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Synthesis of 2-Alkyl(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones and 4-Alkyl(aralkyl)oxy-2-alkyl(aralkyl)sulfanyl-6-methylpyrimidines

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Abstract—2-Alkyl(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones and 4-alkyl(aralkyl)oxy-2-alkyl(aralkyl)-sulfanyl-6-methylpyrimidines having similar or different substituents on the sulfur and oxygen atoms were synthesized by alkylation of sodium salts derived from 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one and 2-alkyl(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones with alkyl (propyl, ethyl, allyl) and aralkyl [benzyl, *m*-phenoxybenzyl, *p*-(1-adamantylbenzyl)] halides. The effects of the alkyl (aralkyl) halide nature and solvent polarity on the rate of nucleophilic substitution and product yield were studied.

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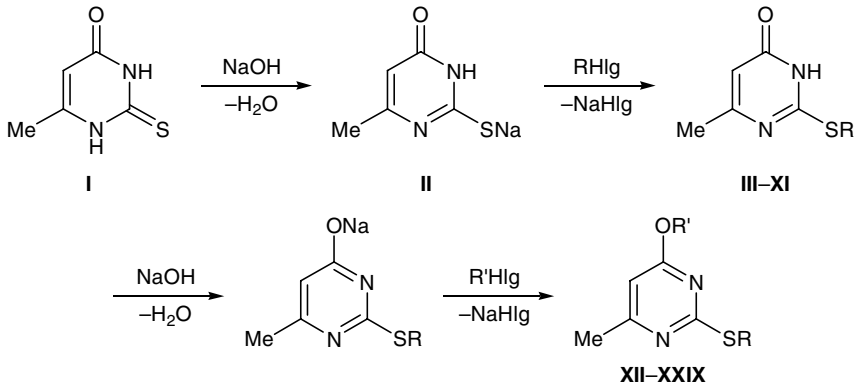
Derivatives of 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**I**, 6-methyl-2-thiouracil) are widely used as medical agents for the treatment of neurological disorders (Alzheimer's, Huntington's, and Parkinson's diseases), migraines, depressions, and memory impairments [1], as well as tranquilizers and related sedative agents [2]. Some derivatives of compound **I** inhibit the HIV-1 reverse transcriptase and exhibit a powerful inhibitory effect against HIV-1 *in vitro* [3–16].

No procedure has been developed so far for the selective preparation of 2-alkyl(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones and 4-alkyl(aralkyl)oxy-2-alkyl(aralkyl)sulfanyl-6-methylpyrimidines. 2-Alkyl-(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones are usually synthesized by reaction of compound **I** with halogen derivatives in the presence of potassium carbonate using DMF as solvent; the reaction takes fairly long time (6–8 h) at 75–80°C, and the yields range from 49 to 71% [7, 17–27]. 4-Alkyl(aralkyl)oxy-2-

Scheme 1.



III, R = $PhCH_2$; **IV**, R = *m*-$PhOC_6H_4CH_2$; **V**, R = *p*-(1-Ad)$C_6H_4CH_2$; **VI**, R = Pr; **VII**, R = Et; **VIII**, R = CH_2=$CHCH_2$; **IX**, R = *p*-$FSO_2C_6H_4CH_2$; **X**, R = *p*-$BrC_6H_4CH_2$; **XI**, R = *o*-$BrC_6H_4CH_2$; **XII**, R = R' = $PhCH_2$; **XIII**, R = R' = *m*-$PhOC_6H_4CH_2$; **XIV**, R = R' = *p*-(1-Ad)$C_6H_4CH_2$; **XV**, R = R' = CH_2=$CHCH_2$; **XVI**, R = R' = Pr; **XVII**, R = *p*-(1-Ad)$C_6H_4CH_2$, R' = Pr; **XVIII**, R = *p*-(1-Ad)$C_6H_4CH_2$, R' = CH_2=$CHCH_2$; **XIX**, R = *p*-(1-Ad)$C_6H_4CH_2$, R' = $PhCH_2$; **XX**, R = *p*-(1-Ad)$C_6H_4CH_2$, R' = *m*-$PhOC_6H_4CH_2$; **XXI**, R = $PhCH_2$, R' = CH_2=$CHCH_2$; **XXII**, R = $PhCH_2$, R' = Pr; **XXIII**, R = $PhCH_2$, R' = Et; **XXIV**, R = $PhCH_2$, R' = *m*-$PhOC_6H_4CH_2$; **XXV**, R = *m*-$PhOC_6H_4CH_2$, R' = CH_2=$CHCH_2$; **XXVI**, R = *m*-$PhOC_6H_4CH_2$, R' = $PhCH_2$; **XXVII**; R = *p*-$BrC_6H_4CH_2$, R' = Pr; **XXVIII**, R = *p*-$BrC_6H_4CH_2$, R' = Et; **XXIX**, R = *p*-$BrC_6H_4CH_2$, R' = CH_2=$CHCH_2$; Hlg = Cl, Br, I.

alkyl(aralkyl)sulfanyl-6-methylpyrimidines are obtained in poor yields by heating 2-R-sulfanyl-6-methylpyrimidin-4(3*H*)-ones for 6–8 h at 60–70°C in protic and aprotic solvents; these reactions often lead to formation of mixtures of products which are difficult to separate [28].

