Chemistry of Heterocyclic Compounds, Vol. 46, No. 2, 2010

THE SPECIFIC CHARACTER OF THE REACTION OF DERIVATIVES OF 2-THIOXO-2,3-DIHYDROPYRIMIDIN-4(1H)-ONE WITH IODOMETHANE AND ALKYL CHLOROMETHYL SULFIDES

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The alkylation of 5-alkyl-6-(2,6-dihalobenzyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones with MeI, $AllSCH_2Cl$, and $MeSCH_2Cl$ in the K_2CO_3–DMF, NaOMe–MeOH, and KOH–EtOH systems was investigated. A hypothetical mechanism for the reaction is examined, and an explanation is proposed for the composition of the reaction products. The presence of high anti-HIV-1 activity was established in the obtained derivatives of 2-{[(allylsulfanyl)methyl]sulfanyl}pyrimidin-4(3H)-one.

Keywords: 5-alkyl-6-(2,6-dihalobenzyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones, allyl chloro-methyl sulfide, iodomethane, methyl chloromethyl sulfide, S_N1- and S_N2-substitution, anti-HIV-1 agents.

Derivatives of 2-thioxo-2,3-dihydropyrimidin-4(1H)-one react ambiguously with various alkylating agents. Thus, MeI [1], AllBr [2], EtI [2], and EtBr [2] in anhydrous DMF in the presence of K_2CO_3 form mixtures of products from S-mono-, S,N(1)-di-, and S,N(3)-dialkylation. In the presence of NaOMe in MeOH [3] and NaOEt in EtOH [4] the same alkylating agents lead exclusively to the formation of the products from S-monoalkylation. Similar results were obtained when the reaction was carried out in DMF in the absence of a base [5]. At the same time more active alkylating agents – alkyl chloromethyl sulfides and alkyl chloromethyl oxides – form the products from S-monoalkylation when the reaction is carried out in DMF in the presence of K_2CO_3 [6]. This effect has not found a convincing explanation in the literature.

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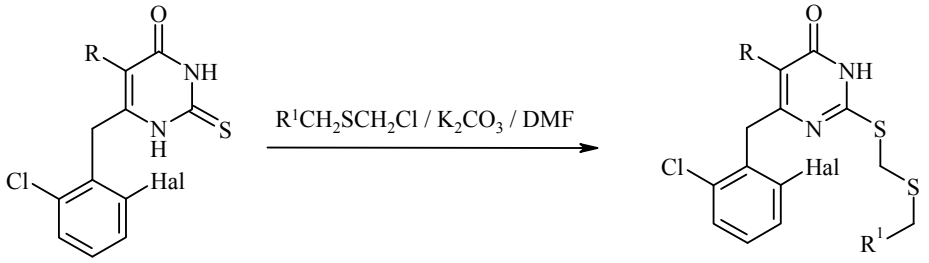
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 248-254, February, 2010. Original article submitted April 29, 2008. Revision submitted January 11, 2009.

 0009-3122/10/4602-0200©2010 Springer Science+Business Media, Inc.

In order to establish the reasons for these difference in reactivity and also to synthesize new probable antiviral agents, we studied the reaction of 6-(arylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones **1a-d** with $AllSCH_2Cl$, $MeSCH_2Cl$, and MeI in the K_2CO_3–DMF, KOH–EtOH, and NaOMe–MeOH systems.

As a result, we established that reaction with $AllSCH_2Cl$ and $MeSCH_2Cl$ in the first system leads to the formation of the S-monoalkylation products **2a**,**b** and **3a-c** with small amounts of dialkylation products as impurities.

When the same reaction was realized in the NaOMe–MeOH system, the corresponding 6-(arylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones were regenerated. In addition to them $AllSCH_2OMe$ and $MeSCH_2OMe$ were obtained.

