Reaction of 6-Methyl-2-Thiouracil and 6-Phenyl-2-Thiouracil with Chloro-β-Dicarbonyl and Bromo-β-Dicarbonyl Compounds and Their Nitrile Analogs

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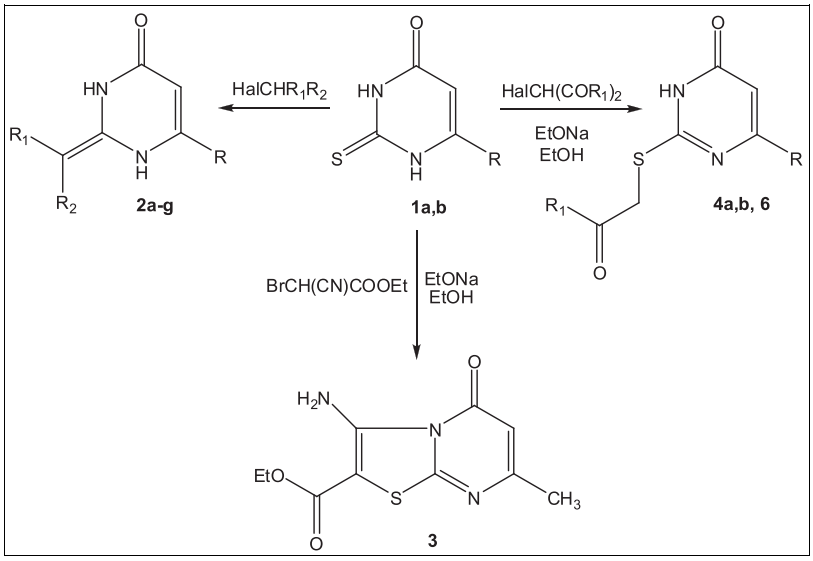

Derivatives of 2-methylidene-1,3-dihydropyrimidin-4-ones **2a-g** were synthesized by interaction of 6-methyl-2-thiouracil and 6-phenyl-2-thiouracil **1a,b** with some activated halogenides: diethyl bromomalonate, ethyl 2-chloro-3-oxobutanoate, ethyl 2-bromocyanoacetate, 2-bromo-5,5-dimethylcyclohexan-1,3-dione, and bromomalononitrile. The boiling of **1a** with ethyl 2-bromocyanoacetate in mixture of ethanol and EtONa results in intramolecular cyclization and formation of thiazolo[3,2-*a*]pyrimidin-5-one **3**. Interaction of **1a** with 3-chloropentane-2,4-dione and 2-bromo-1,3-diphenylpropane-1,3-dione yielded corresponding S-substituted thiopyrimidines **4a**,**b**. In general, the products of **1b** S-alkylation are less prone to sulfur extrusion. Reaction of **1b** with diethyl bromomalonate in the absence of EtONa stops at the S-alkylation step, while in the presence of EtONa in ethanol or PPh_3 in dioxane 2-(ethoxycarbonylmethyl)thio-6-phenyl-1,3-dihydropyrimidin-4(1H)-one **6** is formed exclusively. Molecular structure and crystal structure of 2-(1,1-diethoxycarbonylmethyliden)-6-methyl-1,3-dihydropyrimidin-4(1H)-one **2a** are discussed.

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INTRODUCTION

Because of the intensive growth of the number of different methods and successful search for available reagents to synthesize new functionalized pyrimidines, a huge amount of drugs based on pyrimidine derivatives with anti-inflammatory, antibacterial, antiviral, and antitumor activities have been developed in recent years [1,2]. In this regard, of particular interest are the pyrimidine derivatives bearing alkyl substituents with several electron withdrawing groups (e.g., carbonyl and nitrile) in position "2" of the cycle. Thus, the well-known method for preparing such compounds is cyclization of diaminomethylidene derivatives of dibenzoylmethane or acetoacetic ester by aroylketenes [3].

The present work aimed to search conditions for the C–C bond formation in position "2" of the pyrimidine ring by Eschenmoser reaction of "sulfide contraction" that in generally results in sulfur elimination from α-azomethine-β-oxoalkylsulfides [4]. This method has found application in synthesis of some natural substances and heterocyclic compounds, including preparation of 2-(2-oxo-2-arylethyliden)-1,3-dihydropyrimidin-4(1H)-ones from 2-phenacylthiouracils [5–7]. The required condition for the reaction of "sulfide contraction" is the ability of starting compounds to form the episulfide intermediate, whose desulfurization is facilitated by the high temperature in the presence of base or trivalent phosphorous compounds [4–7].