The goal of the present study was to develop a procedure for the selective synthesis of 2-alkyl(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones **III**–**XI** by reaction of sodium 6-methyl-4-oxo-3,4-dihydropyrimidine-2-thiolate (**II**) with the corresponding halogen derivatives. We also planned to use compounds **III**–**XI** thus obtained for the preparation of 4-alkyl(aralkyl)-oxy-2-alkyl(aralkyl)sulfanyl-6-methylpyrimidines **XII**–**XXIX**. In addition, we were aimed at elucidating the effects of the alkyl (aralkyl) halide nature and solvent polarity on the reaction rate and yield.

For the synthesis of compounds **III**–**XI** we used equimolar amounts of 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**I**) and sodium hydroxide. Treatment of compound **I** with aqueous sodium hydroxide led to the formation of water-soluble sodium salt **II**. The fact that salt **II** was formed via deprotonation of the N^1 atom was proved by the ^{1}H NMR data: no broadening of the downfield signal at δ 12.3 ppm was observed (such broadening is typical of derivatives having a proton on the N^1 atom). The resulting aqueous solution of salt **II** was diluted with dioxane, and a solution of the corresponding halogen derivative in dioxane was added. The mixture was kept for 15–30 min at 30–50°C, and poorly soluble products **III**–**XI** were filtered off. After recrystallization, the yield of 2-alkyl(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones was 72–99% (Scheme 1).

Compounds **III**–**XI** were then treated again with sodium hydroxide in aqueous dioxane to obtain the corresponding sodium salts. For example, 2-benzylsulfanyl-6-methylpyrimidin-4(3*H*)-one (**III**) was thus converted into water-soluble sodium 2-benzylsulfanyl-6-methylpyrimidin-4-olate. The ^{1}H NMR spectrum of that salt contained signals at δ 2.1 and 5.95 ppm, belonging to protons in the 6-methyl group and in position 5 of the heteroring, while no signal at δ 12.2 ppm, typical of N^3H, was present. The IR spectrum of the salt lacked NH and C=O absorption at 3100–3450 and 1712–1644 cm^{-1}, respectively. Sodium 2-benzylsulfanyl-6-methylpyrimidin-4-olate was treated with an equimolar amount of benzyl halide at 50°C for 60–90 min in aqueous dioxane, and 4-benzyloxy-2-benzylsulfanyl-6-methylpyrimidine (**XIII**) separated from the solution and was filtered off.

Table 1. Rate constants for the alkylation of compound **II** with alkyl halides and substituted benzyl halides and yields of 2-alkyl(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones[a]

Alkylating agent	Temperature, °C	Rate constant $k\times10^2$, l mol^{-1} s^{-1}	Yield, %
$PhCH_2Br$	50	5.5	99
	40	3.8	96
	30	2.5	95
$PhCH_2Cl$	50	3.5	91
	40	2.5	87
	30	1.2	82
m-$PhOC_6H_4CH_2Cl$	50	0.6	84
	40	0.4	80
	30	0.2	74
p-$AdC_6H_4CH_2Br$	50	2.9	97
	40	1.5	94
	30	7.5	91
$CH_3CH_2CH_2I$	50	0.5	94
	40	0.25	90
	30	0.1	85
CH_3CH_2Br	50	0.3	84
	40	0.1	82
	30	–	78
p-$BrC_6H_4CH_2Br$,	50	8.0	99
o-$BrC_6H_4CH_2Br$	40	4.2	97
	30	–	–
p-$FSO_2C_6H_4CH_2Br$	50	0.8	72
	40	–	
	30	–	
CH_2=$CHCH_2Br$	50	0.6[b]	98
	40	0.3[b]	95
	30	–	–
CH_2=$CHCH_2I$	50	0.95[b]	99
	40	0.5[b]	96
	30	0.25[b]	92

[a] Volume ratio water–dioxane 1 : 1.6.
[b] $k\times10^2$, s^{-1}.

An advantage of the proposed procedure is that derivatives having both similar (R = R') and different substituents (R ≠ R') on the sulfur and oxygen atoms can be obtained. In such a way we synthesized a number of 4-alkyl(aralkyl)oxy-2-alkyl(aralkyl)sulfanyl-6-methylpyrimidines (Scheme 1).

