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SHORT COMMUNICATIONS

Reaction of 5-Methyl-6-(2-thienylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one with α- and β-(Chloroalkyl) Sulfides

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In extension of our previous research on chemical reactions of 6-substituted derivatives of 2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one [1] and on targeted designing of highly active antiviral agents based thereon [2, 3] we investigated the reaction of 5-methyl-6-(2-thienylmethyl)-2-thioxo-2,3-dihydro-pyrimidin-4(1*H*)-one (**I**) with α- and β-(chloroalkyl) sulfide: (methylsulfanyl)(chloro)methane, 1-(methylsulfanyl)-2-chloroethane, and [(chloromethyl)sulfanyl]benzene **IIa–IIc**. In the first and the third compounds the preferable mechanism of the halogen substitution is unimolecular, whereas in the second one the bimolecular mechanism is more feasible related to the moderate synartetic effect of the methylsulfanyl group [4].

We selected the following systems and conditions for performing the reactions:

1. Method *a*: anhydrous DMF (the pyrimidine derivative plays the role of a neutral nucleophile surrounded by unstable solvate shell, the accumulation of HCl favors the S_N1 mechanism).

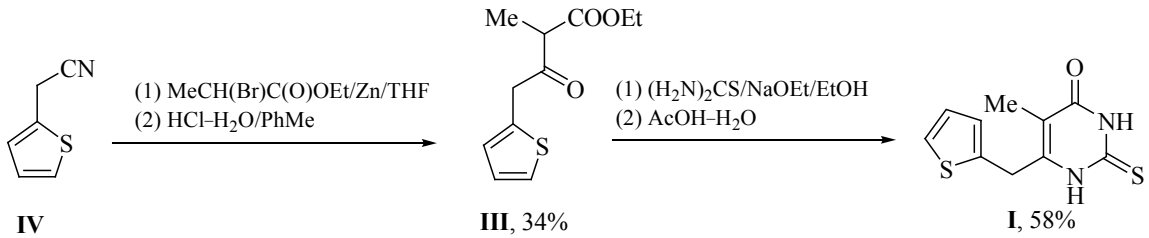
2. Method *b*: anhydrous DMF in the presence of K_2CO_3 (the pyrimidine derivative plays the role of a neutral nucleophile surrounded by unstable solvate shell, the binding of HCl favors the S_N2 mechanism).

3. Method *c*: anhydrous DMF in the presence of K_2CO_3 with preliminary heating (the pyrimidine derivative acts as a charged nucleophile , potassium salt, surrounded by unstable solvate shell, the binding of HCl favors the S_N2 mechanism).

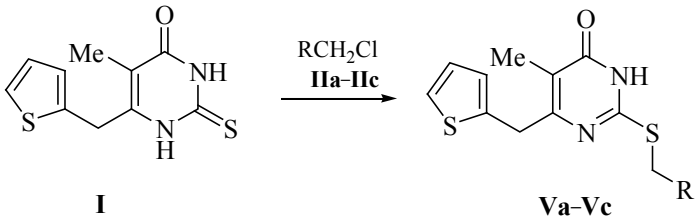
4. Method *d*: 95% EtOH in the presence of KOH (the pyrimidine derivative acts as a charged nucleophile, potassium salt, surrounded by stable solvate shell, the binding of HCl favors the S_N2 mechanism).

Initial reagent **I** was obtained by the condensation of ester **III** with thiourea in basic medium. 3-Oxo ester **III** was prepared by Blaise reaction from thiophen-2-acetonitrile (**IV**) by the procedure we had described [3].

The regioselectivity of the reaction between compound **I** and alkylating agents **IIa–IIc** was evaluated by the yield of the products of *S*-monoalkylation **Va–Vc** (see the table).



IV **III**, 34% **I**, 58%



I **Va–Vc**

R = MeS (**a**), $MeSCH_2$ (**b**), PhS (**c**).

Reagent **IIa** prone to the unimolecular halogen exchange in the polar solvent suffered a total solvolysis. We formerly discussed this phenomenon [5]. The reaction in aprotic solvent resulted in a fair yield of the target product.

With reagent **IIb** (method *d*) the process was of fairly high regioselectively, the application of methods *b* and *c* resulted in polyalkylation of pyrimidine derivative **I** and in the decrease in the yield of the target compound.

Reagent **IIc** like **IIa** in the syntheses along methods *a* and *b* exhibited materially the same regioselectivity. At the same time like with reagent **IIb** the reaction along method *c* provided lower yield of the target product. The synthesis by method *d* afforded the highest yield of the target product, unlike the case of compound **IIa**.

