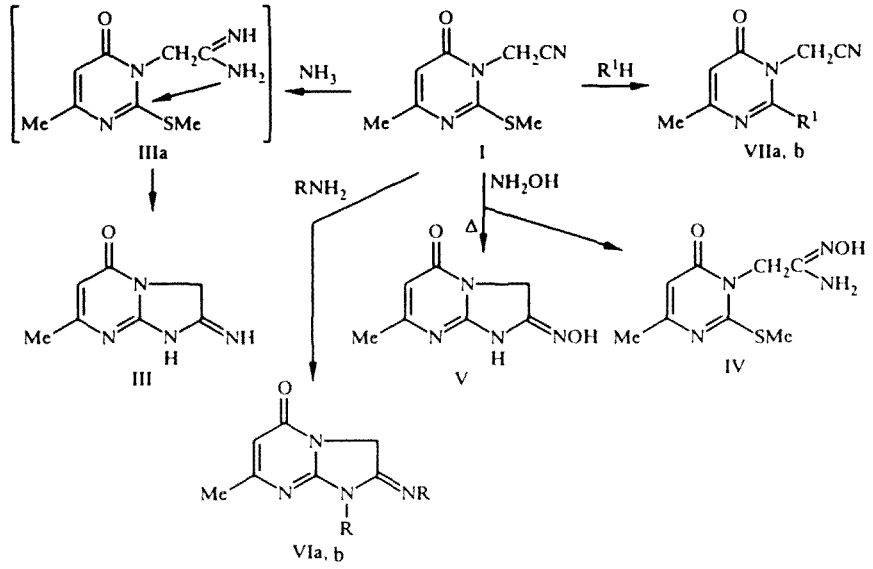
The most common method of synthesizing amidines and amidoximes is based on the addition of ammonia, amines and hydroxylamine to the cyano group [2]. We reacted nitriles I and II with ammonia in methanol. In the case of O-isomer II amidine VIII was isolated after stirring for 3 h at room temperature. With the N_3-isomer the analogous reaction proceeded beyond the stage at which amidine III was formed. The fact that the acetic acid hydrazides (5-alkyl-3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl) related to amidine III have a tendency towards intramolecular nucleophilic attack at position 2 of the pyrimidine ring [3] suggests that the amino group in amidine IIIa formed at the first stage attacks position 2 of the pyrimidine ring. This results in intramolecular nucleophilic substitution, yielding methylmercaptan and imidazo[1,2-a]pyrimidinone-5 III.

After heating for 2 h with hydroxylamine in methanol, O-nitrile II was converted into amidoxime IX. The nature of the reaction between N_3-nitrile I and hydroxylamine was dependent on temperature. At room temperature the reaction ended when amidoxime IV was afforded. When the reaction mixture was boiled in methanol, the amidoxime IV formed at the first stage was cyclized into imidazo[1,2-a]pyrimidinone-5 V due to intramolecular nucleophilic substitution similar to that in the reaction between N_3-isomer I and ammonia.

Vilnius University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 703-707, May, 1996. Original article submitted November 3, 1995.