We performed a kinetic study on nucleophilic substitution of halogen in alkyl- and substituted benzyl halides by anions derived from 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**I**) and 2-alkyl(aralkyl)sulfanyl-6-methylpyrimidin-4(3*H*)-ones in aqueous dioxane. The reaction medium is characterized by

Table 2. Rate constants of the reaction of compound **II** with allyl iodide and benzyl chloride at 50°C at different water–dioxane volume ratios

Alkylating agent	$k\times10^2$, l mol^{-1} s^{-1} or s^{-1}		
	1:1[a]	1:1.3[a]	1:1.6[a]
$PhCH_2Cl$	1.26	2.80	3.50
$CH_2=CHCH_2I$	2.00	–	0.95

[a] Water–dioxane volume ratio.

a high polarity; therefore, it is convenient for generation of anionic species. Another advantage of the water–dioxane system is that it allows the reaction to occur under homogeneous conditions. The kinetic parameters of the process were determined to estimate the reactivity of anions and optimize the reaction conditions. The progress of the reaction was monitored following the concentration of sodium thiolate **II**, which was determined by potentiometric titration with 0.1 N H_2SO_4. Differential–graphical processing of the kinetic curves gave the corresponding rate constants and reaction orders (Table 1). It is seen that the maximal rate of nucleophilic substitution and the maximal yield of compounds **III**–**XI** are attained at 50°C.

The data in Table 1 can also be used to estimate the effect of the hydrocarbon radical structure and halogen nature on the reactivity of halogen derivatives toward sodium 6-methyl-4-oxo-3,4-dihydropyrimidine-2-thiolate (**II**). In going from ethyl bromide to benzyl bromide, the rate of nucleophilic substitution at 50°C increases by a factor of ~18; introduction of a *m*-phenoxy group into benzyl chloride molecule reduces the reaction rate by a factor of 6 as compared to unsubstituted benzyl chloride; the presence of an adamantyl group in the *para* position of benzyl bromide decelerates the reaction twofold, which may be rationalized in terms of the S_N2 mechanism and considerable size of the nucleophile molecule [29]. By contrast, introduction of a bromine atom into the *ortho* or *para* position of benzyl bromide increases the reaction rate by a factor of 1.5, in keeping with the known theory of nucleophilic substitution [30]. Benzyl bromide is more reactive than benzyl chloride by a factor of 1.6; likewise, allyl iodide is more reactive that allyl bromide (the iodide-to-bromide rate ratio is 1.5).

Table 3. Rate constants of the O-alkylation of sodium salts derived from compounds **III**–**XI** with alkyl halides and substituted benzyl halides at 50°C, water–dioxane volume ratio 1:1.6

Alkylating agent	$k\times10^3$, l mol^{-1} s^{-1}
$PhCH_2Cl$	3.6
$PhCH_2Br$	5.6
m-$PhOC_6H_4CH_2Cl$	0.6
p-(1-Ad)$C_6H_4CH_2Br$	2.8
$CH_2=CHCH_2Br$	0.6[a]
$CH_2=CHCH_2I$	1.0[a]
CH_3CH_2Br	0.2

[a] $k\times10^3$, s^{-1}.

Reactions of sodium thiolate **II** with most halogen derivatives are described by the second-order kinetic equation, which is typical of bimolecular nucleophilic substitution. Exceptions were allyl halides (bromide and iodide) which reacted according to the first-order kinetics typical of S_N1 processes (Table 1).

To optimize the reaction conditions, we performed a series of experiments with different water–dioxane ratios. The results are given in Table 2. It might be expected that increase in the fraction of dioxane in the reaction medium (i.e., reduction of its polarity) should reduce the rate of the process if it follows the S_N1 mechanism and accelerate S_N2 reactions due to nucleophilic assistance of the oxygen lone electron pair to the stabilization of transition state. In the reactions with benzyl halides, we observed an appreciable increase of the reaction rate, which is consistent with the S_N2 mechanism. In the reactions with allyl halides, the rate constant decreased as the fraction of dioxane increased, in agreement with their S_N1 mechanism.

The second alkylation leading to 6-methyl-2-thiouracil derivatives with similar substituents on the oxyen and sulfur atoms requires a higher temperature and longer reaction time. The rate constants at this stage are lower by an order of magnitude (Table 3). All the above relations observed for the first nucleophilic substitution stage also apply to the second stage.

