Synthesis of new pyrimido[4,5-*d*]pyrimidine derivatives from 5-acetyl-6-methyl-4-methylsulfanylpyrimidine-2(1*H*)-thiones and guanidine*

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Reactions of 5-acetyl-1-aryl(alkyl)-6-methyl-4-methylsulfanylpyrimidine-2(1*H*)-thiones (prepared from diacetylketene N,S-acetal) with guanidine afforded 3-alkyl- and 3-aryl-7-amino-5-methyl-4-methylidene-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thiones. By-products of these reactions (5-acetyl-1-alkyl(aryl)-6-methyl-2-thiouracils) can also be obtained from the starting pyrimidinethiones and EtONa in EtOH. Pyrimidopyrimidinethiones can react with MeOH at the methylidene group in the presence of MeONa.

Key words: diacetylketene N,S-acetal, isothiocyanates, 5-acetyl-6-methyl-4-methylsulfanylpyrimidine-2(1*H*)-thiones, guanidine, condensation, 7-amino-5-methyl-4-methylidene-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thiones, 4-alkoxy-7-amino-4,5-dimethyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thiones, 5-acetyl-1-aryl(alkyl)-6-methyl-2-thiouracils.

Pyrimido[4,5-*d*]pyrimidines, which are structurally related to pteridines and purines, are of biological interest because of a variety of their pharmacological activity including bronchodilating,[1] antimicrobial,[2,3] antiallergic,[4] antihypertensive effects.[5] In addition, they are phosphodiesterase[1] and dihydrofolate reductase[6] inhibitors.

As a next step in our searching for synthetic routes to pyrimido[4,5-*d*]pyrimidines,[7—12] here we obtained new derivatives of this heterocyclic system, *viz.*, 3-alkyl- and 3-aryl-7-amino-5-methyl-4-methylidene-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thiones and 4-alkoxy-7-amino-4,5-dimethyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thiones.

Earlier,[10] we have demonstrated that diacetylketene N,S-acetal **1** prepared from acetylacetone and methyl thiocyanate in the presence of $Ni(acac)_2$[13] reacts with phenyl isothiocyanate to give 5-acetyl-4-methylsulfanylpyrimidine-2-thione **2a** (Scheme 1). When the MeS group is replaced by an amino group, compound **2a** can be used in reactions with dimethylformamide dimethyl acetal (or diethyl oxalate) and isocyanates to obtain the bicyclic systems pyrimido[4,5-*d*]pyrimidine and pyrido[2,3-*d*]pyrimidine, respectively. However, we found it interesting to study the possibility of employing bifunctional nucleophiles for a single-step synthesis of fused heterocycles from such pyrimidinethiones.

In the present work, we studied reactions of pyrimidinethione **2a** and similarly prepared thiones **2b**,**c** with guanidine.

We found that reactions of pyrimidinethiones **2a**,**b** with guanidine acetate in boiling *n*-butanol in the presence of MeONa give pyrimidopyrimidinethiones **3a**,**b** in 46 and 36% yields, respectively, and 5-acetylthiouracils **4a**,**b** as by-products (see Scheme 1). It should be noted that the pyrimidine ring undergoes reconstruction during the reaction, and compounds **3a**,**b** containing the exocyclic methylidene group, instead of the expected products **5a**,**b**, were obtained.

Under similar conditions, pyrimidinethione **2c** reacts with guanidine to produce compounds **3c** and **4c** and, unexpectedly, pyrimidopyrimidinethione **6c**. Note that the yield of the latter is higher than that of **3c**. Obviously, compound **6c** is formed by addition of Bu^nOH to the exocyclic methylidene group of heterocycle **3c**. The absence of such products in the reactions with pyrimidinethiones **2a**,**b** is probably due to the steric hindrances presented by the 3-aryl substituent, making the exocyclic methylidene group in compounds **3a,b** less accessible to a sufficiently bulky butanol molecule.

To verify this assumption, we carried out a reaction of pyrimidinethione **2c** with guanidine in *tert*-butanol instead

