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Received January 13, 1993

Synthesis of functionalized pyrimidine-4-thiones and derivatives of pyrido[2,3-*d*]pirimidine-5-one from monoacylketene aminals

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Monoacylketene aminals containing an unsubstituted NH_2 group react as C-nucleophiles with benzoyl isothiocyanate to give the corresponding thioamides which undergo cyclization by sodium methoxide in methanol to afford 6-R-amino-5-acetyl-2-phenyl-3*H*-pyrimidine-4-thiones. A scheme for constructing the pyrido[2,3-*d*]pyrimidine system from keteneaminals is offered. The reaction of 6-R-amino-5-acetyl-2-phenyl-3*H*-pyrimidine-4-thiones with dimethylformamide dimethylacetal leads to 8-R-N-4-methylthio-8*H*-pyrido-[2,3-*d*]pyrimidine-5-ones. Cyclization of 5-acetyl-6-benzoylamino-4-methylthio-2-phenylpyrimidine by sodium methoxide yields N-unsubstituted 4-methylthio-8*H*-pyrido-[2,3-*d*]pyrimidine-5-one.

Key words: monoacylketene aminals; benzoyl isothiocyanate; heterocyclization; pyrimidine-4-thiones; pyrido[2,3-*d*]pyrimidine-5-ones; dimethylformamide dimethylacetal.

Efficient methods for the preparation of functionalized pyrimidine-4-thiones are based on reactions of enaminones or monoacylketene N,S-acetals with acyl isothiocyanates.[1—4] Monoacylketene aminals (MAA) have been more rarely used for synthesizing pyrimidine-4-thiones. It has been reported that 1,1-diamino-3-phenyl-3-oxo-1-propene reacts as a C-nucleophile with benzoyl isothiocyanate to give the respective thioamide, which undergoes cyclization by aqueous ammonia to afford 6-amino-5-benzoyl-2-phenyl-3*H*-pyrimidine-4-thione.[5] Thioamides obtained in a similar way from aroylketene *N,N'*-diethylacetals also undergo thermal cyclization into 5-aroylpyrimidine-4-thiones. However, an attempt to synthesize the respective pyrimidine-4-thiones from *N,N'*-diphenyl-MAA has proved to be unsuccessful.[4]

Recently we suggested a simple synthesis of MAA containing a free NH_2 group from β-diketones and cyanamides.[6] Compounds of this type are convenient reagents for the preparation of functionalized triazoles[7] and for the annelation of the pyrrole ring to derivatives of 1,2,4-triazine or quinoxaline.[8] The present work deals with their use in the syntheses of pyrimidine-4-thiones and condensed pyrimidines.

It was found that thioamides (**2a—g**) obtained from benzoyl isothiocyanate and MAA (**1a—g**) containing a free NH_2 group (regardless of the substituents at the second nitrogen atom) smoothly undergo cyclization by sodium methoxide in methanol at ~20 °C or on refluxing to give thiolates (**3a—g**). Upon acidification with AcOH the latter are transformed in high yields into pyrimidine-4-thiones (**4a—g**) (Scheme 1). It is noteworthy that the cyclization of thioamides **2** proceeds rather quickly (TLC monitoring).

The action of MeI on salts **3** results in methylation at the sulfur atom, which was demonstrated for the preparation of pyrimidine **5** from thiolate **3a**. It should be mentioned that salt **3a** should be transformed into thione **4a** or sulfide **5** immediately after formation in order to avoid the debenzoylation side process.

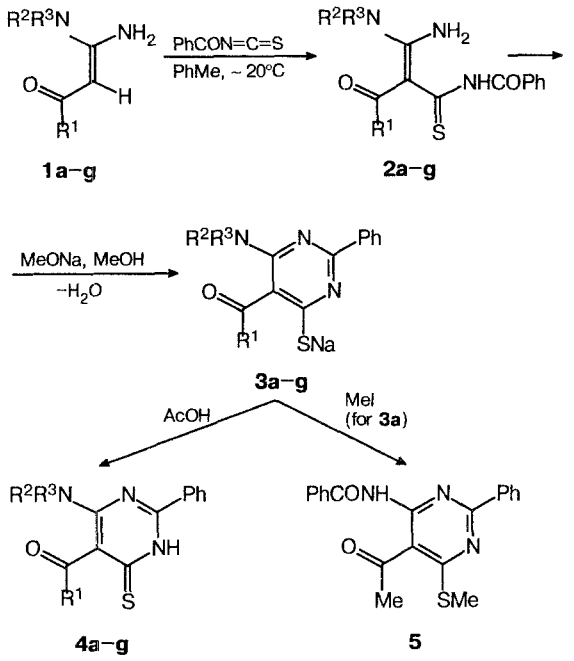
It was also found that 6-morpholinopyrimidine-4-thione (**4e**) undergoes nucleophilic substitution with benzylamine to give 5-acetyl-6-benzylamino-2-phenyl-3*H*-pyrimidine-4-thione (**4h**) in 62 % yield (Scheme 2).