Thus the results of our preparative and kinetic studies showed that it is convenient to perform alkylation 6-methyl-2-thiouracil **I** with alkyl halides and substituted benzyl halides (chlorides, bromides, and iodides) in two steps. In the first step, 2-alkyl(aralkyl)-sulfanyl-6-methylpyrimidin-4(3*H*)-ones are obtained, and in the second, 4-alkyl(arlalkyl)oxy-2-alkyl(aralkyl)sulfanyl-6-methylpyrimidines are formed. The optimal conditions ensuring fairly high reaction rate are as follows: temperature 50°C, water–dioxane volume ratio 1:1.6 for reactions following the S_N2 mechanism and 1:1 for reactions following the S_N1 mechanism.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in DMSO-d_6 on a Varian Mercury-300 spectrometer operating at 300 MHz; the chemical shifts were measured relative to hexamethyldisiloxane as internal reference. The IR spectra were obtained on a Specord M-82 spectrometer (KBr prisms) from samples dispersed in mineral oil. The melting points were determined by the capillary technique.

Kinetic experiments were performed in a reactor equipped with a stirrer and maintained at a constant temperature. Every 2 min, a sample was withdrawn, diluted with distilled water, and analyzed by potentiometric titration with a standard 0.1 N solution of sulfuric acid using an EV-74 universal ionometer equipped with a glass electrode. When the reaction was complete, the mixture was cooled, and the product was filtered off, washed with cold water, and recrystallized.

Sodium 6-methyl-4-oxo-3,4-dihydropyrimidine-2-thiolate (II). Compound **I**, 1.5 g (10.6 mmol), and sodium hydroxide, 0.42 g (10.6 mmol), were dissolved in 7 ml of water, the solvent was evaporated, and the residue was recrystallized from ethanol. Yield 1.7 g (99.9%), mp 370°C. ^{1}H NMR spectrum, δ, ppm: 2.1 s (3H, CH_3), 5.95 s (1H, 5-H), 12.2 s (1H, NH). Found, %: N 17.00. $C_5H_5N_2NaOS$. Calculated, %: N 17.12.

2-Benzylsulfanyl-6-methylpyrimidin-4(3*H*)-one (III). Compound **I**, 1.5 g (10.6 mmol), and sodium hydroxide, 0.42 g (10.6 mmol), were dissolved in 7 ml of water, the solution was diluted with 7 ml of dioxane, and a solution of 1.4 g (10.6 mmol) of benzyl bromide in 4.2 ml of dioxane was added dropwise. The mixture was stirred for 15 min at 50°C and cooled, and the precipitate was filtered off, washed with cold water, dried, and recrystallized from benzene. Yield 2.5 g (99%), colorless crystals, mp 173–174°C; published data [1]: mp 172–173°C. ^{1}H NMR spectrum, δ, ppm: 2.1 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.95 s (1H, 5-H), 7.05–7.39 m (5H, H_{arom}), 12.2 s (1H, NH). Found, %: N 11.77. $C_{12}H_{12}N_2OS$. Calculated, %: N 11.88.

Compounds **IV**–**XI** were synthesized in a similar way.

6-Methyl-2-(3-phenoxybenzylsulfanyl)pyrimidin-4(3*H*)-one (IV) was synthesized from 1.5 g (10.6 mmol) of compound **I**, 0.42 g (10.6 mmol) of NaOH, and 2.8 g (10.6 mmol) of *m*-phenoxybenzyl chloride. Yield 3.0 g (85%), colorless crystals, mp 137–139°C. ^{1}H NMR spectrum, δ, ppm: 2.05 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.95 s (1H, 5-H), 6.8–7.4 m (9H, H_{arom}), 12.2 s (1H, NH). Found, %: N 8.33. $C_{18}H_{16}N_2O_2S$. Calculated, %: N 8.54.

2-[4-(1-Adamantyl)benzylsulfanyl]-6-methylpyrimidin-4(3*H*)-one (V) was synthesized from 1.5 g (10.6 mmol) of compound **I**, 0.42 g (10.6 mmol) of NaOH, and 3.3 g (10.6 mmol) of *p*-(1-adamantyl)benzyl bromide. Yield 2.5 g (97%), colorless crystals, mp 162–164°C. ^{1}H NMR spectrum, δ, ppm: 1.65–1.8 m (15H, adamantyl), 2.15 s (3H, CH_3), 4.25 s (2H, SCH_2), 5.95 s (1H, 5-H), 7.2–7.4 m (4H, H_{arom}), 12.5 s (1H, NH). Found, %: N 7.19. $C_{23}H_{27}N_2OS$. Calculated, %: N 7.25.

6-Methyl-2-propylsulfanylpyrimidin-4(3*H*)-one (VI) was synthesized from 1.5 g (10.6 mmol) of compound **I**, 0.42 g (10.6 mmol) of NaOH, and 1.8 g (10.6 mmol) of propyl iodide. Yield 1.7 g (88%), colorless crystals, mp 99–100°C. ^{1}H NMR spectrum, δ, ppm: 0.85–0.95 t (3H, C**H**$_3$CH$_2$), 1.5–1.75 q (2H, CH$_3$C**H**$_2$), 2.1 s (3H, CH_3), 3.0–3.1 t (2H, SCH_2), 5.95 s (1H, 5-H), 12.2 s (1H, NH). Found, %: N 15.04. $C_8H_{12}N_2OS$. Calculated, %: N 15.20.