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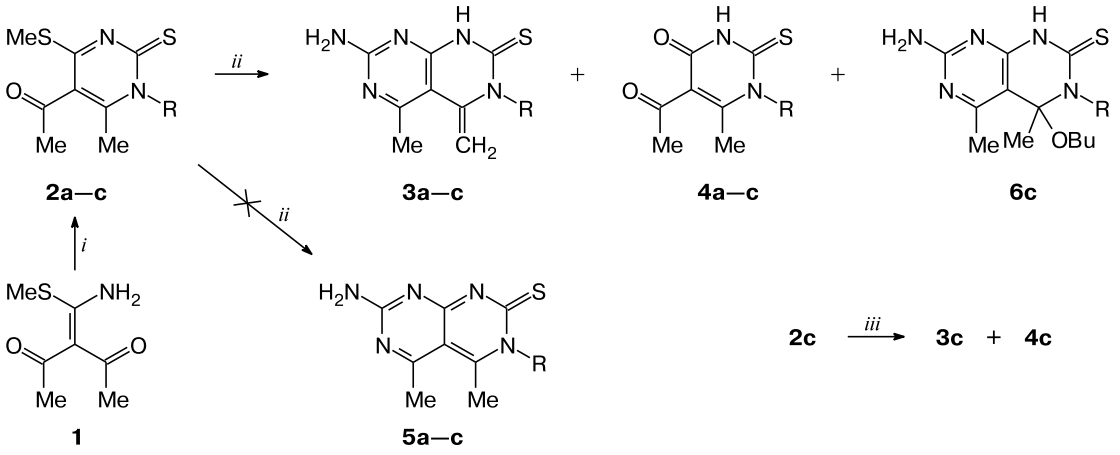
Scheme 1



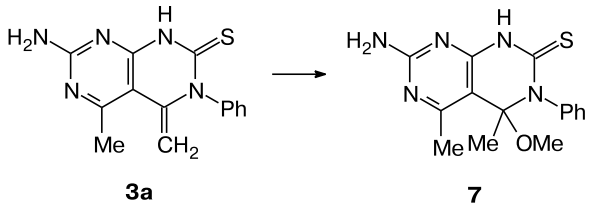
R = Ph (**a**), 2,5-$Me_2C_6H_3$ (**b**), Et (**c**)

Reagents and conditions: *i*. RNCS, toluene, Δ; *ii*. 1) $(NH_2)_2C{=}NH \cdot AcOH$, MeONa, Bu^nOH, Δ; 2) AcOH, 20 °C; *iii*. 1) $NH_2C(=NH)NH_2 \cdot AcOH$, MeONa, Bu^tOH, Δ; 2) AcOH, 20 °C.

of *n*-butanol. Indeed, only compounds **3c** and **4c** were obtained; *tert*-butanol formed no adduct at the exocyclic methylidene group.

We tried to add methanol to the exocyclic methylidene group of pyrimidopyrimidinethione **3a**. It turned out that no reaction occurs even when compound **3a** is refluxed in MeOH. Nevertheless, in the presence of MeONa, we obtained pyrimidopyrimidinethione **7** structurally related to compound **6c** (Scheme 2).

Scheme 2



Reagents and conditions: MeONa, MeOH, Δ.

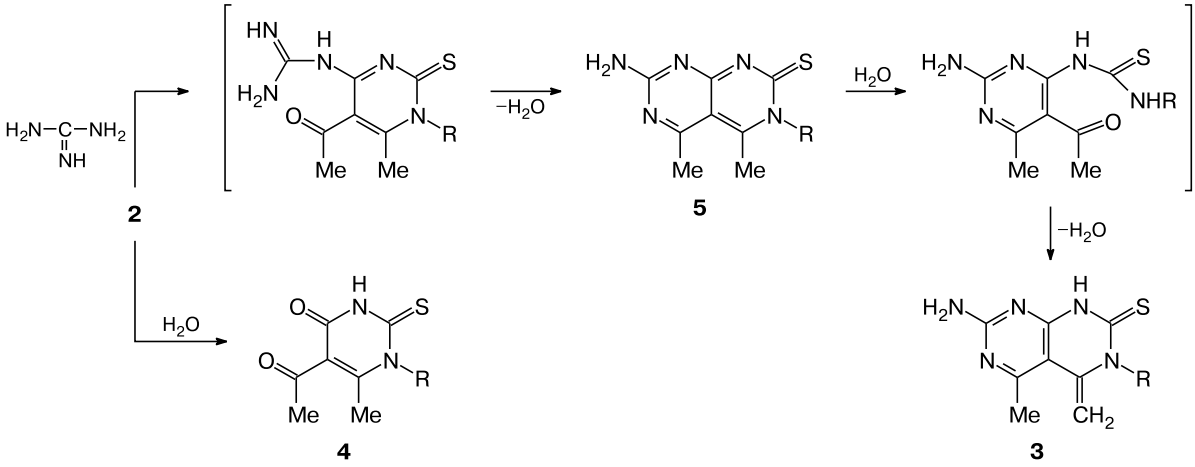
Therefore, the addition of an alcohol to the exocyclic methylidene group of compounds **3** is facilitated by the formation of a thiolate anion under the action of bases (MeONa, guanidine) with subsequent polarization of the double bond of the methylidene fragment. In contrast, MeOH in the presence of MeONa does not react with 1-benzyl-5-methyl-4-methylidene-3,6-diphenyl-7-thioxo-3,4,6,7-tetrahydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one.[10] It is worth noting that heterocycle **3a** in the presence of bases reacts with MeOH, remaining inert to *n*-butanol.