The pyrimidine-4-thiones **4a—h** obtained are yellow crystalline compounds that are easily soluble in DMF and DMSO, moderately soluble in chloroform, acetone, and ethanol, and insoluble in water. The structure of

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1932—1937, November, 1993.

1066-5285/93/4211-1848 $12.50

Scheme 1

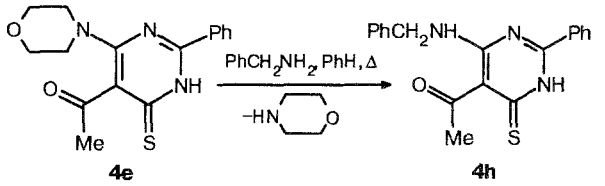


1a–g **2a–g** **3a–g** **4a–g** **5**

a: R^1 = Me, R^2 = H, R^3 = COPh;
b: R^1 = Me, R^2 = H, R^3 = Ph;
c: R^1 = Me, R^2 = H, R^3 = 2-ClC_6H_4;
d: R^1 = Me, R^2 = H, R^3 = 4,6-dimethylpyrimidine-2-yl;
e: R^1 = Me, R^2R^3 = $-(CH_2)_2O(CH_2)_2$;
f: R^1 = Me, R^2R^3 = $-(CH_2)_4-$;
g: R^1 = R^2 = Ph, R^3 = H.

compounds **4a—h** was confirmed by spectral data (mass spectrometry, ^1H and ^{13}C NMR, IR spectroscopy) and by their ability to form water-soluble thiolates **3** upon alkalization (the presence of a S=C–NH— fragment). Compound **5** is a colorless crystalline substance that is easily soluble in chloroform and acetone, moderately soluble in methanol, and insoluble in hexane. Its ^1H spectrum displays two singlets at δ 2.73 and 2.76 corresponding to protons in the MeCO and MeS groups.

Scheme 2



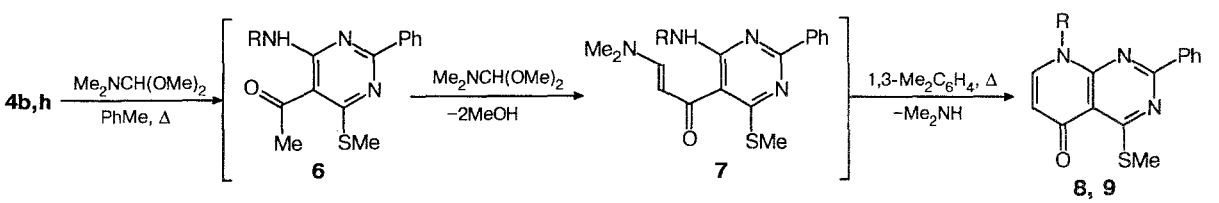
4e **4h**

The presence of vicinal MeCO and NH groups in the molecules of compounds **4a—d,h** and **5** is favorable for the annelation of the second nitrogen-containing ring to the pyrimidine cycle. In particular, this is the basis of the methods for the preparation of some pyrido[2,3-*d*]pyrimidines suggested by us. For example, thiones **4a,h** and dimethylformamide dimethylacetal were used for synthesizing novel derivatives of pyrido-[2,3-*d*]pyrimidine-5-ones. In accordance with Scheme 3, refluxing in toluene results in the alkylation of pyrimidinethiones at the S atom and condensation of methylated pyrimidines (**6**) with the second acetal molecule. Dimethylaminoacryloylpyrimidines (**7**) formed under these conditions during refluxing in xylene undergo cyclization with the abstraction of Me_2NH to give bicyclic compounds (**8, 9**).

The intermediate compounds **6** and **7** can be isolated as crude products. The reaction of DMF dimethylacetal performed under milder conditions (refluxing in benzene) results in the predominant formation of methylthiopyrimidine **6** (R = $PhCH_2$) identified by ^1H NMR spectroscopy. The spectrum of this compound in $CDCl_3$ displays signals of two methyl groups and NH at 2.77, 2.81, and 9.89 ppm, respectively. The structure of compound **7** (R = $PhCH_2$) formed upon refluxing thione **4h** with DMF acetal (1 : 2) in toluene was also confirmed by ^1H and ^{13}C NMR spectra (see Experimental).

The reaction of pyrimidinethione **4a** with DMF acetal in boiling toluene leads directly to pyrido-[2,3-*d*]pyrimidine-5-one (**11**), which is unsubstituted at the N atom of the pyridone fragment, in 71 % yield (Scheme 4). Compound **11** can also be obtained using

Scheme 3

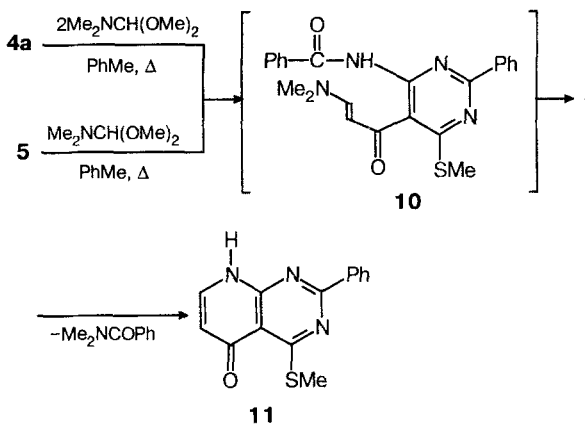


6 **7** **8, 9**

8: R = Ph;
9: R = $PhCH_2$.