2-Ethylsulfanyl-6-methylpyrimidin-4(3*H*)-one (VII) was synthesized from 1.5 g (10.6 mmol) of compound **I**, 0.42 g (10.6 mmol) of NaOH, and 1.3 g (11.6 mmol) of ethyl bromide. Yield 1.5 g (84%), colorless crystals, mp 124–125°C. ^{1}H NMR spectrum, δ, ppm: 1.15–1.22 t (3H, CH$_2$C**H**$_3$), 2.15 s (3H, CH_3), 2.9–3.05 q (2H, C**H**$_2$CH$_3$), 5.95 s (1H, 5-H), 12.5 s (1H, NH). Found, %: N 16.23. $C_{11}H_{10}N_2OS$. Calculated, %: N 16.46.

2-Allylsulfanyl-6-methylpyrimidin-4(3*H*)-one (VIII) was synthesized from 1.5 g (10.6 mmol) of compound **I**, 0.42 g (10.6 mmol) of NaOH, and 1.8 g (10.6 mmol) of allyl iodide or 1.3 g (10.6 mmol) of allyl bromide. Yield 1.92 g (99.6%) or 1.88 g (98%), respectively, colorless crystals, mp 133–134°C. ^{1}H NMR spectrum, δ, ppm: 2.1 s (3H, CH_3), 3.65 d (2H, SCH_2), 5.75–5.9 m (1H, C**H**=), 5.03–5.3 d.d (2H, =C**H**$_2$), 5.9 s (1H, 5-H), 12.5 s (1H, NH). Found, %: N 15.17. $C_8H_{10}N_2OS$. Calculated, %: N 15.37.

2-(4-Fluorosulfonylbenzylsulfanyl)-6-methylpyrimidin-4(3*H*)-one (IX) was synthesized from 1.5 g (10.6 mmol) of compound **I**, 0.42 g (10.6 mmol) of NaOH, and 2.7 g (10.8 mmol) of *p*-bromomethylbenzenesulfonyl fluoride. Yield 1.8 g (54.5%), colorless crystals, mp 230°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 2.1 s (3H, CH_3), 3.5 s (2H, SCH_2), 5.75 s (1H, 5-H), 7.6–8.2 m (4H, H_{arom}), 12.4 s (1H, NH). Found, %: N 8.98. $C_{12}H_{11}FN_2O_4S_2$. Calculated, %: N 9.15.

2-(4-Bromobenzylsulfanyl)-6-methylpyrimidin-4(3*H*)-one (X) and 2-(2-bromobenzylsulfanyl)-6-methylpyrimidin-4(3*H*)-one (XI) were synthesized from 1.5 g (10.6 mmol) of compound **I**, 0.42 g (10.6 mmol) of NaOH, and 1.4 g (10.6 mmol) of a mixture of *o*- and *p*-bromobenzyl bromides. Yield of isomer mixture **X/XI** 3.4 g (99.5%). Isomers **X** and **XI** were separated by recrystallization from ethanol. Compound **X** separated from the solution immediately after cooling, while isomer **XI** separated on storage in the cold. Yield of **X** 2.3 g (99%), colorless crystals, mp 166–168°C. ^{1}H NMR spectrum, δ, ppm: 2.2 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.95 s (1H, 5-H), 7.1–7.7 m (4H, H_{arom}), 12.5 s (1H, NH). Found, %: N 8.81. $C_{12}H_{11}BrN_2OS$. Calculated, %: N 9.00. Yield of **XI** 1 g (98%), colorless crystals, mp 145–147°C. ^{1}H NMR spectrum, δ, ppm: 2.2 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.95 s (1H, 5-H), 7.1–7.7 m (4H, H_{arom}), 12.5 s (1H, NH). Found, %: N 8.72. $C_{12}H_{11}BrN_2OS$. Calculated, %: N 9.00.

4-Benzyloxy-2-benzylsulfanyl-6-methylpyrimidine (XII). Compound **III**, 1 g (4 mmol), and sodium hydroxide, 0.2 g (5 mmol), were dissolved in 9 ml of water, the solution was diluted with 18 ml of dioxane, and 0.7 g (5 mmol) of benzyl chloride was added. The mixture was stirred for 1 h at 50°C and cooled, and the precipitate was filtered off, washed with cold water, and recrystallized from benzene. Yield 1.0 g (84%), colorless crystals, mp 59–61°C. ^{1}H NMR spectrum, δ, ppm: 1.85 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.5 s (CH_2, OCH_2), 6.1 s (1H, 5-H), 7.05–7.39 m (10H, H_{arom}). The filtrate was neutralized with a 20% solution of acetic acid, and the precipitate was filtered off, washed with cold water, dried, and recrystallized from ethanol. We thus isolated 0.3 g of unchanged compound **III** as colorless crystals with mp 173–174°C.