A probable mechanism of the reactions of pyrimidinethiones **2** with guanidine is shown in Scheme 3.

The water released during the intramolecular cyclocondensation leads, in the presence of a strong base (guanidine), to both opening of the pyrimidinethione ring followed by formation of methylidenepyrimidinethiones (compounds **3**) and substitution of the methylsulfanyl group in pyrimidinethiones **2** leading to thiouracils **4**.

Heterocyclic compounds **3**, **4**, **6**, and **7** are nearly colorless solids. Pyrimidopyrimidinethiones **3a—c** are well soluble in DMSO but poorly soluble in other organic solvents. Adducts **6c** and **7** are well soluble in chloroform and acetone; in addition, compound **6c** is soluble in benzene. Acetylthiouracils **4a—c** are well soluble in chloroform, acetonitrile, and acetone. Note that adducts **6c** and **7**, in contrast to compounds **3a—c** and **4a—c**, are not acidic, yielding no salts in reactions with MeONa. The structures of all the heterocycles obtained were determined by mass spectrometry and IR and ^1H NMR spectroscopy. Structures **3a** and **7** were additionally confirmed by ^{13}C NMR spectroscopy and 2D correlation experiments ($^1H—^{13}C$ HSQC and HMBC). The mass spectra of all the compounds contain molecular ion peaks; their main fragmentation pathways are given in Table 1. The ^1H NMR spectra of pyrimidopyrimidinethiones **3a—c** in DMSO-d_6 show signals at δ 6.5—6.8 (NH_2), sufficiently narrow singlets at δ 11.2—11.6 (NH), and two doublets for the protons of the exocyclic methylidene group (AB system). The $^1H—^{13}C$ HSQC spectrum of compound **3a** in DMSO-d_6 reveals couplings between the protons resonating at δ 3.80 and 4.58 and the C atom resonating at δ 95.9, which provides evidence for the presence of the exocyclic methylidene group. The ^1H NMR spectra of adducts **6c** and **7** in DMSO-d_6 also show signals at δ 6.5—6.6 (NH_2) and sufficiently narrow singlets at δ 10.7—11.3 (NH). Instead of the doublets for the methylidene protons, the spectra contain a singlet at δ 1.5—1.7 (4-Me) and signals for the OMe (**7**) or OBu group (**6**) (Table 2). In addition, the CH_2 protons of the ethyl substituent in compound **6c** are non-

Scheme 3



equivalent and so are the *ortho*-protons of the Ph substituent in compound **7** (^{1}H NMR data). All the six C atoms of the Ph substituent in compound **7** are also nonequivalent (^{13}C NMR data). The ^{1}H—^{13}C HMBC spectrum of heterocycle **7** in DMSO-d_6 shows two cross peaks for the protons resonating at δ 1.55 (4-Me) and 3.08 (OMe) and the C atom resonating at δ 91.2 (C(4)) as well as two cross peaks for the proton resonating at δ 11.25 (NH) and the C(4a) and C(2) atoms (δ 99.7 and 178.0, respectively).

The IR spectra of acetylthiouracils **4a**—**c** in KBr pellets contain absorption bands at 1692—1708 (COMe) and 1648—1672 cm^{-1} (CON) (in $CHCl_3$, both the CO groups absorb at ~1688 cm^{-1}). The ^{1}H NMR spectra of compounds **4a**—**c** in DMSO-d_6 show a sufficiently narrow singlet at δ 12.8—13.0 (NH) (see Table 2).

We found that, like pyrimidinethiones **2a**—**c**, 5-acetyl-4-ethylsulfanylpyrimidin-2-one **8** (see Ref. 8) reacts with guanidine acetate in Bu^{n}OH in the presence of MeONa to

Table 1. Elemental analysis data and mass spectra of compounds **3a**—**c**, **4a**—**c**, **6c**, **7**, **9**, and **10**