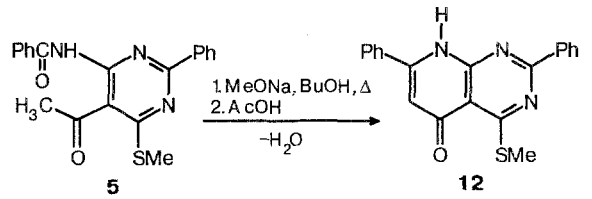
pyrimidine **5**, the product of methylation of thione **4a**. Probably, the reaction also involves the formation of intermediate **10**, similarly to Scheme 3, but this intermediate could not be detected. Evidently, its cyclization is accompanied by the elimination of *N,N*-dimethylbenzamide which is isolated as the second product in the synthesis of pyridopyrimidone **11**.

Scheme 4



An unusual approach to the construction of the pyrido[2,3-*d*]pyrimidine system can be based on the involvement of the benzamide fragment of compound **5** in the annelation of the pyridine ring to the pyrimidine ring. It appeared that compound **5** undergoes cyclization by MeONa in BuOH to give the respective pyrido[2,3-*d*]pyrimidine-5-one (**12**) in 75 % yield (Scheme 5).

Scheme 5



Pyrido[2,3-*d*]pyrimidine-5-ones **8**, **9**, **11**, and **12** prepared are colorless crystalline compounds that are easily soluble in $CHCl_3$, acetone, and EtOH (except for compound **11**) and insoluble in water. The ^1H and ^{13}C NMR spectra are in agreement with the structures ascribed to these compounds. The mass spectra are characterized by the presence of intense peaks for the $[M^+]$ and $[M-HS]^+$ ions. The comparison of all signals in the ^{13}C NMR spectra for heterocycles **8**, **9** with those for compounds **11** and **12** unsubstituted at N in position 8 confirms that the latter exist in solution exclusively in a pyridone form rather than as hydroxypyridines (Table 1). The same conclusion can be drawn on examining the IR spectra for the same compounds, which are characterized by absorption of the carbonyl group in the 1620—1635 cm^{-1} region.

Thus, we have suggested original schemes for constructing the pyrido[2,3-*d*]pyrimidine system on the basis of monoacetylketene aminals. The possibility of synthesizing heterocycles with an unsubstituted N atom that can probably be used for the preparation of nucleoside analogs is worth attention. Compounds of the pyrido[2,3-*d*]pyrimidine series possess a wide spectrum of biological activity (antibacterial, analgesic, and antitumor action, etc.),[9—11] and a great number of

Table 1. ^{13}C NMR spectra for 4-methylthiopyrido[2,3-*d*]pyrimidine-5-ones **8**, **9**, **11**, and **12** (δ, *J*/Hz)

Compound	Solvent		C(2)	C(4)	C(4a)	C(5)	C(6)	C(7)	C(8a)	SMe
8*	$CDCl_3$	161.87	175.50	113.97	178.15	114.93	142.03	155.50		14.17
9**	$CDCl_3$	161.84 s	175.48 q ^3J = 4.0	114.30 s	177.93 d ^2J = 8.7	115.11 d ^1J = 168.9	141.50 dtd ^1J = 177.0 ^3J = 4.7 ^2J = 4.2	154.82 t ^3J = 3.1		14.18 q ^1J = 141.3
11***	$(CD_3)_2SO$	161.26 br.t $^3J \approx 4.0$	173.42 q ^3J = 4.0	112.86 br.d ^3J = 3.0	176.89 d ^2J = 8.0	113.36 d ^1J = 168.4	139.35 dd ^1J = 179.0 ^2J = 3.0	154.97 d ^3J = 9.0		13.02 q ^1J = 142.0
12****	$CDCl_3$	162.96 br.s	174.93 br.s	112.75 d ^3J = 5.0	178.51 s	112.75 d ^1J = 167.0	148.85 br.s.	155.58 s		13.92 q ^1J = 140.0

* 127.54, 128.53, 128.90, 129.11, 129.42, 131.64, 137.01, 140.82 (2 Ph).
** 52.93(CH_2); 127.64, 128.36, 128.56, 129.08, 131.65, 136.18, 137.05 (2 Ph).
*** 128.23, 128.38, 131.25, 136.45 (Ph).
**** 126.53, 128.60, 129.06, 129.58, 131.16, 131.68, 133.36, 136.96 (2 Ph).