RESULTS AND DISCUSSION

The interaction of 6-methyl-2-thiouracil **1a** with diethyl bromomalonate resulted in the corresponding 2-methylidene-1,3-dihydropyrimidin-4-one **2a** in one step (Scheme 1). The reaction was carried out by refluxing of equimolecular amounts of reactants in ethanol in the presence of sodium ethylate. Under similar conditions, pyrimidine derivatives **2b,c** were obtained from reaction of **1a** with 3-oxo-2-chlorobutyrate and/or 2-bromodimedone, respectively. Depending on the absence or presence of a base, reaction of 2-thiouracils **1a,b** with the nitrile containing bromides can occur in two pathways. First, 2-methylidene-pyrimidines **2d-g** containing nitrile groups were obtained by continuous boiling of thiouracils **1a,b** with ethyl 2-bromocyanoacetate or bromomalononitrile in ethanol (Scheme 1) in the absence of sodium ethoxide.

The other pathway, boiling of the thiouracil **1a** with ethyl 2-bromocyanoacetate in the mixture of ethanol and sodium ethoxide, facilitates intramolecular cyclization that affords thiazolo[3,2-*a*]pyrimidin-5-one **3** (Scheme 2).

At the same time, reaction of thiouracil **1a** with 3-chloropentane-2,4-dione and 2-bromo-1,3-diphenylpropane-1,3-dione yielded pyrimidine **4a,b** (Scheme 3).

The similar splitting of one of the C–C bonds has been found previously in alkylation of 2-mercapto-3-ureidopyridines and 5-amino-6-mercaptopyrimidines by symmetric and asymmetric halo-β-diketones [8,9].

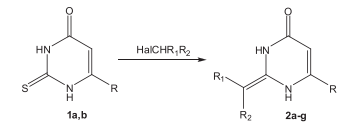
In general, the products of thiouracil **1b** S-alkylation are less prone to sulfur extrusion. Reaction of thiouracil **1b** with diethyl bromomalonate (Scheme 4) in the absence of sodium ethoxide stops at the alkylation step (compound **5**), while in the presence of base (sodium ethoxide in ethanol or triphenylphosphine in dioxane) 2-(1-ethoxycarbonylmethyl)thio-6-phenyl-1,3-dihydropy rimidin-4(1H)-one **6** is formed exclusively (Scheme 4).

Structures of novel compounds have been confirmed by their spectra (MS, ^{1}H NMR) together with the elemental analyses. The mass spectra for compounds **2a-g** reveal intense peaks of molecular ions whose fragmentation corresponds to the expected structures. The resulting pyrimidines **2a-g** formed due to sulfur extrusion can exist in two prototropic isomeric forms, enamine **ea**, and iminoalkyl **ia** ones (Scheme 5).

The availability of two proton signals associated with the amide and amine groups in the absence of the methine proton signal of exocyclic methine group in the ^{1}H NMR spectra of pyrimidines **2a-g** allow assigning them the **ea** structure. The single crystal X-ray structure of 2-(1,1-diethoxycarbonylmethyliden)-6-methyl-1,3-dihydropyrimidin-4(1H)-one **2a** indicates in favor of the **ea** form that is stabilized by two intramolecular NH···O=C hydrogen bonds, N(1)-H(1N)···O(2) 1.73(3), 2.546(3) Å, ∠ NHO = 140(3)°, and N(2)-H(2N)···O(4) 1.78(3), 2.553(3) Å; ∠NHO = 138(2)° (Fig. 1). Compound **2a** crystallizes in the monoclinic crystal system with $P2_1/c$ space group. The single molecule occupies general position in the asymmetric unit. The principle bond distances and angles are summarized in Table 1. Molecule **2a** is almost flat that is indicated by the deviation of non-hydrogen atoms from the mean plane of the molecule skeleton not exceeding 0.071 Å. The two aforementioned intramolecular NH···O hydrogen bonds additionally stabilize the planar skeleton.

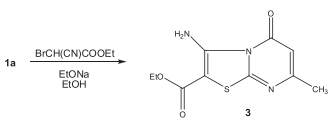
In the crystal, the molecules are linked by the system of weak hydrogen bonds. At the same time, the dimers typical for uracil and thiouracil derivatives [10–12], which are usually formed because of two centrosymmetric NH···O

Scheme 1. Synthesis of 2-methylidene-1,3-dihydropyrimidin-4-one derivatives **2**.