Compound	Found / Calculated (%)				Molecular formula	MS, m/z (I_{rel} (%))
	C	H	N	S		
3a	59.39 59.34	4.81 4.62	24.57 24.72	11.50 11.32	$C_{14}H_{13}N_5S$	283 $[M]^+$ (100), 282 $[M - H]^+$ (95), 268 $[M - Me]^+$ (18)
3b	61.35 61.71	5.65 5.50	22.17 22.49	9.95 10.30	$C_{16}H_{17}N_5S$	311 $[M]^+$ (57), 296 $[M - Me]^+$ (100), 278 $[M - HS]^+$ (19)
3c	51.07 51.04	5.54 5.57	29.62 29.76	13.59 13.63	$C_{10}H_{13}N_5S$	235 $[M]^+$ (100), 220 $[M - Me]^+$ (20), 207 $[M - C_2H_4]^+$ (58), 202 $[M - HS]^+$ (30)
4a	59.86 59.98	4.61 4.65	10.69 10.76	11.99 12.32	$C_{13}H_{12}N_2O_2S$	260 $[M]^+$ (100), 245 $[M - Me]^+$ (69), 218 $[M - COCH_2 - OH]^+$ (37)
4b	62.36 62.48	5.40 5.59	9.60 9.71	10.81 11.12	$C_{15}H_{16}N_2O_2S$	288 $[M]^+$ (100), 273 $[M - Me]^+$ (39), 255 $[M - HS]^+$ (51)
4c	51.09 50.92	5.85 5.70	13.29 13.20	14.81 15.11	$C_9H_{12}N_2O_2S$	212 $[M]^+$ (100), 197 $[M - Me]^+$ (12), 169 $[M - COMe]^+$ (44)
6c	54.45 54.34	7.45 7.49	22.57 22.63	10.28 10.36	$C_{14}H_{23}N_5OS$	309 $[M]^+$ (8), 252 $[M - Bu]^+$ (19), 236 $[M - OBu]^+$ (100), 235 $[M - BuOH]^+$ (95)
7	57.04 57.12	5.55 5.43	22.32 22.20	9.69 10.17	$C_{15}H_{17}N_5OS$	315 $[M]^+$ (3), 284 $[M - OMe]^+$ (33), 283 $[M - MeOH]^+$ (100), 282 $[M - MeOH - H]^+$ (92), 268 $[M - MeOH - Me]^+$ (27)
9	62.86 62.91	5.01 4.90	26.17 26.20	—	$C_{14}H_{13}N_5O$	267 $[M]^+$ (51), 266 $[M - H]^+$ (100), 252 $[M - Me]^+$ (8)
10	64.07 63.93	5.11 4.95	11.52 11.47	—	$C_{13}H_{12}N_2O_3$	244 $[M]^+$ (23), 243 $[M - H]^+$ (39), 229 $[M - Me]^+$ (27), 76 (100)

Table 2. ^{1}H NMR (DMSO-d_6) and IR spectra (KBr) of compounds **3a—c**, **4a—c**, **6c**, **7**, **9**, and **10**