Table 2. Yields, melting points, and ^{1}H NMR spectra for thioamides (**2**) and pyrimidine-4-thiones (**4**)

Compound	Yield* (%)	M.p./°C (solvent used for recrystallization)	Solvent	^{1}H NMR spectrum, δ
2a	84	146—147	$CDCl_3$	2.37 (s, 3 H, Me), 7.20 (m, 1 H, Ph), 7.45—7.70 (m, 5 H,Ph), 7.91 (m, 2 H, Ph), 8.11 (m, 2 H, Ph), 9.37 (br.s, 1 H, NH), 10.41 (br.s, 1 H, NH), 11.20 (br.s, 1 H, NH), 14.58 (br.s, 1 H, NH)
4a	74	207—209 (from ethanol)	$CDCl_3$	3.01 (s, 3 H, Me), 7.50—7.78 (m, 6 H, Ph), 8.05 (m, 2 H, Ph), 8.19 (m, 2 H, Ph), 10.81 (br.s, 1 H, NH), 12.48 (br.s, 1 H, NH)
4b**	54	214—215 (from ethanol)	$CDCl_3$	3.05 (s, 3 H, Me), 7.22 (m, 1 H, Ph), 7.41 (m, 2 H, Ph), 7.50—7.71(m, 5 H, Ph), 7.98 (m, 2 H, Ph), 10.38 (br.s, 1 H, NH), 12.57 (br.s, 1 H, NH)
2c	76	124—125	DMSO-d_6	2.04 (s, 3 H, Me), 7.13—7.30 (m, 1 H, Ph), 7.42—7.71 (m, 6 H, Ph), 8.00 (m, 2 H, Ph), 8.51 (br.s, 1 H, NH), 9.41 (br.s, 1 H, NH), 11.02 (br.s, 1 H, NH), 15.50 (br.s, 1 H, NH)
4c	67	225—226 (from ethanol)	DMSO-d_6	2.85 (s, 3 H, Me), 7.23 (m, 1 H, Ph), 7.41 (m, 1 H, Ph), 7.48—7.68 (m, 4 H, Ph), 7.98—8.13 (m, 3 H, Ph), 11.31 (br.s, 1 H, NH), 13.34 (br.s, 1 H, NH)
4d**	38	204—206 (from benzene, precipitated with hexane)	$CDCl_3$	2.52 (s, 6 H, 2 Me), 2.98 (s, 3 H, Me), 6.87 (s, 1 H, H(5')), 7.45—7.70 (m, 3 H, Ph), 8.15 (m, 2 H, Ph), 12.10 (br.s, 1 H, NH)
2e	80	171—172	DMSO-d_6	1.88 (s, 3 H, Me), 3.58 (t, 4 H, CH_2), 3.75 (t, 4 H, CH_2), 7.45—7.70 (m, 3 H, Ph), 8.15 (m, 2 H, Ph), 8.60 (br.s, 1 H, NH), 9.15 (br.s,1 H, NH), 15.41 (br.s, 1 H, NH)
4e	58	209—210 (from ethanol)	DMSO-d_6	2.70 (s, 3 H, Me), 3.54 (t, 4 H, CH_2), 3.65 (t, 4 H, CH_2), 7.53 (m, 2 H, Ph), 7.62 (m, 1 H, Ph), 8.10 (m, 2 H, Ph), 13.15 (br.s., 1 H, NH)
2f	85	165—167	DMSO-d_6	1.75—2.05 (m, 7 H, 2 CH_2, Me), 3.10—3.50 (m, 4 H, 2 CH_2N), 7.47—7.60 (m, 3 H, Ph), 7.90 (m, 2 H, Ph), 8.13 (br.s, 1 H, NH), 8.80 (br.s, 1 H, NH), 13.90 (br.s, 1 H, NH)
4f	48	199—201 (from ethanol)	DMSO-d_6	1.90—2.10 (m, 4 H, 2 CH_2), 2.85 (s, 3 H, Me), 3.30—3.80 (m, 4 H, 2 CH_2), 7.50—7.65 (m, 3 H, Ph), 7.96 (m, 2 H, Ph), 10.24 (br.s, 1 H, NH)
4g**	58	230—231 (from ethanol)	$CDCl_3$	7.21 (m, 1 H, Ph), 7.35—7.72 (m, 10 H, Ph), 7.91 (m, 2 H, Ph), 8.02 (m, 2 H, Ph), 9.95 (br.s, 1 H, NH), 10.42 (br.s, 1 H, NH)
4h	62	205—206 (from ethanol)	$CDCl_3$	3.02 (s, 3 H, Me), 4.91 (d, 2 H, CH_2, J = 6 Hz), 7.22—7.45 (m, 5 H, Ph), 7.56 (m, 2 H, Ph), 7.65 (m, 1 H, Ph), 8.00 (m, 2 H, Ph), 10.12 (br.s, 1 H, NH), 11.09 (br.s, 1 H, NH)

* The yields of pyrimidine-4-thiones **4a—g** are given with respect to aminals **1a—g**.
** Thioamides **2b,d,g** were used in the syntheses of pyrimidine-4-thiones without identification.

papers and patents, including some reviews,[12—13] have been devoted to them.