Compounds **XIII**–**XXIX** were synthesized in a similar way.

6-Methyl-4-(3-phenoxybenzyloxy)-2-(3-phenoxybenzylsulfanyl)pyrimidine (XIII) was synthesized from 1 g (3 mmol) of compound **IV**, 0.15 g (3.8 mmol) of NaOH, and 1 g (4 mmol) of *m*-phenoxybenzyl chloride. Yield 0.9 g (58%), colorless crystals, mp 78–79°C. ^{1}H NMR spectrum, δ, ppm: 2.0 s (3H, CH_3), 4.2 s (2H, SCH_2), 4.7 s (2H, OCH_2), 5.9 s (1H, 5-H), 6.6–7.45 m (18H, H_{arom}).

4-[4-(1-Adamantyl)benzyloxy]-2-[4-(1-adamantyl)benzylsulfanyl]-6-methylpyrimidine (XIV) was synthesized from 1 g (2.7 mmol) of compound **V**, 0.14 g (3.5 mmol) of NaOH, and 1.1 g (3.7 mmol) of 4-(1-adamantyl)benzyl bromide in a mixture of 12 ml of water and 32 ml of dioxane. Yield 1.3 g (81%), colorless crystals, mp 239–240°C. ^{1}H NMR spectrum, δ, ppm: 1.657–1.99 m (30H, adamantyl), 2.15 s (3H, CH_3), 4.28 s (2H, SCH_2), 4.62 s (2H, OCH_2), 5.95 s (1H, 5-H), 7.2–7.8 m (8H, H_{arom}).

4-Allyloxy-2-allylsulfanyl-6-methylpyrimidine (XV) was synthesized from 1 g (5.5 mmol) of compound **VIII**, 0.24 g (6 mmol) of NaOH, and 1 g (6 mmol) of allyl iodide in a mixture of 8 ml of water and 13 ml of dioxane. Yield 3.4 g (83%), colorless crystals, mp 103–104°C. ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 3.7 d (CH_2, SCH_2), 4.5 d (CH_2, OCH_2), 5.0–5.2 m (2H, $SCH_2CH{=}C\mathbf{H}_2$), 5.2–5.4 m (2H, $OCH_2CH{=}C\mathbf{H}_2$), 5.7–5.95 m (1H, $SCH_2C\mathbf{H}{=}CH_2$), 5.95–6.05 m (1H, $OCH_2C\mathbf{H}{=}CH_2$), 6.45 s (1H, 5-H).

6-Methyl-4-propyloxy-2-propylsulfanylpyrimidine (XVI) was synthesized from 1 g (5.4 mmol) of compound **VI**, 0.24 g (6 mmol) of NaOH, and 1 g (6 mmol) of propyl iodide. Yield 1.1 (69%), colorless crystals, mp 83–85°C. ^{1}H NMR spectrum, δ, ppm: 0.85–0.95 m (6H, $CH_2C\mathbf{H}_3$), 1.5–1.75 m (4H, $C\mathbf{H}_2CH_3$), 2.1 s (3H, CH_3), 3.0–3.1 t (2H, SCH_2), 3.35–3.45 t (2H, OCH_2), 5.9 s (1H, 5-H).

2-[4-(1-Adamantyl)benzylsulfanyl]-6-methyl-4-propyloxypyrimidine (XVII) was synthesized from 0.3 g (0.8 mmol) of compound **V**, 0.04 g (1.0 mmol) of NaOH, and 0.14 g (0.85 mmol) of propyl iodide. Yield 0.22 g (68%), colorless crystals, mp 239–240°C. ^{1}H NMR spectrum, δ, ppm: 0.87–0.96 t (3H, $CH_2C\mathbf{H}_3$), 1.66–1.94 m (15H, adamantyl), 2.15 s (3H, CH_3), 2.22–2.5 m (2H, $C\mathbf{H}_2CH_3$), 3.2 m (2H, OCH_2), 4.3 s (2H, SCH_2), 5.95 s (1H, 5-H), 7.22–7.31 m (4H, H_{arom}). Found, %: N 6.24. $C_{22}H_{30}N_2OS$. Calculated, %: N 6.32.

2-[4-(1-Adamantyl)benzylsulfanyl]-4-allyloxy-6-methylpyrimidine (XVIII) was synthesized from 0.3 g (0.8 mmol) of compound **V**, 0.04 g (1.0 mmol) of NaOH, and 0.13 g (0.85 mmol) of allyl iodide. Yield 0.23 g (70%), colorless crystals, mp 214–215°C. ^{1}H NMR spectrum, δ, ppm: 1.66–2.0 m (15H, adamantyl), 2.15 s (3H, CH_3), 4.61 d (2H, $C\mathbf{H}_2CH{=}$), 5.05–5.3 m (2H, $CH{=}C\mathbf{H}_2$), 5.79–5.92 m (1H, $C\mathbf{H}{=}CH_2$), 5.95 s (1H, 5-H), 7.05–7.5 m (4H, H_{arom}). Found, %: N 6.60. $C_{22}H_{28}N_2OS$. Calculated, %: N 6.69.