0009-3122/96/3205-0605$15.00

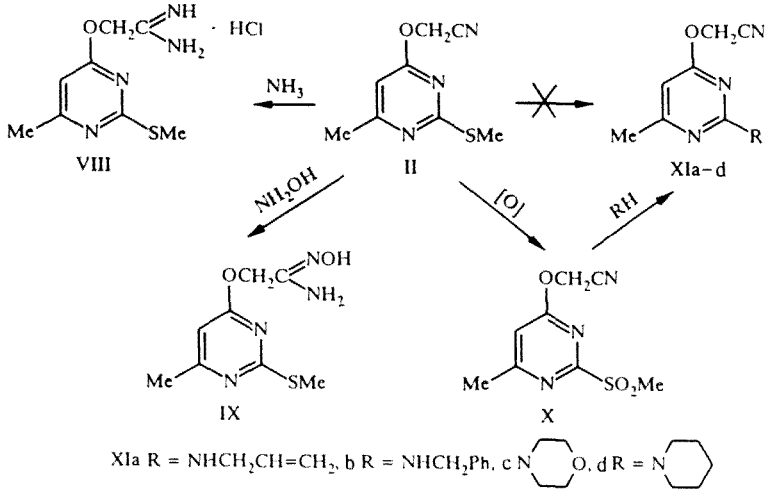
Scheme 1



VIa R = $CH_2CH{=}CH_2$, b R = CH_2Ph; VIIa R^1 = N⟨O⟩, b N⟨ ⟩

O-Nitrile II was unaffected by boiling with primary amines (allylamine, benzylamine) or secondary amines (piperidine, morpholine). With these amines, nucleophilic substitution at position 2 of the pyrimidine ring was accomplished by using the O-nitrile II 2-methylsulfonyl derivative (X).

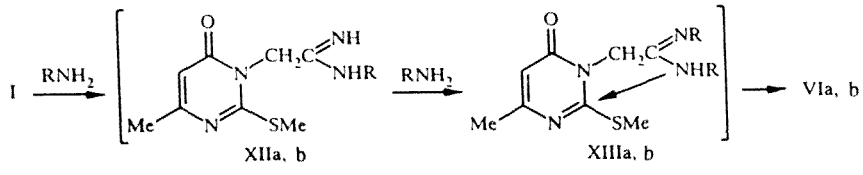
Scheme 2



XIa R = $NHCH_2CH{=}CH_2$, b R = $NHCH_2Ph$, c N⟨O⟩, d R = N⟨ ⟩

A different behavior pattern was displayed by N_3-nitrile I in its reactions with amines. When heated at 110-190°C with excess primary amine, it afforded the imidazo[1,2-a]pyrimidines-5 VIa and VIb. The likely mechanism in this case is the formation of N-monosubstituted amidine XII, its conversion to the N_1,N_2-disubstituted amidine XIII (typical of monosubstituted amidines [4, 5]) and the cyclization of XIII.

Scheme 3



Secondary amines did not react with the cyano group under similar conditions. Instead they replaced the methylthio group in N_3-nitrile I, giving 2-amino derivatives VIIa and VIIb.

TABLE 1. Elemental Analysis Data for Compounds III-XI

Compound	Empirical formula	Found, % / Calculated, %		
		C	H	N
III	$C_7H_8N_4O$	51,35 / 51,24	4,88 / 4,91	33,96 / 34,13
IV	$C_8H_{12}N_4O_2S$	42,00 / 42,09	5,32 / 5,30	24,43 / 24,54
V	$C_7H_8N_4O_2$	46,28 / 46,67	4,51 / 4,48	31,24 / 31,10
VIa	$C_{13}H_{16}N_4O$	63,82 / 63,92	6,71 / 6,60	22,91 / 22,93
VIb	$C_{21}H_{20}N_4O$	73,52 / 73,23	6,20 / 5,85	16,24 / 16,27
VIIa	$C_{11}H_{14}N_4O_2$	56,08 / 56,40	6,29 / 6,02	23,79 / 23,92
VIIb	$C_{12}H_{16}N_4O$	62,46 / 62,05	6,94 / 6,93	24,22 / 24,12
VIII	$C_8H_{12}N_4OS \cdot HCl$	38,45 / 38,63	5,18 / 5,27	22,45 / 22,52
IX	$C_8H_{12}N_4O_2S$	42,41 / 42,09	5,49 / 5,30	24,17 / 24,54
X	$C_8H_9N_3O_3S$	42,01 / 42,28	4,07 / 3,99	18,85 / 18,49
XIa	$C_{10}H_{12}N_4O$	58,86 / 58,81	5,78 / 5,92	27,44 / 27,43
XIb	$C_{14}H_{14}N_4O$	66,31 / 66,13	5,66 / 5,55	22,17 / 22,03
XIc	$C_{11}H_{14}N_4O_2$	56,28 / 56,40	6,00 / 6,02	24,17 / 23,92
XId	$C_{12}H_{16}N_4O$	61,97 / 62,05	6,91 / 6,94	24,37 / 24,12

The typical nitrile I SCH_3 proton signal was not present in the PMR spectra of imidazo[1,2-a]pyrimidinones-5 III, V, VIa or VIb. At the same time the following characteristic resonance frequences were detected: two NH protons at 8.29-8.55 ppm (compound III), NH and OH protons at 10.35 and 11.0 ppm respectively (compound V), and exocyclic NCH_2 group protons at 3.93 and 4.39 ppm (compound VIa) and at 4.46 and 4.97 ppm (compound VIb).