Experimental

^{1}H NMR spectra (δ) were recorded on a Bruker WM-250 spectrometer, and ^{13}C NMR spectra (δ) were recorded on a Bruker AM-300 spectrometer. IR spectra (ν/cm^{-1}) were obtained on a UR-20 spectrophotometer. Mass spectra were obtained on a MAT-311A spectrometer (EI, 70 eV, m/z (I_{rel}, %)). Monoacylketene aminals **1a,b,d,g**[6] and benzoyl isothiocyanate[14] were prepared according to the procedures published previously.

1-Amino-1-*o*-chlorophenylamino-1-butene-3-one (1c). 3-[*o*-Chlorophenylamino(amino)methylene]pentane-2,4-dione (m.p. 57—58 °C) was synthesized[15] in 62 % yield from *o*-chlorophenylcyanamide and acetylacetone; the compound

Table 3. Elemental analysis data, IR, and mass spectra for pyrimidine-4-thiones (**4**)

Compound	Found / Calculated (%) C	H	N	S	Molecular formula	Conditions	IR, ν/cm^{-1}	MS, *m/z* (I_{rel}, %)
4a	65.39 65.31	4.42 4.33	11.82 12.03	9.01 9.18	$C_{19}H_{15}N_3O_2S$	CH_2Cl_2	3355(NH), 3300—2850(NH, CH), 1712(PhCO), 1630 (MeCO), 1600, 1565, 1550	349[M]$^{+\cdot}$(69), 244[M−COPh]$^+$(100)
4b	67.16 67.27	4.99 4.70	12.63 13.07	9.83 9.98	$C_{18}H_{15}N_3OS$	CH_2Cl_2	3375(NH), 3300—2900 (PhNH), 1612(CO), 1600, 1575, 1535	321[M]$^{+\cdot}$(100), 320[M−H]$^+$(63), 244[M−Ph]$^+$(37)
4c*	60.84 60.75	4.22 3.97	11.68 11.81	8.61 9.01	$C_{18}H_{14}ClN_3OS$	CH_2Cl_2	3370(NH), 3300—2900(NH, CH), 1615(CO), 1600, 1590 1565	355[M]$^{+\cdot}$(41), 354[M−H]$^+$(26), 320[M−Cl]$^+$(100),
4d	61.27 61.52	5.29 4.88	19.34 19.93	8.65 9.12	$C_{18}H_{17}N_5OS$	CH_2Cl_2	3370(NH), 3300—2900(NH, CH), 1640(CO), 1605, 1578, 1550, 1540	351[M]$^{+\cdot}$(63), 350[M−H]$^+$(40), 308[M−COMe]$^+$(100)
4e	60.73 60.93	5.53 5.43	13.43 13.32	10.52 10.17	$C_{16}H_{17}N_3O_2S$	KBr	3200—2800(NH, CH), 1670 (CO), 1590, 1560,1540	315[M]$^{+\cdot}$(73), 300[M−Me]$^+$(100),
4f	64.51 64.19	6.06 5.72	14.41 14.03	10.34 10.71	$C_{16}H_{17}N_3OS$	$CHCl_3$	3390(NH), 1680(CO), 1600, 1570, 1545	—
4g	72.38 72.04	4.43 4.47	11.29 10.96	8.59 8.36	$C_{23}H_{17}N_3OS$	CH_2Cl_2	3370(NH), 1620(CO), 1600, 1568, 1528	383[M]$^{+\cdot}$(90), 354[M−CO−H]$^+$(100)
4h	67.85 68.03	5.23 5.11	12.66 12.53	9.51 9.56	$C_{19}H_{17}N_3OS$	CH_2Cl_2	3375(NH), 3280—2900(NH, CH), 1605(CO), 1570, 1525, 1495	335[M]$^{+\cdot}$(19), 244[M−CH_2Ph]$^+$(100)

*Found (%): Cl, 9.52. Calculated (%): Cl, 9.96.

obtained was either transformed[6] to aminal **1c** (an oil) in 86 % yield and used directly in subsequent syntheses.

1-Amino-1-morpholino-1-butene-3-one (1e) was synthesized[6] from 3-[morpholino(amino)methylene]pentane-2,4-dione[16] in 88% yield, m.p. 129—130 °C.

1-Amino-1-pyrrolidino-1-butene-3-one (1f). 3-[Pyrrolidino-(amino)methylene]pentane-2,4-dione (m.p. 181—183 °C) was synthesized[16] in 86 % yield from 3-[methylthio(amino)-methylene]pentane-2,4-dione and pyrrolidine and then transformed to aminal **1f**, yield 92 %, m.p. 185—188 °C.