2-[4-(1-Adamantyl)benzylsulfanyl]-4-benzyloxy-6-methylpyrimidine (XIX) was synthesized from 0.3 g (0.8 mmol) of compound **V**, 0.04 g (1.0 mmol) of NaOH, and 0.11 g (0.85 mmol) of benzyl chloride. Yield 0.28 g (76%), colorless crystals, mp 298–300°C. ^{1}H NMR spectrum, δ, ppm: 1.6–2.0 m (15H, adaman-

tyl), 2.13 s (3H, CH_3), 4.27 s (2H, SCH_2), 4.85 s (CH_2, OCH_2), 5.9 s (1H, 5-H), 7.2–7.3 m (9H, H_{arom}). Found, %: N 5.96. $C_{29}H_{30}N_2OS$. Calculated, %: N 6.03. In addition, 0.07 g of unreacted compound **V** was isolated as colorless crystals with mp 162–164°C.

2-[4-(1-Adamantyl)benzylsulfanyl]-6-methyl-4-(3-phenoxybenzyloxy)pyrimidine (XX) was synthesized from 0.3 g (0.8 mmol) of compound **V**, 0.04 g (1.0 mmol) of NaOH, and 0.20 g (0.8 mmol) of *m*-phenoxybenzyl bromide. Yield 0.29 g (68%), colorless crystals, mp 256–258°C. ^{1}H NMR spectrum, δ, ppm: 1.66–2.0 m (15H, adamantyl), 2.15 s (3H, CH_3), 4.25 s (2H, SCH_2), 4.78 s (CH_2, OCH_2), 5.95 s (1H, 5-H), 6.9–7.48 m (13H, H_{arom}). Found, %: N 4.97. $C_{35}H_{34}N_2O_2S$. Calculated, %: N 5.03. In addition, 1 g of unreacted compound **V** was isolated as colorless crystals with mp 162–164°C.

4-Allyloxy-2-benzylsulfanyl-6-methylpyrimidine (XXI) was synthesized from 0.5 g (2.0 mmol) of compound **III**, 0.09 g (2.1 mmol) of NaOH, and 0.34 g (2.1 mmol) of allyl iodide. Yield 0.38 g (70%), colorless crystals, mp 150–152°C. ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 4.3 s (2H, SCH_2), 4.5 d (2H, CH_2CH=), 5.05–5.27 m (2H, CH=C**H**$_2$), 5.82–5.94 m (1H, C**H**=CH_2), 5.95 s (1H, 5-H), 7.2–7.39 m (5H, H_{arom}). Found, %: N 9.93. $C_{15}H_{16}N_2OS$. Calculated, %: N 10.09.

2-Benzylsulfanyl-6-methyl-4-propyloxypyrimidine (XXII) was synthesized from 0.5 g (2.0 mmol) of compound **III**, 0.09 g (2.1 mmol) of NaOH, and 0.33 g (2.1 mmol) of propyl iodide. Yield 0.35 g (63%), colorless crystals, mp 146–147°C. ^{1}H NMR spectrum, δ, ppm: 0.87–0.92 t (3H, CH_2CH_3), 1.55–1.63, (2H, C**H**$_2$CH$_3$), 2.15 s (3H, CH_3), 3.0–3.1 m (2H, OCH_2), 4.3 s (2H, SCH_2), 5.95 s (1H, 5-H), 7.2–7.39 m (5H, H_{arom}). Found, %: N 9.88. $C_{15}H_{18}N_2OS$. Calculated, %: N 10.00. In addition, 0.14 g of unreacted initial compound **III** was isolated as colorless crystals with mp 172–173°C.

2-Benzylsulfanyl-4-ethoxy-6-methylpyrimidine (XXIII) was synthesized from 0.5 g (2.0 mmol) of compound **III**, 0.09 g (2.1 mmol) of NaOH, and 0.43 g (2.5 mmol) of ethyl bromide. Yield 0.28 g (53%), colorless crystals, mp 150–152°C. ^{1}H NMR spectrum, δ, ppm: 1.05–1.1 m (CH_2CH_3), 2.15 s (CH_3), 4.28 s (SCH_2), 5.6 s (OCH_2), 6.0 s (1H, 5-H), 7.1–7.5 m (5H, H_{arom}). Found, %: N 10.68. $C_{14}H_{16}N_2OS$. Calculated, %: N 10.76.