The reason of the observed phenomena cannot be attributed to the preferred occurrence of the halogen substitution by the unimolecular mechanism both in alkyl (chloromethyl) sulfides and their aromatic analogs [6]. Our results indicate that the negative resonance effect of the aromatic ring significantly distorts the stability of the (arylsulfanyl)methyl cation favoring to a greater extent the halogen exchange by the S_N2 mechanism.

Ethyl 2-methyl-3-oxo-4-(2-thienyl)-butanoate (III). To a mixture of 500 ml of anhydrous THF and 80 g (1.22 g-atom) of freshly cut zinc turnings was added 250 mg of $HgCl_2$ and 0.5 ml of ethyl 2-bromopropanoate, the mixture was heated at reflux under stirring and protection from moisture and CO_2 till the solution turned green. Then in one portion a solution was added of 25 ml (29 g, 0.24 mol) of reagent **IV** in 250 ml of anhydrous THF, and within 2 h was added dropwise 120 ml (~167 g, 0.92 mol) of ethyl 2- bromopropanoate, the mixture was heated at reflux for 30 min more. The organic solution was decanted from the zinc residues, the latter were washed with several portions of 50 ml of anhydrous THF. The combined organic solutions were evaporated in a vacuum, to the residue were added 500 ml of toluene and 600 ml of 12%-ной HCl, the reaction mixture was stirred for 2.5 h, the organic phase was washed with water till neutral reaction, filtered through a thin bed of silica gel of TLC grade, and dried with anhydrous $MgSO_4$. The solvent was removed under a reduced pressure, the residue was distilled in a vacuum and then it was subjected to vacuum fractionation on a Vigreux's column. The first fraction contained mainly ethyl 2-methyl-3-oxopentanoate. The collected target fraction had bp 128–131°C (2 mm Hg). Yield 18.5 g (34%). Found, %: C 58.30; H 6.24; S 13.99. $[M]^+$ 226. $C_{11}H_{14}O_3S$. Calculated, %: C 58.38; H 6.24; S 14.17. *M* 226.29.

5-Methyl-6-(2-thienylmethyl)-2-thioxo-2,3-dihydro-pyrimidin-4(1*H*)-one (I). A mixture of 300 ml of 20% solution of EtONa in EtOH (54.5 g, 801 mmol EtONa), 8.4 g (37 mmol) of compound **III**, and 28 g (368 mmol) of thiourea was boiled at stirring for 38 h under protection from moisture and CO_2. The solvent was removed under a reduced pressure, the residue was dissolved in 150 ml of water and neutralized with 50 ml of AcOH. The precipitate was separated and washed with water (3 × 50 ml), ether (2 × 50 ml), and dried. Yield 5.16 g (58%), mp 236–237.5°C (aqueous AcOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.79 s (3H, 5-CH_3), 3.95 s (2H, Th$C\underline{H}_2$), 6.90–6.93 m (2H, $H^{4,5}$ Th), 7.33–7.36 m (1H, H^3 Th), 12.28 s (1H, N^{1}H), 12.39 s

Methods of synthesis and yields of *S*-monoalkylation products

Alkylating agent	Method of synthesis	Yield of the product of *S*-monoalkylation, %
IIa (2 equiv)	*a*	84
IIa	*b*	68
IIa	*c*	51
IIa	*d*	0
IIb	*b*	31
IIb	*c*	25
IIb	*d*	58
IIc (2 equiv)	*a*	51
IIc	*b*	63
IIc	*c*	14
IIc	*d*	53

(1H, N^{3}H). Found, %: C 50.47; H 4.30; N 11.62; S 27.00. M^+ 238. $C_{23}H_{29}N_3O$. Calculated, %: C 50.40; H 4.23; N 11.75; S 26.91. *M* 238.33.

5-Methyl-6-(2-thienylmethyl)-2-{[(phenyl-sulfanyl) methyl]sulfanyl}pyrimidin-4(3*H*)-one (Vc). *a.* A mixture of 1 g (4.2 mmol) of reagent **I**, 1.08 ml (1.28 g, 8.1 mmol) of reagent **IIc**, and 10 ml of anhydrous DMF was stirred for 18 h at room temperature (TLC monitoring), the mixture was diluted with water, the precipitate was crystallized from MeCN. Yield 0.77 g (51%), mp 161–163°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.91 s (3H, 5-CH_3), 3.99 s (2H, ThC$\underline{H}_2$), 4.75 d (2H, SCH_2S, *J* 3.42 Hz), 6.86–6.90 m (2H, H^{4,5} Th), 7.15–7.21 m (1H, H^3 Th), 7.23–7.35 m (5H, Ph), 12.59 br.s (1H, N^{3}H). Found, %: C 56.70; H 4.49; N 7.81; S 26.58. $[M]^+$ 360. $C_{17}H_{16}N_2OS_3$. Calculated, %: C 56.64; H 4.47; N 7.77; S 26.68. *M* 360.52.

