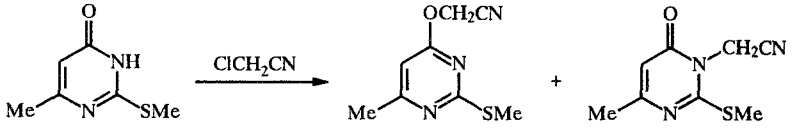
ALKYLATION OF 4-HYDROXY-6-METHYL-2-METHYLTHIO-PYRIMIDINE WITH CHLOROACETONITRILE

V. Syadyaryavichyute and P. Vainilavichyus

The sodium salt of 4-hydroxy-6-methyl-2-methylthiopyrimidine is alkylated with chloroacetonitrile in hexamethyltriamidophosphate on the O-atom, and in dioxane or tetrahydrofuran on the N_3-atom, with the formation of 6-methyl-2-methylthio-4-cyanomethoxypyrimidine and 6-methyl-2-methylthio-3-cyanomethyl-4-pyrimidone, respectively.

Earlier [1, 2] we studied the alkylation of 2-alkylthio-4-hydroxypyrimidine with esters of haloacetic acids and suggested a method for the selected synthesis of O- and N_3-alkoxycarbonylmethyl substituted 2-alkylthio-4-hydroxypyrimidines.

With the aim of expanding the application of the method and the synthesis of O- and N_3-cyanomethyl-substituted pyrimidines, we studied the alkylation of 4-hydroxy-6-methyl-2-methylthiopyrimidines (I) with chloroacetonitrile.



I II III

It was established earlier [1, 2] that the essential factor influencing the direction of alkylation of compounds I is the nature of the solvent. Nonpolar and low-polarity aprotic solvents promoted N_3-alkylation, and aprotic dipolar solvents promote O-alkylation. We therefore studied the alkylation of the sodium salt of the 4-hydroxypyrimidines I with chloroacetonitrile in different solvents (Table 1). Alkylation in dioxane or tetrahydrofuran proceeded as in the case of the haloacetic acid esters [1, 2]; selectively on the N_3 with the formation of compounds III. However, the reaction in carbon tetrachloride, in contrast to the reaction with the haloacetic esters, did not generally take place in acetone, alkylation of the sodium salt of compound I with chloroacetonitrile and with the methyl ester of bromoacetic acid gave mixtures of the O- and the N_3-isomers in a ratio of ~1:1 in the first case and 1:3 in the second [2]. Alkylation of compounds I with chloroacetonitrile in the methanol–sodium methylate system gave a complex mixture of products, the separation of which into individual components was not successful. It is possible that in this case the cyanogroup reacts with methanol, which leads to an analogous reaction course.

In an attempt to synthesize the O-cyanomethyl-substituted derivative of II we alkylated the sodium salt of 4-hydroxypyrimidine I with chloroacetonitrile in hexamethyltriamidophosphate. The selectivity of the process depends upon the temperature. At low temperatures (0-5°C) only the O-isomer II was formed, while 20°C gave a mixture of compounds II and III in a ratio of 2:1. This dependence was not observed in the alkylation of the sodium salt of I with methyl bromoacetate. Use of hexamethyltriamidophosphate gives the possibility of obtaining the O-isomer at high temperatures [2].

Earlier [2] we succeeded in alkylating 2-alkylthio-4-hydroxypyrimidines with ester of haloacetic acids regioselectively on the oxygen atom by using trimethylamine as base and solvent and with tetrabutylammonium bromide as phase-transfer catalyst. Since the regioselectivity of the process in this case depends upon the temperature, we studied the alkylation of compound I with chloroacetonitrile at different temperatures. As is shown in Table 2, in all cases we obtained a mixture of the O-isomer II and the N_3-isomer III. In contrast to the alkylation with methyl bromoacetate where the N_3 alkylation increases with increasing temperature [2], in this case the amount of O-isomer II increases with increasing temperature.

Vilnius University, Vilnius 232734. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1525-1527, November, 1992. Original article submitted July 7, 1992.

 0009-3122/92/2811-1304$12.50

TABLE 1. Influence of Solvent on the Alkylation of the Sodium Salt of 4-Hydroxy-6-methyl-2-methylthiopyrimidine (I) with Chloroacetonitrile

Solvent	Overall yield, %	Relative yields, %	
		O-isomer	N_3-isomer
CCl_4	0	—	—
Dioxane	65	0	100
Tetrahydrofuran	62	0	100
Acetone	72	47	53
Hexamethyltriamidophosphate	53	100	0

TABLE 2. Influence of Temperature on the Alkylation of 4-Hydroxy-6-methyl-2-methylthiopyrimidine (I) with Chloroacetonitrile in Triethylamine

Temperature, °C	Reaction time, h	Overall yield, %	Relative yields, %	
			4. O-isomer	N_3-isomer
0...10	7	13	38	62
20	4	78	47	53
50...60	0,5	49	56	44
89	0,5	78	60	40

The structures of compounds II and III were verified by UV, IR, and H NMR spectroscopy. Establishment of the structures of the O-isomer II or N_3-isomer III was not difficult because of agreement of characteristic parameters with analogous parameters in the spectra of O- and N_3-alkoxycarbonylmethyl-substituted 2-alkylthio-4-hydroxypyrimidines [1, 2].