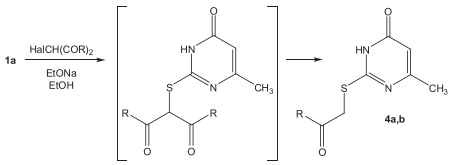


2a R=CH$_3$, R$_1$=R$_2$=CO$_2$C$_2$H$_5$; **2b** R=CH$_3$, R$_1$=COCH$_3$, R$_2$=CO$_2$C$_2$H$_5$;
2c R=CH$_3$, R$_1$R$_2$=COCH$_2$C(CH$_3$)$_2$CH$_2$CO; **2d** R=CH$_3$, R$_1$=CN, R$_2$=CO$_2$C$_2$H$_5$;
2e R=Ph, R$_1$=CN, R$_2$=CO$_2$C$_2$H$_5$; **2f** R=CH$_3$, R$_1$=R$_2$=CN; **2g** R=Ph, R$_1$=R$_2$=CN

Scheme 2. Reaction of **1a** with ethyl 2-bromocyanoacetate in the presence of sodium ethoxide.

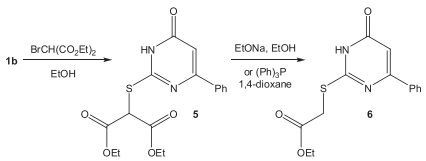


Scheme 3. Reaction of **1a** with halo-β-diketones.

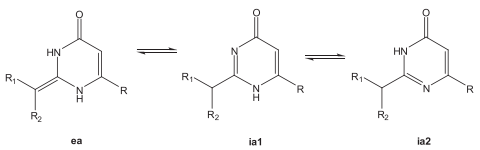


a R=CH$_3$; **b** R=Ph

Scheme 4. Synthesis and splitting of **5**.



Scheme 5. Prototropic isomeric forms of pyrimidines **2a-g**.



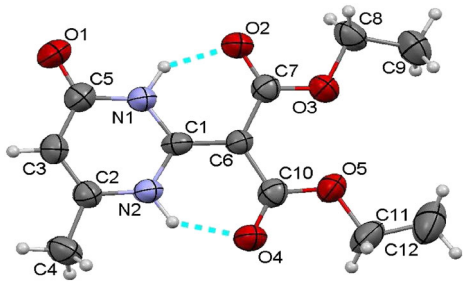


Figure 1. Molecular structure of 2-(1,1-diethoxycarbonylmethyliden)-6-methyl-1,3-dihydropyrimidin-4(1H)-one (**2a**). Thermal ellipsoids are shown with 50% probability level. Dashed lines show hydrogen bonds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Bond lengths (Å) and angles (deg) in compound **2a**.

O(1)-C(5)	1.216(4)	N(2)-C(2)	1.377(4)
O(2)-C(7)	1.227(4)	C(1)-C(6)	1.409(4)
O(3)-C(7)	1.328(4)	C(2)-C(3)	1.333(4)
O(3)-C(8)	1.450(4)	C(2)-C(4)	1.491(6)
O(4)-C(10)	1.229(5)	C(3)-C(5)	1.428(6)
O(5)-C(10)	1.328(4)	C(6)-C(7)	1.461(5)
O(5)-C(11)	1.444(4)	C(6)-C(10)	1.451(4)
N(1)-C(1)	1.344(4)	C(8)-C(9)	1.496(4)
N(1)-C(5)	1.397(4)	C(11)-C(12)	1.492(5)
N(2)-C(1)	1.352(4)		
C(7)-O(3)-C(8)	116.5(2)	O(1)-C(5)-N(1)	119.1(3)
C(10)-O(5)-C(11)	117.3(2)	O(1)-C(5)-C(3)	126.9(3)
C(1)-N(1)-C(5)	126.7(3)	N(1)-C(5)-C(3)	114.0(3)
C(1)-N(2)-C(2)	123.9(3)	C(1)-C(6)-C(7)	116.8(3)
N(1)-C(1)-N(2)	114.8(3)	C(1)-C(6)-C(10)	118.1(3)
N(1)-C(1)-C(6)	123.2(3)	C(7)-C(6)-C(10)	125.0(3)
N(2)-C(1)-C(6)	122.0(3)	O(2)-C(7)-O(3)	120.1(3)
N(2)-C(2)-C(3)	119.6(3)	O(2)-C(7)-C(6)	124.4(3)
N(2)-C(2)-C(4)	115.3(3)	O(3)-C(7)-C(6)	115.5(3)
C(3)-C(2)-C(4)	125.1(3)	O(3)-C(8)-C(9)	105.8(2)
C(2)-C(3)-C(5)	120.9(3)		