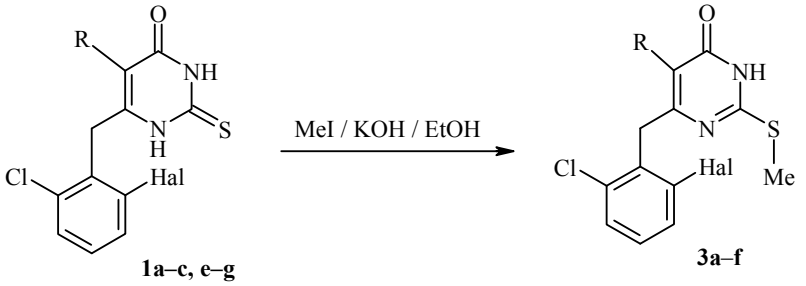


1a–d **2a–e**

1a,b, **2a–c** R = H, **1c**, **2d** R = Me, **1d**, **2e** R = *i*-Pr; **2a,d,e** $R^1 = H_2C{=}CH$, **2b,c** R^1 = H;
1a, 2a,b Hal = Cl, **1b,c,d**, **2c,d,e** Hal = F

The initial 6-(arylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones were also regenerated when this reaction was carried out in the presence of KOH in 96% ethanol. In addition $AllSCH_2OMe$ and $MeSCH_2OMe$ and also small amounts of $AllSCH_2OCH_2SAll$ and $MeSCH_2OCH_2SMe$ were also obtained.

However, during the reaction of 6-(arylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones **1-c**, **e-g** with MeI in the K_2CO_3–DMF system complex mixtures of polyalkylation products were obtained, and this agrees with published data [1]. At the same time the S-monoalkylation products **3a-f** were obtained almost exclusively both in the KOH–EtOH system and in the NaOMe–MeOH system.



1a–c, e–g **3a–f**

1a, **3a** R = H, Hal = Cl; **1b**, **3b** R = H, Hal = F; **1c**, **3d** R = Me, Hal = F; **1e**, **3c** R = Me, Hal = Cl; **1f**, **3e** R = Et, Hal = Cl; **1g**, **3f** R = Et, Hal = F

The explanation of this effect clearly involves not so much the absolute level of reactivity of the employed alkylating agents as the dominant mechanism of their realization. It is known that alkyl chloromethyl sulfides enter into nucleophilic substitution predominantly by the S_N1 mechanism, due to the formation of a stable (alkylsulfanyl)methyl cation [7]. At the same time the S_N1 mechanism is not the main one in the case of these compounds. The S_N2 mechanism is dominant in the case of halomethanes.