2-Acetyl-3-amino-3-R^2,R^3-amino-N-benzoylthioacrylamides (2) and 5-acyl-6-R^2,R^3-amino-2-phenyl-3*H*-pyrimidine-4-thiones (4a—g) (general procedure). A mixture of aminal **1a—g** (2 mmol) and benzoyl isothiocyanate (4 mmol) in toluene (6 mL) was kept for 24 h at ~20 °C. The precipitate that formed was filtered off and washed with pentane to give thioamides **2a—g**. MeONa (2 mmol) in MeOH (20 mL) was added to thioamides **2a—g**, and the mixture was left at ~20 °C until the residue dissolved completely (this took 15 min in the synthesis of **4a**, or 2 h for **4b—d,g**; the mixture was refluxed for 5 min in the case of **4e,f**). Methanol was evaporated *in vacuo* at ~20 °C, water (25 mL) was added to the residue, and the undissolved precipitate was filtered off. The filtrate containing thiolates **3a—g** was acidified with AcOH to pH ~ 5; the resulting residue was filtered off, washed with water, and dried to give pyrimidine-4-thiones **4a—g**. The yields, melting points, and ^{1}H NMR spectral data for thioamides **2** and pyrimidine-4-thiones **4** are given in Table 2. Elemental analysis data, IR and mass spectra for compounds **4** are given in Table 3.

Thioamide **2a**. Found (%): C, 62.19; H, 5.00; N, 10.99; S, 8.25. $C_{19}H_{17}N_3O_3S$. Calculated (%): C, 62.11; H, 4.66; N, 11.44; S, 8.73.

^{13}C NMR spectrum for pyrimidine-4-thione **4b** (DMSO-d_6), δ: 32.94 (Me), 113.28 (C(5)), 123.54, 124.93, 128.59, 128.66, 128.88, 130.72, 132.73, 137.49 (2Ph), 156.04, 156.53 (C(2), C(6)), 180.76 (C(4)), 202.41 (CO). ^{13}C NMR spectrum for compound **4d** (DMSO-d_6), δ: 23.00 (2 Me), 31.93 (COMe), 118.79 (C(5)), 115.05 (C(5′)), 128.33, 128.63, 130.41, 132.44 (Ph), 152.90, 155.70, 156.95 (C(2), C(6), C(2′)), 167.28 (C(4′), C(6′)), 180.58 (C(4)), 201.54 (CO).

^{13}C NMR spectrum for pyrimidine-4-thione **4e** (DMSO-d_6), δ: 32.44 (Me), 47.22 (CH_2), 65.59 (CH_2), 116.33 (C(5)), 128.37, 130.96, 132.09 (Ph), 154.65, 155.41 (C(2), C(6)), 177.08 (C(4)), 202.48 (CO).

5-Acetyl-6-benzylamino-2-phenyl-3*H*-pyrimidine-4-thione (4h). A mixture of pyrimidine-4-thione **4e** (0.315 g, 1 mmol) and benzylamine (0.22 mL, 2 mmol) in benzene (8 mL) was refluxed for 6 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on a column with SiO_2 (with benzene as the eluent) to give 0.21 g of compound **4h** (the yield, melting point, elemental analysis data, and spectral data are given in Tables 2 and 3).

5-Acetyl-6-benzoylamino-4-methylthio-2-phenylpyrimidine (5). A mixture of thioamide **2a** (0.55 g, 1.5 mmol) and MeONa (1.5 mmol) in MeOH (17 mL) was stirred for 15 min at ~20 °C, then MeI (0.19 mL, 3 mmol) was quickly added, and the mixture was left at ~20 °C for 1 h. The resulting precipitate was filtered off to give 0.45 g (82 %) of product **5**, m.p. 176—177 °C (from MeOH). Found (%): C, 66.11; H, 4.79; N, 11.49; S, 8.60. $C_{20}H_{17}N_3O_2S$. Calculated (%): C, 66.10; H, 4.71; N, 11.56; S, 8.82. IR (CH_2Cl_2): 3400 (NH), 1703 (CO), 1640 (CO), 1570, 1515. ^1H NMR ($CDCl_3$): 2.73 (s, 3 H, Me), 2.76 (s, 3 H, Me), 7.45—7.70 (m, 6 H, Ph), 8.02 (m, 2 H, Ph), 8.52 (m, 2 H, Ph), 10.40 (br.s, 1 H, NH). MS: 363 $[M]^{+\cdot}$ (10), 348 $[M-Me]^+$ (100), 320 $[M-COMe]^+$ (47).