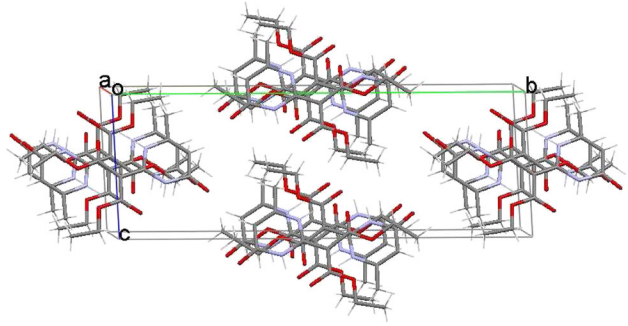


Figure 2. Crystal packing in **2a** with stacks along the crystallographic *a* direction**.** [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

hydrogen bonds are absent in **2a** (Fig. 2), which is obviously explained by the preference of intramolecular interactions. Instead, the molecules are packed in the antiparallel stacks along the crystallographic *a* direction with big overlapping areas and interplanar separation of 3.458 Å.

CONCLUSION

Thus, we developed an efficient method for synthesis of 2-methylidene-1,3-dihydropyrimidin-4-one derivatives from corresponding 2-thiouracils. Depending on the absence or presence of a base, reaction of studied 2-thiouracils with ethyl 2-bromocyanoacetate or bromomalononitrile can occur in two synthetic pathways. In general, the products of 6-phenylthiouracil S-alkylation are less prone to sulfur extrusion.

EXPERIMENTAL

The TLC analysis was carried out on the Silufol UV-254-VIS plates using chloroform-acetonitrile 5:1 and 1:1 systems. Mass spectra were obtained on a mass-spectrometer MX-1321 using the direct sample introduction system with ionizing radiation energy electrons of 70 eV and ion source temperature 220°C. ^{1}H NMR spectra were recorded on a Varian WXP-300 spectrometer with working frequency 299.95 MHz in DMSO-d_6; chemical shifts were measured relative to TMS as internal standard.

2-(1,1-Diethoxycarbonylmethylidene)-6-methyl-1,3-dihydropyrimidin-4(1H)-one (2a). To a solution of sodium ethoxide obtained by dissolving sodium (0.23 g, 0.01 mol) in anhydrous ethanol (250 mL), 6-methyl-2-thiouracil (**1a**) [13] (1.42 g, 0.01 mol) was added with stirring. The mixture was stirred at 18–20°C for 30 min, and a solution of diethyl bromomalonate [14] (2.39 g, 0.01 mol) in anhydrous ethanol (50 mL) was added slowly. The resulting mixture was kept at room temperature for 30 min and refluxed for 4–6 h. The reaction mixture evaporated in a rotary evaporator under water pump vacuum. The residue washed with cold water and crystallized from ethanol as white crystals, 1.53 g (57%), mp 139–140°C; ^{1}H NMR δ12.62 (s, 1H, NH), 12.55 (s, 1H, NH), 5.79 (s, 1H, CH pyrimid.), 4.16 (q, J = 6.0 Hz, 4H, CH_2 ester), 2.26 (s, 3H, CH_3 pyrimid.), 1.25 (t, J = 6.0 Hz, 6H, CH_3 ester); MS *m/z* (%) 268 (M^+, 72), 222 (100), 196 (45), 177 (24), 124 (46), 109 (11). *Anal.* Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44%. Found: C, 53.71; H, 6.03; N, 10.43%.

2-(1-Acetyl-1-ethoxycarbonylmethylidene)-6-methyl-1,3-dihydropyrimidin-4(1H)-one (2b) was synthesized similar to **2a** from **1a** (1.42 g, 0.01 mol) and ethyl 2-chloro-3-oxobutanoate [15] (1.64 g, 0.01 mol). White crystals (ethanol), 1.5 g (63%), mp 121–122°C; ^{1}H NMR δ 13.84 (br. s, 1H, NH), 13.39 (br. s, 1H, NH), 5.92 (s, 1H, CH pyrimid.), 4.24 (q, J = 7.5 Hz, 2H, CH_2 ester), 2.42 (s, 3H, CH_3CO), 2.27 (s, 3H, CH_3 pyrimid.), 1.30 (t, J = 7.5 Hz, 3H, CH_3 ester); MS *m/z* (%) 238 (M^+, 100), 228(14), 223 (43), 195(6), 193(17), 192(23), 182(10),

177(57), 166(25). *Anal.* Calcd. for $C_{13}H_{16}N_2O_3$: C, 55.46; H, 5.92; N, 11.76%. Found: C, 55.44; H, 5.90; N, 11.74%.