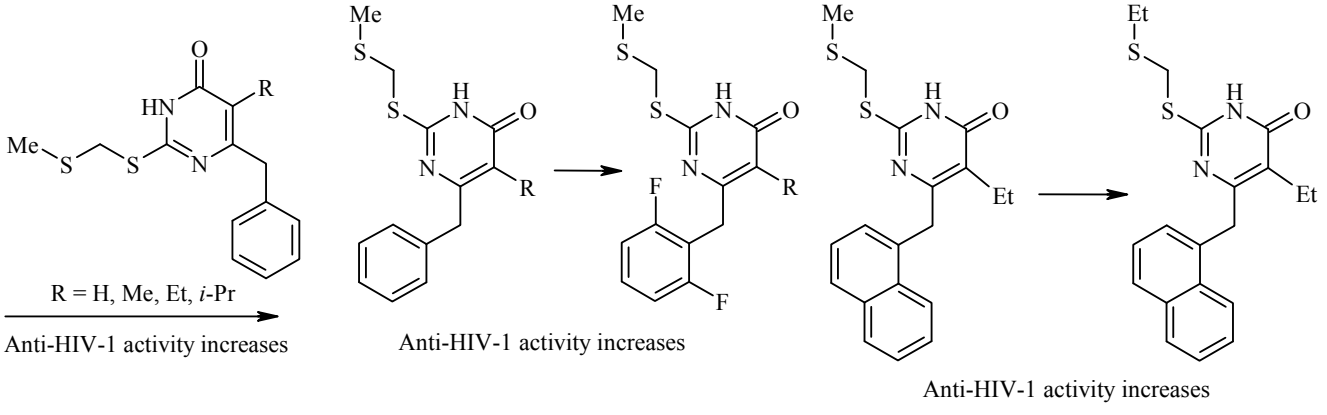
Thus, if the reaction is carried out in a protic solvent, the 4-(arylmethyl)-6-oxo-1,6-dihydro-2-pyrimidinethiolate anion is in a compact solvate shell due to the presence of a significant amount of hydrogen bonds. Destruction of this solvate shell obviously involves significant energy expenditures. Because of this it is mainly the most nucleophilic tautomeric form, the 4-(arylmethyl)-6-oxo-1,6-dihydro-2-pyrimidinethiolate anion, that enters into reaction with the iodomethane. At the same time $AllSCH_2Cl$ and $MeSCH_2Cl$ enter into reaction with the solvent molecules (a neutral nucleophile) contained in the solvate shell, reacting predominantly by the S_N1 mechanism. In turn the 4-(arylmethyl)-6-oxo-1,6-dihydro-2-pyrimidinethiolate anion acts only as an acceptor of the hydrogen chloride formed during this reaction.

When the reaction is carried out in DMF the anion is not surrounded by such a compact solvate shell since the DMF is an aprotic solvent and is not susceptible to the formation of strong hydrogen bonds. Thus, the solvate shell is unstable, and the MeI reacts both with the more nucleophilic 4-(arylmethyl)-6-oxo-1,6-dihydro-2-pyrimidinethiolate anion and with other tautomeric forms of this anion, in which the negative charge is delocalized predominantly on one of the nitrogen atoms and/or the oxygen atom. The small differences in the activation energies of these reactions are probably balanced by the high reactivity of the MeI.

The $AllCH_2Cl$ and $MeSCH_2Cl$ are inclined to react by the S_N1 mechanism, but the moderately well defined basic character of the solvent and the weakly solvated anion favour reaction by the S_N2 mechanism. In reactions taking place by the S_N2 mechanism the activity of the corresponding alkylating agents is appreciably lower than in the case of the S_N1 mechanism, and this gives rise to the relatively high selectivity of their reaction with the most nucleophilic 4-(arylmethyl)-6-oxo-1,6-dihydro-2-pyrimidinethiolate anion.

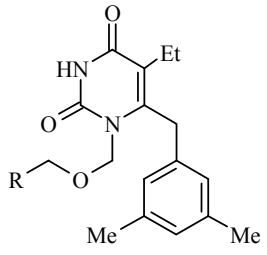
The experiments also prove that the alkali metal cation does not have a significant effect on the selectivity of the alkylation reaction.

Whereas the obtained derivatives of 2-(methylsulfanyl)-4(3H)-pyrimidinone are of considerable interest as intermediate products in the synthesis of 2-amino-6-(arylmethyl)pyrimidin-4(3H)-ones having anti-HIV-1 activity, the corresponding derivatives of 2-[(alkylsulfanyl)methyl]sulfanylpyrimidin-4(3H)-one in themselves are often highly active inhibitors of the replication of HIV-1. Here it had been shown earlier that the activity of these derivatives increases during the transition from the 5-unsubstituted compounds to the 5-isopropyl-substituted derivatives [8], during the insertion of 2,6-dihalobenzyl at position 6 [9], and also during the transition from the 2-[(methylsulfanyl)methylsulfanyl]-substituted compounds to the 2-[(ethylsulfanyl)methyl-sulfanyl]-substituted analogs [10].