5-Methyl-2-{[(methylsulfanyl)methyl]sulfanyl}-6-(2-thienylmethyl)pyrimidin-4(3*H*)-one (Va). *b*. A mixture of 1 g (4.2 mmol) of reagent **I**, 0.4 ml (0.46 g, 4.8 mmol) of reagent **IIa**, 0.61 g (4.4 mmol) of K_2CO_3 and 10 ml of anhydrous DMF was stirred for 18 h at room temperature (TLC monitoring), the mixture was diluted with water and extracted with EtOAc. The organic solutions were combined, washed with brine, dried with anhydrous $MgSO_4$, and filtered through a thin bed of silica gel of TLC grade. The filtrate was concentrated at a reduced pressure; the residue was crystallized from cyclohexane. Yield 0.87 g (68%), mp 155–156°C. ^{1}H NMR spectrum NMR spectrum ($CDCl_3$), δ, ppm: 2.06 s (3H, 5-CH_3), 2.14 s (3H, SCH_3), 4.02 s (2H, ThC$\underline{H}_2$), 4.31 s (2H, SCH_2S), 6.80–6.90 m (2H, H^{4,5} Th), 7.08–7.13 m (1H, H^3 Th). Found, %: C 48.11; H 4.70; N 9.51; S 32.23. $[M]^+$ 298. $C_{12}H_{14}N_2OS_3$. Calculated, %: C 48.29; H 4.73; N 9.39; S 32.23. *M* 298.45.

c. Similarly to the procedure *b* a mixture of reagent **I**, K_2CO_3, and anhydrous DMF was stirred at heating to 90–100°C for 1 h, cooled, and the alkylating agent was added. Yield 51%.

5-Methyl-2-{[2-(methylsulfanyl)ethyl]sulfanyl}-6-(2-thienylmethyl)pyrimidin-4(3*H*)-one (Vb). *d*. A mixture of 1 g (4.2 mmol) of reagent **I** and a solution of 277 mg (4.2 mmol) of KOH in 20 ml of 95% EtOH was stirred for 1 h at room temperature, and afterwards 0.5 ml (0.56 g, 5.0 mmol) of compound **IIb** was added, the mixture was stirred for 1 h more and was left overnight. Then the reaction mixture was boiled at stirring till complete consumption of the initial compound (TLC monitoring of acidified probe), diluted with water and extracted with EtOAc (3 × 75 ml). The organic solutions were combined, washed with brine, dried with anhydrous $MgSO_4$, and filtered through a thin bed of silica gel of TLC grade. The filtrate was concentrated at a reduced pressure; the residue was crystallized from cyclohexane. Yield 0.76 g (58%), mp 147–148.5°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.06 s (3H, 5-CH_3), 2.09 s (3H, SCH_3), 2.71–2.76 m (2H, $CH_2C\underline{H}_2SCH_3$), 3.29–3.34 m (2H, $SC\underline{H}_2CH_2$), 4.00 s (2H, ThC$\underline{H}_2$), 6.81 d (1H, H^5, Th, *J* 3.42 Hz), 6.87 d.d (1H, H^4, Th, J_1 3.42, J_2 1.71 Hz), 7.10 d (1H, H^3 Th, *J* 5.13 Hz). Found, %: C 50.01; H 5.14; N 9.05; S 30.80. $[M]^+$ 312. $C_{13}H_{16}N_2OS_3$. Calculated, %: C 49.97; H 5.16; N 8.97; S 30.78. *M* 312.47.

^{1}H NMR spectra were registered on a spectrometer Varian-Mercury 300BB (300.73 MHz), internal reference HMDS. Melting points were measured on a Cole-Palmer instrument. TLC was carried out on ALUGRAM Nano-SIL G/UV_{254} plates, eluent hexane–EtOAc–MeOH, 12 : 3 : 1.

Commercial reagents used in the syntheses contained no less than 95% of the main substance. The purification and drying of solvents was performed by conventional procedures [7].

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