Compound	^{1}H NMR (δ, *J*/Hz)	IR, ν/cm^{-1}
3a	2.38 (s, 3 H, Me); 3.80, 4.58 (both d, each 1 H, CH_2=, *J* = 2.0); 6.81 (br.s, 2 H, NH_2); 7.23 (d, 2 H, *o*-H_{Ph}, *J* = 7.5); 7.42 (t, 1 H, *p*-H_{Ph}, *J* = 7.5); 7.51 (t, 2 H, *m*-H_{Ph}, *J* = 7.5); 11.62 (s, 1 H, NH)	3316, 3152, 1660, 1608, 1544, 1520
3b	2.05 (s, 3 H, Me); 2.31 (s, 3 H, Me); 2.42 (s, 3 H, 5-Me); 3.83, 4.58 (both d, each 1 H, CH_2=, *J* = 2.0); 6.61 (br.s, 2 H, NH_2); 6.97 (s, 1 H, *o*-$H_{C_6H_3}$); 7.14, 7.24 (both d, each 1 H, *m*-$H_{C_6H_3}$, *p*-$H_{C_6H_3}$, *J* = 8.0); 11.25 (s, 1 H, NH)	3332, 3180, 1648, 1624, 1608, 1552, 1508
3c	1.28 (t, 3 H, MeCH$_2$, *J* = 8.0); 2.38 (s, 3 H, Me); 4.30 (q, 2 H, CH_2N, *J* = 8.0); 4.68, 4.92 (both d, each 1 H, CH_2=, *J* = 2.0); 6.67 (br.s, 2 H, NH_2); 11.20 (s, 1 H, NH)	3324, 3148, 1656, 1624, 1600, 1548, 1516
4a	1.82 (s, 3 H, 6-Me); 2.48 (s, 3 H, COMe); 7.32—7.62 (m, 5 H, Ph); 12.93 (s, 1 H, NH)	3164, 1692 (C=O); 1652 (C=O), 1580 3364* (NH), 1688 (C=O), 1580
4b	1.78 (s, 3 H, 6-Me); 2.05 (s, 3 H, Me); 2.31 (s, 3 H, Me); 2.48 (s, 3 H, COMe); 7.09 (s, 1 H, *o*-$H_{C_6H_3}$); 7.17, 7.25 (both d, each 1 H, *m*-$H_{C_6H_3}$, *p*-$H_{C_6H_3}$, *J* = 8.0); 13.03 (s, 1 H, NH)	3164, 1700 (C=O); 1672 (C=O); 1600, 1508
4c	1.27 (t, 3 H, MeCH$_2$, *J* = 8.0); 2.32 (s, 3 H, Me); 2.38 (s, 3 H, Me); 4.42 (q, 2 H, CH_2, *J* = 8.0); 12.83 (s, 1 H, NH)	3172, 1708 (C=O); 1648 (C=O)
6c	0.84 (t, 3 H, Me_{Bu}, *J* = 8.0); 1.20—1.58 (m, 7 H, Me_{Et}, 2 $CH_{2\ Bu}$); 1.74 (s, 3 H, 4-Me); 2.32 (s, 3 H, 5-Me); 2.85 (m, 2 H, CH_2O); 3.77, 4.02 (both m, each 1 H, CH_2N); 6.48 (br.s, 2 H, NH_2); 10.73 (s, 1 H, NH) 0.88** (t, 3 H, Me_{Bu}, *J* = 8.0); 1.20—1.68 (m, 7 H, Me_{Et}, 2 $CH_{2\ Bu}$); 1.45 (s, 3 H, 4-Me); 2.50 (s, 3 H, 5-Me); 2.82 (m, 2 H, CH_2O); 3.88, 4.35 (both m, each 1 H, CH_2N); 6.62 (br.s, 2 H, NH_2); 11.20 (s, 1 H, NH)	3324, 3150, 1652, 1612, 1560, 1524
7	1.55 (s, 3 H, 4-Me); 2.35 (s, 3 H, 5-Me); 3.08 (s, 3 H, OMe); 6.64 (br.s, 2 H, NH_2); 7.14, 7.29 (both d, each 1 H, *o*-H_{Ph}, *J* = 8.0); 7.32—7.46 (m, 3 H, *m*-H_{Ph}, *p*-H_{Ph}); 11.25 (s, 1 H, NH)	3468, 3312, 3148, 1636, 1608, 1560, 1532
9	2.41 (s, 3 H, Me); 3.78, 4.47 (both d, each 1 H, CH_2=, *J* = 2.0); 6.61 (br.s, 2 H, NH_2); 7.25 (d, 2 H, *o*-H_{Ph}, *J* = 8.0); 7.42 (t, 1 H, *p*-H_{Ph}, *J* = 8.0); 7.51 (t, 2 H, *m*-H_{Ph}, *J* = 8.0) 10.44 (s, 1 H, NH)	3356, 3196, 1684 (C=O), 1660, 1644, 1620, 1600, 1548
10	1.83 (s, 3 H, 6-Me); 2.46 (s, 3 H, COMe); 7.32—7.62 (m, 5 H, Ph); 11.71 (s, 1 H, NH)	3176, 1728 (C=O); 1700 (C=O), 1652 (C=O), 1596 3380* (NH), 1724 (C=O), 1688 (C=O), 1576

* In $CHCl_3$.
** In C_6D_6.

give pyrimidopyrimidinone **9** and acetyluracil **10**, which are structurally related to compounds **3a** and **4a** (Scheme 4). The lower yields of compounds **9** and **10** are consistent with our previous observations: the alkylsulfanyl group in position 4 of pyrimidine-2-thiones is much more susceptible to nucleophilic substitution than that in related pyrimidin-2-ones. For instance, a reaction of compound **2a** with *N*-methylpiperazine in boiling toluene results in displacement of the methylsulfanyl group by this nucleophilic agent, while pyrimidin-2-one remains intact under the same conditions.

In contrast to the exocyclic methylidene group in thione **3a**, that in compound **9** proved to be very inert: even its prolonged (12 h) reflux with a twofold amount of MeONa in MeOH yields no adduct like compound **11**.

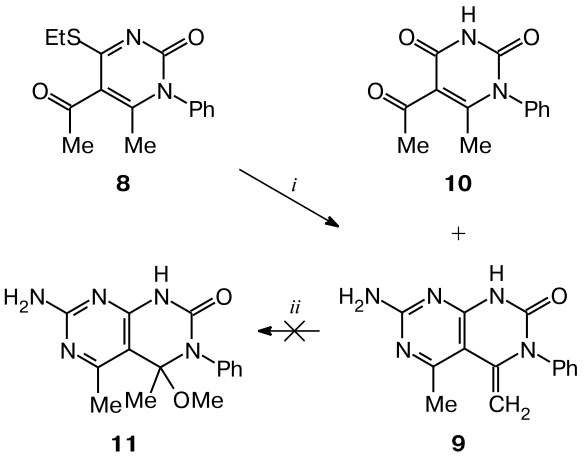
Unlike its analog **3a**, pyrimidopyrimidinone **9** is sparingly soluble in DMSO; in contrast, acetyluracil **10** is soluble in organic solvents better than acetylthiouracil **4a**. Structures **9** and **10** were confirmed by spectroscopic methods (see Tables 1 and 2).