At the same time we took account of the fact that for 1-(alkoxymethyl)-5-alkyl-6-(arylmethyl)-pyrimidine-2,4(1H,3H)-diones the activity increases from the 1-(methoxymethyl)- and 1-(ethoxymethyl)-substituted compounds to the 1-[(allyloxy)methyl]-substituted analogs [11].

Here it had been established earlier that in the series of 5-alkyl-2-(alkylsulfanyl)-6-(arylmethyl)-4(3H)-pyrimidinones the substituent at the sulfur atom interacts with the same section of HIV-1 revertase as the substituent at position 1 in 1-(alkoxymethyl)-5-alkyl-6-(arylmethyl)pyrimidine-2,4-(1H,3H)-diones [12]. On the basis of these data it seemed appropriate to insert an [(allylsulfanyl)methyl]sulfanyl group at position 2 of the targeted derivatives and to compare their activity with the activity of the corresponding 2-[(methylsulfanyl)methylsulfanyl]-substituted analogs [3]. The antiviral activity of the investigated compounds is presented in Table 1.



R = H, Me, H_2C=CH

Anti-HIV-1 activity increases

Thus, it was established that the activity of the allyl analogs significantly exceeds that of the methyl-substituted compounds [3]; this confirms the proposed hypothesis and demonstrates the prospects of further search for new highly active anti-HIV-1 agents in the investigated series of compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian-Mercury 300BB instrument (300 MHz) with HMDS as internal standard. The melting points of the synthesized compounds were determined on a Cole-Palmer instrument.

Allyl chloromethyl sulfide was prepared by the previously described method [13, 14]. The derivatives **1a**,**d** [12], **1e** [15], **1b** [3], and **1c**,**f**,**g** [16] were obtained by known methods. During the syntheses we used reagents from Lancaster Synthesis [$MeSCH_2Cl$ (content of main substance 95%), MeI (content of main substance 99%), K_2CO_3 (content of main substance 99%)], Acros [AllSH (content of main substance 70%)], and LaChema [KOH (content of main substance 84.5%)]. The solvents were prepared, purified, and dried by standard procedures [17].

2-{[(Allylsulfanyl)methyl]sulfanyl}-6-(2,6-dichlorobenzyl)pyrimidin-4(3H)-one (2a). To a solution of 6-(2,6-dichlorobenzyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (**1a)** (287 mg, 1 mmol) in absolute DMF (2 ml) we added anhydrous K_2CO_3 (145 mg, 1.05 mmol). The mixture was stirred at 90-100°C for 1 h, and cooled to room temperature, $AllSCH_2Cl$ (135 mg, 1.1 mmol) was added, and the mixture was stirred until the initial compound had been completely converted (TLC, 3% MeOH in $CHCl_3$). The solution was diluted with water (50 ml), neutralized with 1 N acetic acid, and filtered. The precipitate was washed with water (20 ml), dried, and crystallized. The yield was 217 mg (58%); mp 162.5-163.5°C (PhMe). ^{1}H NMR spectrum (CCl_4), δ, ppm (*J*, Hz): 13.34 (1H, s, NH); 7.25 (2H, d, *J* = 7.9, H-3,5 Ar); 7.09 (1H, d, *J* = 7.6, H-4 Ar); 5.70 (1H, s, H-5 pyrimidine); 5.67-5.59 (1H, m, $CH_2C\underline{H}CH_2S$); 5.12-4.95 (2H, m, $C\underline{H}_2CHCH_2S$); 4.11 (2H, s, $ArCH_2$); 4.09 (2H, s, SCH_2S); 3.12 (2H, d, *J* = 7.3, $CH_2CHC\underline{H}_2S$). Found, %: C 48.66; H 4.01. $C_{15}H_{14}Cl_2N_2OS_2$. Calculated, %: C 48.26; H 3.78.