2-(4,4-Dimethyl-2,6-dioxocyclohexylidene)-6-methyl-1,3-dihydropyrimidin-4(1H)-one (2c) was synthesized similar to **2a** from **1a** (1.42 g, 0.01 mmol) and 2-bromo-5,5-dimethylcyclohexan-1,3-dione [16] (2.19 g, 0.01 mmol). White solid (ethanol), 1.42 g (57%), mp 186°C; ^{1}H NMR δ14.16 (br. s, 1H, NH), 13.84 (br. s, 1H, NH), 6.03 (s, 1H, CH pyrimid.), 6.41 (s, 4H, CH_2), 2.30 (s, 3H, CH_3 pyrimid.), 1.00 (s, 6H, CH_3); MS *m/z* (%) 248 (M^+, 100), 233(5), 220 (10), 205(6), 192(9), 179(8), 164(27), 151(74). *Anal.* Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28%. Found: C, 62.81; H, 6.57; N, 11.21%.

2-(1-Cyano-1-ethoxycarbonylmethylidene)-6-methyl-1,3-dihydropyrimidin-4(1H)-one (2d). To a solution of 6-methyl-2-thiouracil (**1a**) (1.42 g, 0.01 mol) in anhydrous ethanol (250 mL), a solution of ethyl 2-bromocyanoacetate [14] (1.92 g, 0.01 mol) in anhydrous ethanol (50 mL) was added slowly under stirring at 18–20°C. The resulting mixture kept at room temperature for 30 min and refluxed for 8 h. The reaction mixture evaporated in a rotary evaporator underwater pump vacuum. The residue washed with cold water and crystallized from ethanol as white needles, 0.99 g (45%), mp 247–248°C; ^{1}H NMR δ11.97 (br. s, 1H, NH), 11.96 (br. s, 1H, NH), 5.77 (s, 1H, CH pyrimid.), 4.18 (q, J = 7.5 Hz, 2H, CH_2 ester), 2.22 s (3H, CH_3 pyrimid.), 1.24 (t, J = 7.5 Hz, 3H, CH_3 ester); MS *m/z* (%) 221(M^+, 100), 193(21), 175(80), 149(44). *Anal.* Calcd. for $C_{13}H_{16}N_2O_3$: C, 54.30; H, 5.01; N, 18.99%. Found: C, 54.28; H, 4.99; N, 18.97%.

2-(1-Cyano-1-ethoxycarbonylmethylidene)-6-phenyl-1,3-dihydropyrimidin-4(1H)-one (2e). To a solution of 6-phenyl-2-thiouracil (**1b)** [17] (2.04 g, 0.01 mol) in anhydrous ethanol (250 mL) a solution of ethyl 2-bromocyanoacetate (1.92 g, 0.01 mol) in anhydrous ethanol (50 mL) was gradually added under stirring at 18–20°C. The resulting mixture kept at room temperature for 30 min and refluxed for 16 h. The reaction mixture evaporated in a rotary evaporator under water pump vacuum. The residue was washed with cold water and crystallized from acetonitrile as white needles, 1.36 g (48%), mp. 239–240°C; ^{1}H NMR δ 12.97 (br. s, 1H, NH), 11.98 (br. s, 1H, NH), 7.78–7.50 (m, 5H phenyl), 6.41 (s, 1H, CH pyrimid.), 4.22 (q, J = 7.5 Hz, 2H, CH_2 ester), 1.26 (t, J = 7.5 Hz, 3H, CH_3 ester); MS *m/z* (%) 283 (M^+, 100), 255(28), 237(85), 211(85), 186(30), 181(15), 172(13), 155(6), 148(10), 141(14),129(24), 117(15), 104(52), 93(10), 89(11), 77(34). *Anal.* Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83%. Found: C, 63.65; H, 4.62; N, 14.84%.

2-(1,1-Dicyanomethylidene)-6-methyl-1,3-dihydro pyrimidin-4(1H)-one (2f) was synthesized similar to **2d** from **1a** (1.42 g, 0.01 mol) and bromomalononitrile [18] (1.45 g, 0.01 mol). White solid (C_6H_6), 0.89 g (51%), mp 280°C subl.; ^{1}H NMR δ 11.80 (br. s, 2H, NH), 5.74 (s, 1H, CH pyrimid.), 2.20 (s, 3H, CH_3 pyrimid.); MS *m/z* (%) 174 (M^+, 100), 148(7), 146(13), 145(23), 120(5), 119 (10), 92(7), 83(6), 68(24), 67(30). *Anal.* Calcd. for $C_8H_6N_4O$: C, 55.17; H, 3.47; N, 32.17%. Found: C, 55.23; H, 3.46; N, 32.14%.