2-Benzylsulfanyl-6-methyl-4-(3-phenoxybenzyloxy)pyrimidine (XXIV) was synthesized from 0.5 g (2.0 mmol) of compound **III**, 0.09 g (2.1 mmol) of NaOH, and 0.5 g (2.1 mmol) of *m*-phenoxybenzyl chloride. Yield 0.49 g (62%), colorless crystals, mp 134–135°C. ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.5 s (CH_2, OCH_2), 5.95 s (1H, 5-H), 6.82–7.37 m (14H, H_{arom}). Found, %: N 6.78. $C_{22}H_{28}N_2O_2S$. Calculated, %: N 6.85. In addition, 0.14 g of unreacted compound **III** was isolated as colorless crystals with mp 172–173°C.

4-Allyloxy-6-methyl-2-(3-phenoxybenzylsulfanyl)pyrimidine (XXV) was synthesized from 0.5 g (1.5 mmol) of compound **IV**, 0.07 g (1.65 mmol) of NaOH, and 0.26 g (1.6 mmol) of allyl iodide. Yield 0.31 g (60%), colorless crystals, mp 119–120°C. ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 4.3 s (2H, SCH_2), 4.5 d (2H, OCH_2), 5.05–5.27 m (2H, CH=C**H**$_2$), 5.82–5.94 m (1H, C**H**=CH_2), 5.95 s (1H, 5-H), 6.85–7.33 m (9H, H_{arom}). Found, %: N 7.78. $C_{18}H_{20}N_2O_2S$. Calculated, %: N 8.04. In addition, 0.2 g of unreacted compound **IV** was isolated as colorless crystals with mp 137–139°C.

4-Benzyloxy-6-methyl-2-(3-phenoxybenzylsulfanyl)pyrimidine (XXVI) was synthesized from 0.5 g (1.5 mmol) of compound **IV**, 0.07 g (1.65 mmol) of NaOH, and 0.26 g (1.6 mmol) of benzyl bromide. Yield 0.36 g (61%), colorless crystals, mp 127–128°C. ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.65 s (CH_2, OCH_2), 5.93 s (1H, 5-H), 6.8–7.43 m (14H, H_{arom}). Found, %: N 6.81. $C_{25}H_{22}N_2O_2S$. Calculated, %: N 6.93. In addition, 0.21 g of unreacted compound **IV** was isolated as colorless crystals with mp 137–139°C.

2-(4-Bromobenzylsulfanyl)-6-methyl-4-propoxypyrimidine (XXVII) was synthesized from 0.5 g (1.6 mmol) of compound **X**, 0.08 g (2 mmol) of NaOH, and 0.28 g (2.5 mmol) of propyl iodide. Yield 0.34 g (60%), colorless crystals, mp 130–132°C. ^{1}H NMR spectrum, δ, ppm: 0.8–0.95 t (CH_2CH_3), 1.5–1.7 m (C**H**$_2$CH$_3$), 2.05 s (CH_3), 3.0–3.1 t (OCH_2), 4.25 s (SCH_2), 5.93 s (1H, 5-H), 7.1–7.6 m (4H, H_{arom}). Found, %: N 7.58. $C_{15}H_{17}BrN_2OS$. Calculated, %: N 7.66.

2-(4-Bromobenzylsulfanyl)-4-ethoxy-6-methylpyrimidine (XXVIII) was synthesized from 0.5 g (1.6 mmol) of compound **X**, 0.08 g (2 mmol) of NaOH, and 0.43 g (2.5 mmol) of ethyl bromide. Yield 0.35 g (52%), colorless crystals, mp 142–143°C. ^{1}H NMR spectrum, δ, ppm: 1.05–1.15 m (CH_2CH_3), 2.15 s (CH_3), 4.2–4.45 m (OCH_2), 5.65 s (SCH_2), 6.0 s (1H, 5-H), 7.1–7.6 m (4H, H_{arom}). Found, %: N 8.0. $C_{14}H_{15}BrN_2OS$. Calculated, %: N 8.25.

4-Allyloxy-2-(4-bromobenzylsulfanyl)-6-methylpyrimidine (XXIX) was synthesized from 0.5 g (1.6 mmol) of compound **X**, 0.08 g (2 mmol) of NaOH, and 0.42 g (2.5 mmol) of allyl iodide. Yield 0.48 g (69%), colorless crystals, mp 139–141°C. ^{1}H NMR spectrum, δ, ppm: 2.15 s (CH_3), 4.22 s (SCH_2), 5.05–5.3 d.d (CH=C**H**$_2$), 5.8–5.9 m (C**H**=CH_2), 5.95 s (1H, 5-H), 7.1–7.6 m (4H, H_{arom}). Found, %: N 7.65. $C_{15}H_{15}BrN_2OS$. Calculated, %: N 7.97.

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