2-{[(Allylsulfanyl)methyl]sulfanyl}-6-(6-chloro-2-fluorobenzyl)-5-methylpyrimidin-4(3H)-one (2d). The compound was obtained similarly to compound **2a** with a yield of 40%; mp 152-154.5°C (*cyclo*-

TABLE 1. Antiviral Activity of Compounds **3a-c**

Compound	c_{max}, μmol	Effective concentration, EC_{50}				
		NL4-3 wt	K103N	Y181C	Y188L	Noninfected colony of cells, CC_{50}*
Nevirapine*[2]	8	0.026	1.92	2.78	>8	>8
Ifavirenz*[2]	0.3	0.0025	0.108	0.0041	>0.3	>0.3
3a	13	0.75	8.68	>13	>13	>13
3b	13	0.051	4.31	1.78	>13	>13
3c	13	0.075	8.70	1.62	>13	>13

* CC_{50} is the cytotoxic concentration.
*[2] Reference standard.

C_6H_{12}). ^{1}H NMR spectrum (CCl_4), δ, ppm (*J*, Hz): 13.52 (1H, s, NH); 7.19-7.04 (2H, m, H-3,5 Ar); 6.96-6.85 (1H, m, H-4 Ar); 5.68-5.52 (1H, m, $CH_2C\underline{H}CH_2S$); 5.03-4.89 (2H, m, $C\underline{H_2}CHCH_2S$); 3.99 (2H, s, $ArCH_2$); 3.81 (2H, s, SCH_2S); 3.04 (2H, d, *J* = 7.3, $CH_2CHC\underline{H_2}S$); 2.13 (3H, s, CH_3). Found, %: C 51.97; H 4.00. $C_{16}H_{16}ClFN_2OS_2$. Calculated, %: C 51.81; H 4.35.

2-{[(Allylsulfanyl)methyl]sulfanyl}-6-(6-chloro-2-fluorobenzyl)-5-isopropylpyrimidin-4(3H)-one (2e). The compound was obtained similarly to compound **2a** with a yield of 36%; mp 162-165°C (C_6H_{14}–*cyclo*-C_6H_{12}). ^{1}H NMR spectrum (CCl_4), δ, ppm (*J*, Hz): 13.47 (1H, s, NH); 7.20-7.04 (2H, m, H-3,5 Ar); 6.99-6.83 (1H, m, H-4 Ar); 5.67–5.51 (1H, m, $CH_2C\underline{H}CH_2S$); 5.10-4.94 (2H, m, $C\underline{H_2}CHCH_2S$); 4.05 (2H, s, $ArCH_2$); 3.84-3.68 (2H, m, SCH_2S); 3.19-3.08 (1H, m, $(CH_3)_2C\underline{H}$); 1.43-1.26 (6H, m, $(C\underline{H_3})_2CH$). Found, %: C 53.97; H 5.25. $C_{18}H_{20}ClFN_2OS_2$. Calculated, %: C 54.19; H 5.05.

6-(6-Chloro-2-fluorobenzyl)-2-{[(methylsulfanyl)methyl]sulfanyl}pyrimidin-4(3H)-one (2c). The compound was obtained similarly to compound **2a** with a yield of 54%; mp 154.5-156.5°C (EtOH) (corresponds to data in [3]).

6-(2,6-Dichlorobenzyl)-2-{[(methylsulfanyl)methyl]sulfanyl}pyrimidin-4(3H)-one (2b). The compound was obtained similarly to compound **2a** with a yield of 55%; mp 180.5-182°C (EtOH) (corresponds to data in [3]).