2-(1,1-Dicyalomethylidene)-6-phenyl-1,3-dihydropyrimidin-4(1H)-one (2g) was synthesized similar to **2e** from **1b** (2.04 g, 0.01 mol) and bromomalononitrile (1.45 g, 0.01 mol). White needles (C_6H_6), 1.1 g (46%), mp >300°C subl.; ^{1}H NMR δ 11.35 (br. s, 2H, NH), 7.69–7.55 (m, 5H phenyl), 6.12 (s, 1H, CH pyrimid.), 2.50 (s, 3H, CH_3 pyrimid.); MS *m/z* (%) 236 (M^+, 100), 210(20), 129(34), 117(12), 104(65), 89(7). *Anal.* Calcd. for $C_{13}H_8N_4O$: C, 66.10; H, 3.41; N, 23.72%. Found: C, 66.18; H, 3.40; N, 23.74%.

3-Amino-7-methyl-2-ethoxycarbonyl-thiazolo[3,2-a]pyrimidin-5-one (3). To a solution of sodium ethoxide obtained by dissolving sodium (0.23 g, 0.01 mol) in anhydrous ethanol (250 mL), 6-methyl-2-thiouracil (**1a)** (1.42 g, 0.01 mol) was added with stirring. The mixture was stirred at 18–20°C for 30 min, and a solution of ethyl bromocyanoacetate (1.92 g, 0.01 mol) in anhydrous ethanol (50 mL) was added slowly. The resulting mixture was kept at room temperature for 30 min and refluxed for 3 h. The reaction mixture was evaporated in a rotary evaporator under water pump vacuum. The residue was washed with cold water and crystallized from isopropyl alcohol as yellow needles, 1.52 g (60%), mp 134–135°C; ^{1}H NMR δ 8.13 (br. s, 2H, NH_2), 6.11 (s, 1H, CH pyrimidin.), 4.25 (q, J = 7.5 Hz, 2H, CH_2 ester), 2.23 (s, 3H, CH_3 pyrimid.), 1.27 (t, J = 7.5 Hz, 3H, CH_3 ester); ms *m/z* (%) 253 (M^+, 100), 225(15), 207(14), 181(12), 154(15), 142(5), 121(7), 109(45). *Anal.* Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.42; H, 4.38; N, 16.59%. Found: C, 47.38; H, 4.36; N, 16.57%.

6-Methyl-2-[(2-oxopropyl)thio]pyrimidin-4(3H)-one (4a). To a solution of sodium ethoxide obtained by dissolving sodium (0.23 g, 0.01 mol) in anhydrous ethanol (250 mL), 6-methyl-2-thiouracil (**1a**) (1.42 g, 0.01 mol) was added with stirring. The mixture was stirred at 18–20°C for 30 min, and a solution of 3-chloropentane-2,4-dione [19] (1.34 g, 0.01 mol) in anhydrous ethanol (50 mL) was added slowly. The resulting mixture was kept at room temperature for 30 min and refluxed for 3 h. The reaction mixture was evaporated in a rotary evaporator underwater pump vacuum. The residue was washed with cold water and recrystallized from isopropyl alcohol as white solid, 1.15 g (58%), mp 97–98°C (lit. 97°C [20]); ^{1}H NMR δ 12.52 (br. s, 1H, NH), 5.92 (s, 1H, CH pyrimid.), 4.05 (s, 2H, CH_2S), 2.10 (s, 3H, CH_3CO), 1.91 (s, 3H, CH_3 pyrimid.); MS *m/z* (%) 198 (M^+, 17), 156(30), 155(29), 127(5), 107(18), 109(26). *Anal.* Calcd. for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13%. Found: C, 48.45; H, 5.06; N, 14.11%.

6-Methyl-2-[(2-oxo-2-phenylethyl)thio]pyrimidin-4(3H)-one (4b) was synthesized similar to **4a** from 6-methyl-2-thiouracil (**1a)** (1.42 g, 0.01 mol) and 2-bromo-1,3-diphenylpropane-1,3-dione [21] (3.03 g, 0.01 mol). White solid (isopropyl alcohol), 1.23 g (47%), mp 175–176°C (lit. 179–181°C [5]); ^{1}H NMR δ 12.50 (br. s, 1H, NH), 7.98–7.54 (m, 5H phenyl), 5.95 (s, 1H, CH pyrimid.), 4.74 (s, 2H, CH_2S), 1.96 (s, 3H, CH_3 pyrimid.); MS *m/z* (%) 260 (M^+, 12), 227(5), 155(8), 134(8), 105 (100), 77(21). *Anal.* Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76%. Found: C, 59.96; H, 4.64; N, 10.75%.