Since 5-acetyl-2-thiouracils **4** and 5-acetyluracil **10** were synthesized from 4-alkylsulfanylpyrimidin(ethi)ones **2** and **8** in the presence of the strong base guanidine, we assumed that the use of another base instead of guanidine could make this reaction pathway predominant.

Indeed, it turned out that reactions of compounds **2a**,**c** and **8** with EtONa in boiling 96% EtOH afford acetylthiouracils **4a**,**c** in 81 and 86% yields and acetyluracil **10** in 39% yield (Scheme 5).

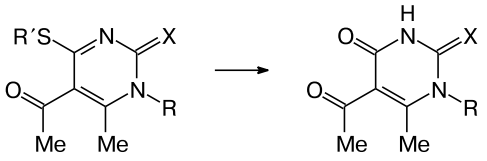
Earlier, the synthesis of 5-acetyluracils from diketene and urethan followed by treatment of intermediate *N*-acetoacet-

Scheme 4



Reagents and conditions: *i*. 1) $(NH_2)_2C{=}NH \cdot AcOH$, MeONa, Bu^nOH, Δ; 2) AcOH, 20 °C; *ii*. MeONa, MeOH, Δ.

Scheme 5



R = Ph (**2a**, **4a**, **8**, **10**), Et (**2c**, **4c**); R′ = Me (**2**), Et (**8**); X = S (**2**, **4**), O (**8**, **10**)

Reagents and conditions: EtONa, 96% EtOH, Δ.

ylurethan with ethyl orthoformate and amines has been reported.[14] 5-Acetyl-2-thiouracils have been obtained from amines and 5-acetyl-2-ethylsulfanyl-1,3-thiazin-4-one.[15] Here we proposed a simple alternative route to such compounds.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument (300 MHz) in DMSO-d_6 and C_6D_6. The residual proton signals of these deuterated solvents (δ 2.50 and 7.32, respectively) served as internal standards. ^{13}C NMR and 2D correlation spectra (^{1}H—^{13}C HSQC and HMBC) were recorded on a Bruker Avance 600 instrument (600 (^{1}H) and 150 MHz (^{13}C)) with reference to multiplet signals of DMSO-d_6 (δ_C 39.50). The signals in the ^{1}H and ^{13}C NMR spectra were assigned using 2D correlation experiments (^{1}H—^{13}C HSQC and HMBC). IR spectra were recorded on a Specord-M 82 instrument. Mass spectra were measured on a Kratos MS-30 instrument (EI, 70 eV, ion source temperature 250 °C, direct inlet probe).

Commercial isothiocyanates (Acros) were used. 5-Acetyl-6-methyl-4-methylsulfanyl-1-phenylpyrimidine-2(1*H*)-thione (**2a**)[10] and 5-acetyl-4-ethylsulfanyl-6-methyl-1-phenylpyrimidin-2(1*H*)-one (**8**)[8] were prepared according to known procedures.

5-Acetyl-1-(2,5-dimethylphenyl)-6-methyl-4-methylsulfanylpyrimidine-2(1*H*)-thione (2b). A mixture of diacetylketene N,S-acetal **1** (1.0 g, 5.78 mmol) and 2,5-dimethylphenyl isothiocyanate (1.88 g, 11.56 mmol) in toluene (10 mL) was refluxed for 7 h and cooled to 20 °C. Then light petroleum (6 mL) was added, and the precipitate that formed was filtered off and recrystallized from EtOH (5 mL). Yield 0.61 g (33%), m.p. 169—170 °C. Found (%): C, 60.39; H, 6.00; N, 8.68; S, 19.98. $C_{16}H_{18}N_2OS_2$. Calculated (%): C, 60.35; H, 5.70; N, 8.80; S, 20.14. IR (KBr), ν/cm^{-1}: 1700 (C=O); 1584, 1572, 1560, 1508. ^{1}H NMR (DMSO-d_6), δ: 1.85 (s, 3 H, 6-Me); 2.01, 2.32 (both s, 3 H each, 2 Me); 2.57 (s, 6 H, COMe, SMe); 7.06 (s, 1 H, *o*-$H_{C_6H_3}$); 7.20, 7.30 (both d, 1 H each, *m*-$H_{C_6H_3}$, *p*-$H_{C_6H_3}$, J = 8.0 Hz).