6-(6-Chloro-2-fluorobenzyl)-5-ethyl-2-(methylsulfanyl)pyrimidin-4(3H)-one (3f). To a solution of 500 mg (7.53 mmol) of 84.5% KOH in 100 ml of 96% EtOH we added 6-(6-chloro-2-fluorobenzyl)-5-ethyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (**1g**) (2 g, 7.39 mmol). The mixture was stirred at 40-50°C until dissolved and cooled to room temperature, and MeI (2.3 ml, 5.24 g, 36.91 mmol) was added. The reaction mass was stirred at room temperature for 2 h, diluted with an equal volume of water, neutralized with acetic acid, and filtered. The precipitate was washed with water (50 ml) and dried. The yield of the product was practically quantitative. The yield (after recrystallization) was 2.1 g (75%); mp 209-211°C (MeCN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.49 (1H, br. s, NH); 7.32-7.25 (2H, m, H-3,5 Ar); 7.17-7.11 (1H, m, H-4 Ar); 3.98 (2H, s, $ArCH_2$); 1.99 (2H, s, SCH_3); 1.03-0.98 (3H, m, $CH_2C\underline{H_3}$). The signal of the protons of the CH_2 group in Et is overlapped by the signal of the DMSO impurity in the DMSO-d_6. Found, %: C 54.10; H 4.11. $C_{14}H_{14}ClFN_2OS$. Calculated, %: C 53.76; H 4.51.

6-(6-Chloro-2-fluorobenzyl)-2-(methylsulfanyl)pyrimidin-4(3H)-one (3b). The compound was obtained similarly to compound **3f** with a yield of 60%; mp 217-219.5 °C (MeCN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.33-7.26 (2H, m, H-3,5 Ar); 7.22-7.19 (1H, m, H-4 Ar); 5.70 (1H, s, H-5 pyrimidine); 3.90 (2H, s, $ArCH_2$); 2.30 (3H, s, CH_3). The proton of the pyrimidine ring NH group has the form of a broad singlet with extremely low intensity, which does not make it possible to make an appropriate assignment. Found, %: C 50.20; H 3.96. $C_{12}H_{10}ClFN_2OS$. Calculated, %: C 50.62; H 3.54.

6-(6-Chloro-2-fluorobenzyl)-5-methyl-2-(methylsulfanyl)pyrimidin-4(3H)-one (3d). The compound was obtained similarly to compound **3f** with a yield of 62%; mp 241-241.5°C (MeCN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 11.68 (1H, br. s, NH); 7.10-7.06 (2H, m, H-3,5 Ar); 6.93-6.89 (1H, m, H-4 Ar); 3.99 (2H, s, $ArCH_2$); 2.13 (3H, s, SCH_3); 2.12 (3H, s, CH_3). Found, %: C 52.27; H 4.11. $C_{13}H_{12}ClFN_2OS$. Calculated, %: C 52.26; H 4.05.

6-(2,6-Dichlorobenzyl)-2-(methylsulfanyl)pyrimidin-4(3H)-one (3a). The compound was obtained similarly to compound **3f** with a yield of 65%; mp 238-241°C (MeCN) (corresponds to data in [12]).

6-(2,6-Dichlorobenzyl)-5-methyl-2-(methylsulfanyl)pyrimidin-4(3H-one (3c). The compound was obtained similarly to compound **3f** with a yield of 65%; mp 262-264°C (MeCN) (corresponds to data in [12]).

6-(2,6-Dichlorobenzyl)-5-ethyl-2-(methylsulfanyl)pyrimidin-4(3H)-one (3e). The compound was obtained similarly to compound **3f** with a yield of 66%; mp 246-249°C (MeCN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.41–7.35 (2H, m, H-3,5 Ar); 7.27–7.21 (1H, m, H-4 Ar); 4.14 (2H, s, $ArCH_2$); 1.94 (3H, s, SCH_3); 1.09-1.00 (3H, m, $CH_2C\underline{H}_3$). The proton of the NH group of the pyrimidine ring has the form of a broad singlet with extremely low intensity, which does not make it possible to make an appropriate assignment. The signal of the protons of the CH_2 group in Et is overlapped by the signal of the DMSO impurity in the DMSO-d_6. Found, %: C 51.10; H 4.30. $C_{14}H_{14}Cl_2N_2OS$. Calculated, %: C 51.07; H 4.29.

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