2-(1,1-Diethoxycarbonylmethylene)thio-6-phenyl-1,3-dihydro-pyrimidin-4(1H)-one (5). To a solution of 6-phenyl-2-thiouracil (**1b)** (2.04 g, 0.01 mol) in anhydrous ethanol (250 mL), a solution of diethyl bromomalonate (2.39 g, 0.01 mol) in anhydrous ethanol (50 mL) was gradually added under stirring at 18–20°C. The resulting mixture was kept at room temperature for 30 min and refluxed for 16 h. The reaction mixture was evaporated in a rotary evaporator under water pump vacuum. The residue was washed with cold water and crystallized from acetonitrile as white needles, 2.32 g (64%), mp 184–186°C dec.; ms *m/z* (%) 362(M^+, 47), 316(43), 289 (88), 217(87), 204(100), 188(21), 171(77), 156(27), 146 (16), 129(47), 116(71), 103(96). *Anal.* Calcd. for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73%. Found: C, 56.40; H, 5.00; N, 7.74%.

2-(1-Ethoxycarbonylmethylene)thio-6-phenyl-1,3-dihydro pyrimidin-4(1H)-one (6). ***Method A:*** A mixture of 2-(1,1-diethoxycarbonylmethylene)thio-6-phenyl-1,3-dihydropyrimidin-4 (1H)-one (**5**) (1.81 g, 0.005 mol) and triphenylphosphine (1.31 g, 0.005 mol) in anhydrous 1,4-dioxane (250 mL) was refluxed for 6 h. The reaction mixture was evaporated in a rotary evaporator under water pump vacuum. The residue was washed with cold benzene and crystallized from ethanol as white needles, 0.83 g (57%).

Method B: To a solution of sodium ethoxide obtained by dissolving sodium (0.115 g, 0.005 mol) in anhydrous ethanol (100 mL) was added 2-(1,1-diethoxycarbonylmethylene) thio-6-phenyl-1,3-dihydropyrimidin-4 (1H)-one (**5**) (1.81 g, 0.005 mol) and refluxed for 24 h. The reaction mixture was evaporated in a rotary evaporator under water pump vacuum. The residue was washed with cold water and crystallized from ethanol as white needles, 0.9 g (62%), mp 226–227°C; ^{1}H NMR δ 12.81 (br. s, 1H, NH), 8.06–7.50 (m, 5H phenyl), 6.75 (s, 1H, CH pyrimidin.), 4.12 (s, 2H, SCH_2), 4.10 (q, J = 7.5 Hz, 2H, CH_2 ester), 1.18 (t, J = 7.53 Hz, 3H, CH_3 ester); MS *m/z* (%) 290 (M^+, 37), 244(26), 217(100), 204(12), 171(20), 158(8), 129(7), 116(12), 103(23). *Anal.* Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65%. Found: C, 57.98; H, 4.81; N, 9.66%.

Crystal structure determination of 2a. Single crystals of 2-(1,1-diethoxycarbonylmethyliden)-6-methyl-1,3-dihydro pyrimidin-4(1H)-one **(2a)** were grown by slow crystallization from ethanol solution. Intensity data were collected on a small crystal ($0.24 \times 0.08 \times 0.04$ mm^3) on an automatic four-circle CCD diffractometer «Xcalibur-III», MoKα-radiation, graphite monochromator, θ/2θ scan, $2\theta_{max} = 50.0°$. The crystal structure was solved by direct methods using SHELX97 program package [22]. Non-H atoms were first refined isotropically, followed by anisotropic refinement by full-matrix least squares calculation based on F^2 using SHELX97. N-bound H-atoms were found from the differential Fourier maps and refined freely in isotropic approximation. C-bound hydrogen atoms were positioned geometrically and allowed to ride on their respective parent atoms. Figures were generated using MERCURY [23]. **Crystal data.** Molecular formula $C_{12}H_{16}N_2O_5$, M = 268.27; monoclinic; a = 8.2162(15), b = 21.567(2), c = 8.992(3) Å; $\alpha = \gamma = 90°$, β = 122.232(15)°, V = 1347.8(5) Å^3; T = 293(2) K; space group $P2_1/c$ (no. 14); Z = 4; 4331 reflections measured, 2363 unique (R_{int} = 0.028), which were used in all calculations. Refinement as described earlier with 183 parameters gave GOF = 0.968 and final R indices R_1 = 0.0570 [$I > 2\sigma(I)$], wR_1 = 0. 0947 and R_2 = 0.1324, wR_2 = 0.1211 (all data). Selected bond lengths and bond angles are shown in Table 1. CCDC 1052298 contains the supplementary crystallographic data for **2a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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REFERENCES AND NOTES