The mass spectra of compounds III and V exhibited molecular ion peaks with m/z (I_{rel}, %) of 164 (100) and 180 (100) respectively.

Compounds III and V can exist in several tautomeric forms. The close proximity between the $\nu_{C=O}$ frequency in the IR spectra of compounds III (1672 cm^{-1}) and V (1680 cm^{-1}) and that in the IR spectra of compounds VIa (1680 cm^{-1}) and VIb (1676 cm^{-1}) (where position 1 is fixed in the molecules), together with the similarity of their UV spectra, suggests that compounds III and V exist as a tautomer in which the mobile hydrogen atom is located at the imidazole ring nitrogen atom.

EXPERIMENTAL

Reaction course and compound purity were monitored using Silufol UV-254 plates. PMR spectra were recorded on a Tesla BS-587 A (80 MHz), internal standard HMDS. UV spectra were taken on a Specord UV-vis, IR spectra on a Specord 80 in Vaseline oil suspension and mass spectra on a Kratos MS-50 (70 eV) with direct sample feed into the ion source.

Elemental analysis data were in line with calculated values.

Compounds I and II were synthesized using the method outlined in work [1].

2,3-Dihydro-2-imino-7-methyl-1H-imidazo[1,2-a]pyrimidinone-5 (III, $C_7H_8N_4O$) and (6-Methyl-2-methylthio-4-pyrimidinyloxy)acetamidine Hydrochloride (VIII, $C_8H_{12}N_4OS \cdot HCl$). When 1.95 g (10 mmoles) of compound I or II had been added to a methanol solution of sodium methoxide prepared from 0.046 g sodium (2 mmoles) and 15 ml methanol, the mixture was stirred for 1 h at room temp. After addition of 0.59 g (11 mmoles) ammonium chloride, the mixture was stirred for a further 3 h at the same temperature. Then the precipitate was filtered off, washed with ether and crystallized.

Yield of compound III 73%, mp 308-310°C (from water). UV spectrum (in water), λ_{max} (log ε): 246 (4.05), 296 nm (3.88). IR spectrum: (1672) (C=O), 3248 cm^{-1} (NH). PMR spectrum (in DMSO-D_6): 2.12 (3H, s, CH_3), 4.64 (2H, s, NCH_2), 5.76 (1H, s, CH), 8.29-8.55 ppm (2H, m, NH).

Yield of compound VIII 77%, mp 179-180°C (from 2:1 isopropanol–ethyl acetate mixt.). UV spectrum (in water), λ_{max} (log ε): 252 nm (4.20). PMR spectrum (in DMSO-D_6): 2.36 (3H, s, CH_3), 2.48 (3H, s, SCH_3), 5.19 (2H, s, OCH_2), 6.63 ppm (1H, s, CH).

3,4-Dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetamidoxime (IV, $C_8H_{12}N_4O_2S$), 2,3-Dihydro-2-hydroxyimino-7-methyl-1H-imidazo[1,2-a]pyrimidinone-5 (V, $C_7H_8N_4O_2$) and (6-Methyl-2-methylthio-4-pyrimidinyloxy)-acetamidoxime (IX, $C_8H_{12}N_4O_2S$). When 0.7 g (10 mmoles) hydroxylamine hydrochloride had been added to a methanol solution of sodium methoxide prepared from 0.23 g (10 mmoles) sodium and 15 ml methanol, the mixture was boiled for 1 h. Precipitated NaCl was filtered off and 1.95 g (10 mmoles) of compound I or II was added to the filtrate, cooled to 20°C. When the reaction mixture had been stirred at the same temperature (boiled in the case of V and IX) for 2 h, the precipitate was filtered off (after cooling for V and IX), washed with a 1:1 ether–methanol mixture and crystallized.