4-Methylthio-2,8-diphenyl-8*H*-pyrido[2,3-*d*]pyrimidine-5-one (8). A mixture of thione **4b** (0.16 g, 0.5 mmol) and $Me_2NCH(OMe)_2$ (0.13 mL, 1 mmol) in toluene (5 mL) was refluxed for 3 h. The solvent was evaporated to dryness *in vacuo*, *m*-xylene (7 mL) was added to the residue, and the mixture was refluxed for 30 h. The reaction mixture was left for 12 h at ~20 °C, and the resulting precipitate was filtered off to give 0.086 g of compound **8**. Evaporation of the solvent from the filtrate followed by chromatography of the residue on a column with SiO_2 (with C_6H_6 : $CHCl_3$, 1 : 1, and then $CHCl_3$ as eluents) afforded an additional amount (0.06 g) of product **8** (overall yield 84 %), m.p. 232—233 °C (from a benzene : heptane mixture, 1 : 2). Found (%): C, 69.44; H, 4.51; N, 11.94; S, 9.03. $C_{20}H_{15}N_3OS$. Calculated (%): C, 69.54; H, 4.38; N, 12.17; S, 9.28. IR (CH_2Cl_2): 1635 (CO), 1595, 1535, 1510. ^1H NMR ($CDCl_3$): 2.69 (s, 3 H, SMe), 6.43 (d, J = 8.0 Hz, 1 H, H-6), 7.32—7.60 (m, 8 H, Ph), 7.63 (d, J = 8.0 Hz, 1 H, H-7). 8.27 (m, 2 H, Ph). MS: 345 $[M]^{+\cdot}$ (65), 312 $[M-SH]^+$ (100).

8-Benzyl-4-methylthio-2-phenyl-8*H*-pyrido[2,3-*d*]pyrimidine-5-one (9). A mixture of thione **4h** (0.168 g, 0.5 mmol) and $Me_2NCH(OMe)_2$ (0.13 mL, 1 mmol) in toluene (5 mL) was refluxed for 4 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on a column with SiO_2 (with C_6H_6 and then $CHCl_3$ as eluents) to give an oil containing pyrimidine **7** (R = CH_2Ph) with an admixture of compound **9**. ^1H NMR ($CDCl_3$) for compound **7**: 2.67 (s, 3 H, Me), 2.94 (s, 3 H) and 3.12 (s, 3 H) (NMe_2), 4.81 (d, J = 5.8 Hz, 2 H, CH_2), 5.81 (d, J = 12.51 Hz, 1 H, CH=), 7.22—7.58 (m, 8 H, Ph), 7.69 (d, J = 12.5 Hz, 1 H, CH=), 7.89 (br.s, 1 H, NH), 8.40—8.56 (m, 2 H, Ph). ^{13}C NMR ($CDCl_3$) for compound **7**: 14.09 (SMe), 37.50 and 45.50 (NMe_2), 44.88 (CH_2), 98.63 (CH=), 112.22 (C-5), 127.01, 127.72, 128.16, 128.51, 129.07, 130.48, 138.23, 139.58 (2Ph), 154.19 (CH=), 160.21, 161.06 (C-2, C-6), 165.83 (C-4), 188.78 (CO). *m*-Xylene (10 mL) was added to the oil, and the mixture was refluxed for 8 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on a column with SiO_2 (with $CHCl_3$ as the eluent) to give 0.12 g (67 %) of product **9**, m.p. 250—251 °C (from C_6H_6). Found (%): C, 69.68; H, 4.57; N, 11.67; S, 8.71. $C_{21}H_{17}N_3OS$. Calculated (%): C, 70.17; H, 4.77; N, 11.69; S, 8.92. IR (CH_2Cl_2): 1635 (CO), 1600, 1540, 1510. ^1H NMR ($CDCl_3$): 2.70 (s, 3 H, SMe), 5.60 (s, 2 H, CH_2), 6.38 (d, J = 8.0 Hz, 1 H, H-6), 7.25—7.40 (m, 5 H, Ph), 7.45—7.60 (m, 3 H, Ph), 7.56 (d, J = 8.0 Hz, 1 H, H-7), 8.55 (m, 2 H, Ph). MS: 359 $[M]^{+\cdot}$ (100), 326 $[M-SH]^+$ (73), 268 $[M-PhCH_2]^+$ (60).

4-Methylthio-2-phenyl-8*H*-pyrido[2,3-*d*]pyrimidine-5-one (11). Procedure A. A mixture of thione **4a** (0.35 g, 1 mmol) and $Me_2NCH(OMe)_2$ (0.27 mL, 2 mmol) in toluene (12 mL) was refluxed for 3 h. The reaction mixture was cooled to ~20 °C; the resulting precipitate was filtered off and washed with toluene (5 mL) to give 0.19 g (71 %) of product **11**, m.p. 343—345 °C. Found (%): C, 62.31; H, 4.44; N, 16.07; S, 11.30. $C_{14}H_{11}N_3OS$. Calculated (%): C, 62.43; H, 4.12; N, 15.60; S, 11.91. IR (KBr): 3100—2400 (NH), 1620 (CO), 1600, 1580, 1560, 1525. ^1H NMR (DMSO-d_6): 2.57 (s, 3 H, SMe), 6.16 (d, J = 7.5 Hz, 1 H, H-6), 7.64—7.48 (m, 3 H, Ph), 7.83 (d, J = 7.5 Hz, 1 H, H-7), 8.38—8.52 (m, 2 H, Ph). MS: 269 $[M]^{+\cdot}$ (69), 236 $[M-HS]^+$ (100). Evaporation of the solvent from the filtrate followed by chromatography on a column with SiO_2 (with benzene and then $CHCl_3$ as eluents) gave successively 0.061 g of pyrimidine **5** and 0.067 g of *N,N*-dimethylbenzamide as an oil. IR (CH_2Cl_2): 1630 (CO), 1505. ^1H NMR ($CDCl_3$): 2.93 (s, 3 H) and 3.08 (s, 3 H) (NMe_2), 7.37 (s, 5 H, Ph). MS: 149 $[M]^{+\cdot}$.