[1] Jain, K. S.; Chitre, T. S.; Miniyar, P. B.; Kathiravan, M. K.; Bendre, V.; Veer, V.; Shahane, S.; Shishoo, C. Curr Sci 2006, 90, 793.

[2] Novikov, M. S.; Geisman, A. N. Chem Heterocycl Compd 2014, 49, 1426.

[3] Gein, V. L.; Pitirimova, S. G.; Vinokurova, O. V.; Andreichikov, Yu. S.; Komkov, A. V.; Bogdanov, V. S.; Dorokhov, V. A. Russ Chem Bull 1994, 43, 1398.

[4] Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. Helv Chim Acta 1971, 54, 710.

[5] Harst, D. T.; Beaumont, C.; Jones, D. T. E.; Kingsley, D. A.; Partridge, J. D.; Rutherford, T. J Austr J Chem 1988, 41, 1209.

[6] Shawali, A. S.; Farghaly, T. A. Tetrahedron 2004, 60, 3051.

[7] Yavolovskii, A. A.; Grishchuk, L. V.; Rakipov, I. M.; Ivanov, Yu. E.; Stepanov, D. E.; Kamalov, G. L. Russ J Gen Chem 2012, 82, 725.

[8] Safonova, T. S.; Mamaeva, I. E. Chem Heterocycl Compd 1973, 9, 108.

[9] Traven', N. I.; Safonova, T. S. Chem Heterocycl Compd 1980, 16, 607.

[10] Reck, G.; Kretschmer, R.-G.; Kutschabsky, L.; Pritzkow, W. Acta Crystallogr 1988, A44, 417.

[11] Leonidov, N. B.; Zorky, P. M.; Masunov, A. E.; Gladkikh, O. P.; Belsky, V. K.; Dzyabchenko, A. V.; Ivanov, S. A. Russ J Phys Chem 1993, 67, 199.

[12] Simonov, Yu. A.; Fonari, M. S.; Lipkowski, J.; Ganin, E. V.; Yavolovskii, A. A.; Kamalov, G. L. J Struct Chem 2009, 50, 136.

[13] Busev, A. I. Sintez novykh organicheskikh reagentov dlya neorganicheskogo analiza (Synthesis of New Organic Reagents for Inorganic Analysis); Moscow University Press: Moscow, 1972, pp 115–116.

[14] Palmer, C. S.; McWherter, P. W. In Organic Syntheses. An Annual Publication of Satisfactory Methods for the Preparation of Organic Chemicals; Whitmore, F. C., Ed.; J. Wiley & Sons: New York, 1927; Vol 7, pp 34–35.

[15] Boehme, W. R. In Organic Syntheses. An Annual Publication of Satisfactory Methods for the Preparation of Organic Chemicals; Price, C. C., Ed.; J. Wiley & Sons: New York, 1953; Vol 33, pp 43–46.

[16] Vorlander, D.; Kohlman, M. Lieb Ann 1902, 322, 248.

[17] Johnson, T. B.; Hemingway, E. H. J Am Chem Soc 1915, 37, 378. http://pubs.acs.org/doi/abs/10.1021/ja02271a014

[18] Ferris, J. P.; Orgel, L. E. J Org Chem 1965, 30, 2365.

[19] Verhe, R.; De Buyck, L.; De Kimpe, N.; De Rooze, A.; Schamp, N. Bull Soc Chim Belg 1978, 87, 143.

[20] Abdel-Fattah, A.-S. M.; Negm, A. M.; Gaafar, A. E. Phosphorus, Sulfur Silicon Relat Elem 1992, 72, 145.

[21] Krasnokutskaya, E. A.; Lesina, Yu. A.; Gorlushko, D. A.; Filimonov, V. D. Russ J Org Chem 2005, 41, 855.

[22] Sheldrick, G. M. Acta Crystallogr 2008, A64, 112.

[23] Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. J Appl Crystallogr 2006, 39, 453. DOI:10.1107/S002188980600731X.