Yield of compound IV 74%, mp 185-186°C (from acetonitrile). UV spectrum (in ethanol), λ_{max} (log ε): 223, 240, 293 (3.75) nm. PMR spectrum (in DMSO-D_6): 2.16 (3H, s, CH_3), 2.48 (3H, s, SCH_3), 4.58 (2H, s, NCH_2), 5.53 (2H, s, NH_2), 6.03 (1H, s, CH), 9.23 ppm (1H, s, OH).

Yield of compound V 45%, mp 189-190°C (from water). UV spectrum (in water), λ_{max} (log ε): 240 (4.02), 290 nm (3.80). IR spectrum: 1680 (C=O), 3368 cm^{-1} (NH, OH). PMR spectrum (in DMSO-D_6): 2.14 (3H, s, CH_3), 4.59 (2H, S, NCH_2), 5.77 (1H, s, CH), 10.35 (1H, s, NH), 11.0 ppm (1H, s, OH).

Yield of compound IX 69%, mp 178-179°C (from ethanol). UV spectrum (in ethanol), λ_{max} (log ε): 251 nm (4.13). PMR spectrum (in DMSO-D_6): 2.24 (3H, s, CH_3), 2.40 (3H, s, SCH_3), 4.61 (2H, s, OCH_2), 5.34 (2H, s, NH_2), 6.43 (1H, s, CH), 9.06 ppm (1H, s, OH).

1-Allyl-2-allylimino-2,3-dihydro-7-methyl-1H-imidazo[1,2-a]-pyrimidinone-5 (VIa, $C_{13}H_{16}N_4O$), 1-Benzyl-2-benzylimino-2,3-dihydro-7-methyl-1H-imidazo[1,2-a]pyrimidinone-5 (VIb, $C_{21}H_{20}N_4O$), (3,4-Dihydro-6-methyl-2-morpholino-4-oxo-3-pyrimidinyl)acetonitrile (VIIa, $C_{11}H_{14}N_4O_2$) and 3,4-Dihydro-6-methyl-4-oxo-2-piperidino-3-pyrimidinyl)-acetonitrile (VIIb, $C_{12}H_{16}N_4O$). A reaction mixture comprising 1.95 g (10 mmoles) of compound I and 24 mmoles allyl- or benzylamine (in case of VIa and VIb) or 12 mmoles morpholine or piperidine (VIIa and VIIb) was heated on an oil bath for 7 h at 120-130°C (VIa), for 1 h at 180-190°C (VIb), for 0.5 h at 130-150°C (VIIa) or for 0.5 h at 110-130°C (VIIb). With compound VIa the reaction mixture was cooled, and the precipitate was filtered off and crystallized. In the case of VIb, VIIa and VIIb the reaction mixture was cooled to 80°C, then isopropanol was added until the precipitate had dissolved. After boiling the solution for 10 min, then cooling, the precipitate was filtered off and crystallized.

Yield of compound VIa 64%, mp 67-68°C (from hexane). UV spectrum (in ethanol), λ_{max} (log ε): 236 (4.08), 292 (3.83). IR spectrum: 1680 cm^{-1} (C=O). PMR spectrum (in $CDCl_3$): 2.22 (3H, s, CH_3), 3.93 (2H, d, J = 6 Hz, NCH_2), 4.39 (2H, d, J = 6 Hz, $=NCH_2$), 4.54 (2H, s, NCH_2), 5.13-5.34 (4H, m, $CH=\underline{CH_2}$), 5.72-6.12 ppm (3H, m, CH).

Yield of compound VIb 65%, mp 152-153°C (from ethanol). UV spectrum (in ethanol), λ_{max} (log ε): 238 (4.25), 293 nm (4.06). IR spectrum: 1676 cm^{-1} (C=O). PMR spectrum (in $CDCl_3$): 2.24 (3H, s, CH_3), 4.46 and 4.51 (4H, 2s, CH_2), 4.97 (2H, s, NCH_2), 5.84 (1H, s, CH), 7.26-7.57 ppm (10H, m, H_{arom}).

Yield of compound VIIa 68%, mp 250-252°C (from isopropanol). UV spectrum (in ethanol), λ_{max} (log ε): 254 (4.22), 307 nm (4.21). IR spectrum: 1672 cm^{-1} (C=O). PMR spectrum (in $CDCl_3$): 2.25 (3H, s, CH_3), 3.41-3.52 (2H, m, NCH_2), 3.83-3.96 (6H, m, NCH_2, $O(CH_2)_2$), 5.87 ppm (1H, s, CH).