5-Acetyl-1-ethyl-6-methyl-4-methylsulfanylpyrimidine-2(1*H*)-thione (2c). A mixture of diacetylketene N,S-acetal **1** (1.6 g, 9.2 mmol) and ethyl isothiocyanate (1.6 mL, 18.4 mmol) in toluene (10 mL) was refluxed for 6 h and cooled to 20 °C. The precipitate that formed was filtered off and washed with light petroleum. Yield 1.28 g (57%), m.p. 176—177 °C. Found (%): C, 49.58; H, 6.03; N, 11.49; S, 26.44. $C_{10}H_{14}N_2OS_2$. Calculated (%): C, 49.56; H, 5.82; N, 11.56; S, 26.46. IR (KBr), ν/cm^{-1}: 1700 (C=O); 1580. ^{1}H NMR (DMSO-d_6), δ: 1.32 (t, 3 H, MeCH$_2$, J = 8.0 Hz); 2.41 (s, 3 H, Me); 2.50 (s, 3 H, Me); 2.53 (s, 3 H, Me); 4.58 (q, 2 H, CH_2, J = 8.0 Hz).

7-Amino-5-methyl-4-methylidene-3-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thione (3a). *n*-Butanol (5 mL), guanidine acetate (0.185 g, 1.55 mmol), and pyrimidinethione **2a** (0.3 g, 1.03 mmol) were added to MeONa (1.7 mmol) subsequent to removal of MeOH *in vacuo*. The reaction mixture was refluxed for 2 h. The solvent was removed *in vacuo*. Acetonitrile (3 mL), water (10 mL), and AcOH (0.5 mL) were added to the residue. The resulting mixture was stirred for 10 min. The precipitate that formed was filtered off, washed with water (20 mL), dried, and heated to boiling in MeCN (10 mL). On cooling to 20 °C, the precipitate of compound **3a** was filtered off. Yield 0.134 g (46%), m.p. 303—305 °C. The elemental analysis data and mass spectrum of compound **3a** are given in Table 1. The ^{1}H NMR and IR spectra are given in Table 2. ^{13}C NMR (DMSO-d_6), δ: 24.7 (Me); 95.9 (CH_2=); 100.4 (C(4a)); 128.0, 129.3, 129.5, 141.5 (Ph); 140.0 (C(4)); 153.4, 161.6 (C(7), C(8a)); 164.6 (C(5)); 176.0 (C(2)). The acetonitrile filtrate was concentrated. Recrystallization of the residue from benzene (6 mL) gave 5-acetyl-6-methyl-1-phenyl-2-thiouracil (**4a**) (0.042 g, 16%), m.p. 264—265 °C. Its elemental analysis data and spectral characteristics are given in Tables 1 and 2.

7-Amino-3-(2,5-dimethylphenyl)-5-methyl-4-methylidene-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thione (3b) was obtained from pyrimidinethione **2b** (0.182 g, 0.57 mmol), guanidine acetate (0.088 g, 0.74 mmol), and MeONa in Bu^nOH as described for compound **3a**. Compound **3b** was separated from thiouracil **4b** by treatment with boiling benzene (10 mL). Yield 0.064 g (36%), m.p. 303—305 °C (see Tables 1 and 2). 5-Acetyl-1-(2,5-dimethylphenyl)-6-methyl-2-thiouracil (**4b**) was isolated from the benzene filtrate by column chromatography on SiO_2 with $CHCl_3$—EtOH (100 : 1) as an eluent. Yield 0.020 g (12%), m.p. 214—215 °C (see Tables 1 and 2).

7-Amino-3-ethyl-5-methyl-4-methylidene-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thione (3c). *tert*-Butanol (5 mL), guanidine acetate (0.295 g, 2.47 mmol), and pyrimidinethione **2c** (0.3 g, 1.23 mmol) were added to MeONa (2.7 mmol) subsequent to removal of MeOH *in vacuo*. The reaction mixture was refluxed for 1 h. The solvent was removed *in vacuo*. Acetonitrile

(4 mL), water (10 mL), and AcOH (0.4 mL) were added to the residue. The resulting mixture was stirred for 10 min. The precipitate that formed was filtered off, washed with water, dried, and heated to boiling in MeCN (5 mL). On cooling to 20 °C, the precipitate of compound **3c** was filtered off. Yield 0.086 g (33%), m.p. 272—273 °C (see Tables 1 and 2). Organic matter from the combined filtrates was extracted with $CHCl_3$ (2×30 mL). The extracts were concentrated *in vacuo*. The residue was washed with light petroleum. The yield of 5-acetyl-1-ethyl-6-methyl-2-thiouracil (**4c**) was 0.13 g (50%), m.p. 214—215 °C (see Tables 1 and 2).