Procedure B. A mixture of sulfide **5** (0.45 g, 1.2 mmol) and $Me_2NCH(OMe)_2$ (0.16 mL, 1.2 mmol) in toluene (15 mL) was refluxed for 3 h. Then 0.23 g (70 %) of compound **11** was isolated similarly to procedure A.

4-Methylthio-2,7-diphenyl-8*H*-pyrido[2,3-*d*]pyrimidine-5-one (12). A mixture of sulfide **5** (0.182 g, 0.5 mmol) and MeONa (0.5 mmol) in butanol (8 mL) was refluxed for 1 h and cooled to ~20 °C. Then AcOH (0.5 mL) was added, and the mixture was stirred for 20 min. The solvent was evaporated to dryness; $CHCl_3$ (50 mL) was added to the residue, and AcONa was filtered off. The filtrate was concentrated, and the residue was chromatographed on a column with SiO_2 (with C_6H_6 and then $CHCl_3$ as eluents) to give 0.133 g (77 %) of product **12**, m.p. 269—271 °C (from $CHCl_3$). Found (%): C, 69.59; H, 4.44; N, 12.19; S, 8.86. $C_{20}H_{15}N_3OS$. Calculated (%): C, 69.54; H, 4.38; N, 12.17; S, 9.28. IR (CH_2Cl_2): 3400 (NH), 1632 (CO), 1605, 1590, 1580, 1530. ^1H NMR ($CDCl_3$): 2.69 (s, 3 H, SMe), 6.61 (s, 1 H, H-6), 7.42—7.60 (m, 6 H, Ph), 7.67 (m, 2 H, Ph), 8.50 (m, 2 H, Ph), 9.05 (br.s, 1 H, NH). MS: 345 $[M]^{+\cdot}$ (68), 312 $[M-HS]^+$ (100).

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Received May 13, 1993

Synthesis of 1,3-thiazoline derivatives from β-dicarbonyl compounds and phenacyl thiocyanate

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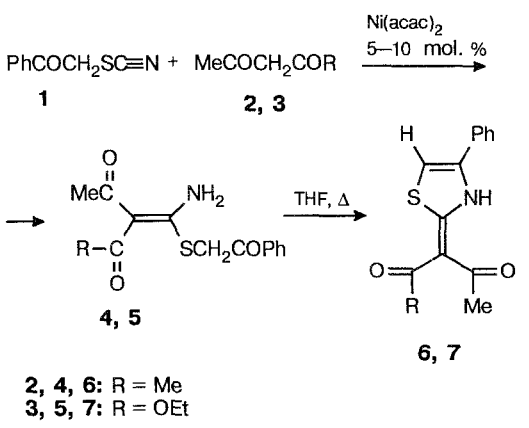
Acetylacetone and ethyl acetoacetate undergo addition at the C≡N bond of phenacyl thiocyanate in the presence of $Ni(acac)_2$ to give the respective ketene *N,S*-acetals, which undergo smooth cyclization to afford 2-methylene-4-phenyl-1,3-thiazoline derivatives when refluxed in THF .

Key words: phenacyl thiocyanate, β-dicarbonyl compounds, ketene *N,S*-acetals, nickel acetylacetonate, 1,3-thiazoline derivatives, boron chelates.

Previously[1] we suggested a convenient procedure for the preparation of diacyl- and alkoxycarbonyl(acyl)-ketene *N,S*-acetals from esters of thiocyanic acid and β-diketones or esters of β-ketoacids in the presence of catalytic amounts of $Ni(acac)_2$. *N,S*-Acetals of this type were shown to be suitable starting reagents for synthesizing heterocyclic compounds.[2,3] Therefore, it seemed interesting to use functionally substituted thiocyanates in reactions with β-dicarbonyl compounds, since the formation of the respective *N,S*-acetals capable of direct heterocyclization could be expected in some cases.

The reaction of phenacyl thiocyanate (**1**) with acetylacetone (**2**) and ethyl acetoacetate (**3**) was studied in this work. Attempts to perform the addition of compounds **2** and **3** to thiocyanate **1** without a catalyst or in the presence of a base (MeONa) were unsuccessful. However, the above β-dicarbonyl compounds smoothly undergo addition to the C≡N bond of thiocyanate **1** under mild conditions in the presence of $Ni(acac)_2$, which results in the respective *N,S*-acetals (**4,5**).



The structures of the resulting compounds were confirmed by spectroscopic data. For example, the mass spectra for reaction products **4—7** display molecular ion peaks. The IR spectra for compounds **4** and **5** display absorption characteristic of free NH groups and those involved in intramolecular hydrogen bonds (a band at

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 1938—1940, November, 1993.