Thus, the alkylation of the sodium salt of 4-hydroxy-6-methyl-2-methylthiopyrimidine (I) with chloroacetonitrile, with minor exceptions, is probably connected with the influence of the cyano group on the stability and polarizability of the C–Cl bond, and also on the stability of the transition state, and conforms to the same mechanism as in the alkylation with haloacetic esters.

EXPERIMENTAL

Control of the course of the reaction and with the purity of the compounds was accomplished on Silufol plates, visualized with iodine vapor. Silica gel (L 100/160 Chemapol) was used for column chromatography: A mixture of chloroform and ethyl acetate (5:1) was used for elution. The UV spectra were determined with a Specord UV-VIS instrument in ethanol. The IR spectra were recorded with an IR-75 in mineral oil suspension. The ^1H NMR were measured with a Tesla BS-487C (80 MHz) instrument in $CDCl_3$, with HMDS as internal standard.

Elemental analyses data for C, H, and N agreed with the calculated values.

4-Hydroxy-6-methyl-2-methylthiopyrimidine (I, $C_6H_8N_2OS$) was synthesized according to [3], and its sodium salt ($C_6H_7NaN_2OS$) according to [4].

6-Methyl-2-methythio-4-cyanomethoxypyrimidine (II, $C_8H_9N_3OS$) and 6-Methyl-2-methylthio-3-cyanomethyl-4-pyrimidone (III, $C_8H_9N_3OS$). To a boiling solution of 1.78 g (0.01 mole) of the sodium slat of compound I in 50 ml of acetone was added dropwise 0.9 g (0.012 mole) of chloroacetonitrile. The mixture was boiled for 3 h, the solvent was evaporated under vacuum, the residue was treated with 50 ml of water, and the precipitate was filtered and dried to give 1.4 (72%) of a mixture of isomers of II and III. The isomer mixture was separated on a column. The fraction with R_f 0.72 consisted of compound II, 0.59 g (30%), mp 64-65°C (hexane). IR spectrum: 2247 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 254 nm (3.89). ^1H NMR spectrum: 2.33 (3H, s, CH_3); 2.50 (3H, s, SCH_3); 4.94 (2H, s, OCH_2); 6.26 ppm (1H, s, 5-CH).

The fraction with R_f 0.52 consisted of compounds III, 0.65 g (34%), mp 120-122°C (hexane). IR spectrum: 1653 (C=O), 2240 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 235 (3.76), 293 nm (3.95). ^1H NMR spectrum: 2.16 (3H, s, CH_3); 2.56 (3H, s, SCH_3); 4.90 (2H, s, NCH_2); 6.0 ppm (1H, s, 5-CH).

6-Methyl-2-methylthio-4-cyanomethoxypyrimidine (II). The sodium salt of compound I (1.78 g, 0.01 mole) was dissolved in 25 ml of hexamethyltriamidophosphate, cooled to 0-5°C, and 0.9 g (0.012 mole) of chloroacetonitrile was added dropwise over 5 h. The reaction mixture was stirred at the same temperature for 2 h and added to 150 ml of cold water. The precipitate was filtered off, dried, and crystallized from hexane to give 1.03 g (53%).

6-Methyl-2-methylthio-3-cyanomethyl-4-pyrimidone (III). To the sodium salt of compound I (1.78 g, 0.01 mole) in 5 ml of dioxane or tetrahydrofuran was added dropwise 0.9 g (0.012 mole) of chloroacetonitrile. The mixture was boiled for 3 h, the solvent was evaporated under vacuum, the residue was treated with 50 ml of water, and the precipitate was filtered off, dried, and crystallized from hexane to give 1.27 g (65%) or 1.21 g (62%), respectively.

Alkylation of 4-Hydroxy-6-methyl-2-methylthiopyrimidine (I) with Chloroacetonitrile in Triethylamine. To a stirred suspension of 1.56 g (0.01 mole) of compound I and 0.32 g (1 mmole) of tetrabutylammonium bromide in 4 ml of triethylamine was added dropwise 0.9 g (0.012 mole) of chloroacetonitrile (see Table 2). The reaction mixture was cooled and diluted with 150 ml of water, and the precipitate was filtered off and dried. The mixture of isomers was separated on a column.

REFERENCES

1. P. I. Vainilavichyus and V. Yu. Syadyaryavichyushe, Zh. Geterotsikl. Khim., No. 11, 1520 (1987).
2. P. I. Vainilavichyus and V. Yu. Syadyaryavichyushe, Zh. Geterotsikl. Khim., No. 12, 1655 (1987).
3. H. L. Wheeler and H. F. Merriam, Am. J. Chem., **29**, 478 (1903).
4. J. P. Jonak, G. C. Hopkins, H. J. Minnemeyer, and H. Tieckelman, J. Org. Chem., **35**, 2512 (1970).