7-Amino-4-butoxy-3-ethyl-4,5-dimethyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thione (6c). *n*-Butanol (5 mL), guanidine acetate (0.19 g, 1.6 mmol), and pyrimidinethione **2c** (0.3 g, 1.2 mmol) were added to MeONa (1.76 mmol) subsequent to removal of MeOH *in vacuo*. The reaction mixture was refluxed for 1 h. The solvent was removed *in vacuo*. Acetonitrile (3 mL), water (20 mL), and AcOH (0.4 mL) were added to the residue. The resulting mixture was stirred at 20 °C for 10 min. The precipitate that formed was filtered off, washed with water, dried, and heated to boiling in benzene (10 mL). On cooling to 20 °C, the precipitate that formed was filtered off and heated to boiling in MeCN (5 mL). On cooling to 20 °C, the precipitate of pyrimidopyrimidinethione **3c** was filtered off. Yield 0.062 g (21%), m.p. 272—273 °C. The elemental analysis data and mass spectrum of compound **3c** are given in Table 1. The ^{1}H NMR and IR spectra are given in Table 2. The benzene filtrate was concentrated *in vacuo*. The residue was washed with light petroleum (5 mL). The yield of compound **6c** was 0.113 g (30%), m.p. 186—187 °C (see Tables 1 and 2). The acetonitrile filtrate was concentrated *in vacuo*. The residue was washed with light petroleum to give thiouracil **4c** (0.070 g, 27%).

7-Amino-4-methoxy-4,5-dimethyl-3-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thione (7). A mixture of pyrimidopyrimidinethione **3a** (0.057 g, 0.2 mmol) and MeONa (0.4 mmol) in MeOH (6 mL) was refluxed for 6 h. On cooling to 20 °C, the precipitate that formed was filtered off. Yield 0.043 g (68%), m.p. 300—303 °C. ^{13}C NMR (DMSO-d_6), δ: 22.9 (5-Me); 29.8 (4-Me); 50.8 (OMe); 91.2 (C(4)); 99.8 (C(4a)); 127.6, 127.8, 128.2, 129.5, 132.3, 140.5 (Ph); 153.2, 162.6 (C(7), C(8a)); 167.0 (C(5)); 178.0 (C(2)). The elemental analysis data and other spectral characteristics of compound **7** are given in Tables 1 and 2.

7-Amino-5-methyl-4-methylidene-3-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (9). *n*-Butanol (5 mL), guanidine acetate (0.248 g, 2.08 mmol), and pyrimidinone **8** (0.3 g, 1.04 mmol) were added to MeONa (2.3 mmol) subsequent to removal of MeOH *in vacuo*. The reaction mixture was refluxed for 2 h. The solvent was removed *in vacuo*. Acetonitrile (3 mL), water (10 mL), and AcOH (0.4 mL) were added to the residue. The resulting mixture was stirred for 10 min. The precipitate of compound **9** was filtered off, washed with water, and dried. Yield 0.043 g (15%), m.p. 338—340 °C (see Tables 1 and 2). Organic matter from the filtrate was extracted with $CHCl_3$ (2×20 mL). The combined extracts were concentrated *in vacuo*. The residue was triturated with light petroleum and recrystallized from benzene (4 mL) to give 5-acetyl-6-methyl-1-phenyluracil **10**. Yield 0.067 g (26%), m.p. 192—193 °C (see Tables 1 and 2).

5-Acetyl-6-methyl-1-phenyl-2-thiouracil (4a). A mixture of pyrimidinethione **2a** (0.2 g, 0.69 mmol) and EtONa (0.76 mmol) in 96% EtOH (10 mL) was refluxed for 1 h. The solvent was removed *in vacuo*. Water (10 mL) and AcOH (0.4 mL) were added to the residue. The precipitate that formed was filtered off and washed with water. The yield of compound **4a** was 0.145 g (81%), m.p. 264—265 °C (from benzene). The product is identical in spectral characteristics with compound **4a** obtained from pyrimidinethione **2a** and guanidine.

5-Acetyl-1-ethyl-6-methyl-2-thiouracil (4c) was obtained from pyrimidinethione **2c** and EtONa in EtOH as described above for compound **4a**. Yield 86%, m.p. 214—215 °C.

5-Acetyl-6-methyl-1-phenyluracil (10). A mixture of pyrimidinone **8** (0.2 g, 0.69 mmol) and EtONa (0.83 mmol) in 96% EtOH (10 mL) was refluxed for 2 h and cooled to 20 °C. Acetic acid (0.4 mL) was added, and the mixture was concentrated *in vacuo*. The residue was diluted with water (10 mL), and the product was extracted with $CHCl_3$ (2×10 mL). The combined organic extracts were concentrated *in vacuo*. The residue was dissolved in benzene (2 mL), whereupon light petroleum (4 mL) was added. The precipitate that formed was filtered off. The yield of compound **10** was 0.066 g (39%), m.p. 193—194 °C. The product is identical in spectral characteristics with compound **10** obtained from pyrimidinone **8** and guanidine.

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