Yield of compound VIIb 56%, mp 203-205°C (from isopropanol). UV spectrum (in ethanol), λ_{max} (log ε): 252 (4.32), 306 nm (4.28). IR spectrum: 1670 cm^{-1} (C=O). PMR spectrum (in $CDCl_3$): 1.72 (6H, s, CH_2), 2.24 (3H, s, CH_3), 3.39 and 3.84 (4H, 2s, NCH_2), 4.71 (2H, s, NCH_2), 5.83 ppm (1H, s, CH).

(6-Methyl-2-methylsufonyl-4-pyrimidinyloxy)acetonitrile (X, $C_8H_9N_3O_3S$). Chlorine gas was passed at (−10)-(−5)°C with stirring through a suspension of 1.95 g (10 mmoles) of compound I in 15 ml of 70% methanol until the starting compound precipitate had dissolved. The solution turned green and another precipitate was formed. This was filtered off, washed with a 0.1% $Na_2S_2O_3$ solution and water, dried in a desiccator over Na_2SO_4 and crystallized from ethyl acetate. Yield 1.45 g (64%), mp 90-92°C. PMR spectrum (in $CDCl_3$): 2.50 (3H, s, CH_3), 3.24 (3H, s, SO_2CH_3), 5.03 (2H, s, OCH_2), 6.75 ppm (1H, s, CH).

(2-Amino-substituted 6-Methyl-4-Pyrimidinyloxy)acetonitriles (XIa, $C_{10}H_{12}N_4O$; XIb, $C_{14}H_{14}N_4O$; XIc, $C_{11}H_{14}N_4O_2$; XId, $C_{12}H_{16}N_4O$). A reaction mixture comprising 1.95 g (10 mmoles) of compound II, 11 mmoles of the appropriate amine and 15 ml hexamethyltriamide phosphate was heated on an oil bath for 1 h at 70-90°C, then cooled to room temperature and poured into 100 ml cold water. The precipitate was filtered off, washed with water, dried in air and crystallized.

Yield of compound XIa 59%, mp 95-96°C (from water). UV spectrum (in ethanol), λ_{max} (log ε): 239 (4.29), 285 nm (3.70). PMR spectrum (in $CDCl_3$): 2.30 (3H, s, CH_3), 4.04 (2H, t, J = 4 Hz, $NH\underline{CH_2}$), 4.90 (2H, s, OCH_2), 4.96-5.10 (2H, m, $CH{=}\underline{CH_2}$), 5.30 (1H, m, NH), 5.70 (1H, t, J = 4 Hz, $\underline{CH}{=}CH_2$), 5.96 ppm (1H, s, CH).

Yield of compound XIb 70%, mp 134-135°C (from hexane). UV spectrum (in ethanol), λ_{max} (log ε): 240 (4.37), 285 nm (3.74). PMR spectrum (in $CDCl_3$): 2.26 (3H, s, CH_3), 4.61 (2H, d, J = 5 Hz, $NH\underline{CH_2}$), 4.80 (2H, s, OCH_2), 5.32 (1H, m, NH), 5.96 (1H, s, CH), 7.30 ppm (5H, s, $H_{arom.}$).

Yield of compound XIc 90%, mp 101-102°C (from 2:1 ethanol–water mixture). UV spectrum (in ethanol), λ_{max} (log ε): 246 (4.35), 287 nm (3.64). PMR spectrum (in $CDCl_3$): 2.19 (3H, s, CH_3), 3.60 (8H, s, CH_2), 4.78 (2H, s, OCH_2), 5.80 ppm (1H, s, CH).

Yield of compound XId 60%, mp 67-68°C (from 2:1 ethanol–water mixture). UV spectrum (in ethanol), λ_{max} (log ε): 250 (4.35), 292 nm (3.59). PMR spectrum (in $CDCl_3$): 1.53 (6H, s, CH_2), 2.16 (3H, s, CH_3), 3.45 (4H, s, NCH_2), 4.77 (2H, s, OCH_2), 5.70 ppm (1H, s, CH).

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