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STUDIES ON FUNCTIONALLY-SUBSTITUTED AZINES. 9.* REACTION OF (6-METHOXY-4-METHYL-2-PYRIMIDINYL)-TRIMETHYLAMMONIUM CHLORIDE WITH O- AND C-NUCLEOPHILES

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The reactions of (4-methyl-6-methoxy-2-pyrimidyl)trimethylammonium chloride with a mixture of formaldehyde and sodium cyanide and mixtures of sodium cyanamide and guanidine derivatives in the presence of alkali lead to the formation of 2-substituted pyrimidines.

Keywords: arylsulfoguanidine, O-nucleophiles, N-nucleophiles, cyanaminopyrimidine, cyanomethylpyrimidine.

The action of ethylene chlorohydrin on pyrimidinyltrimethylammonium chlorides in the presence of alkali leads to chloroethoxypyrimidines [2]. The smooth formation of these compounds requires primarily a low reaction temperature, which provides stability for the alkali-sensitive starting compounds and permits the reaction to proceed in the desired direction.

In the present work, we studied the reactions of such salts with other O- and N-nucleophiles in an attempt to develop convenient methods for the functionalization of pyrimidine (Scheme 1).

(6-Methoxy-4-methyl-2-pyrimidinyl)trimethylammonium chloride (**1**) reacts with a cyanomethylating mixture to give cyanomethoxypyrimidine **2** and with sodium cyanamide to give cyanaminopyrimidine **3**. The reactions of **1** with substituted guanidines is largely regioselective. Thus, cyanoguanidine reacts predominantly at the cyanamino NH fragment, while **5** with an alternative structure is formed in 12% yield. Arylsulfoguanidine, despite the presence of an amide function, behaves as an amine to give symmetrical pyrimidinylarylsulfoguanidines **6a** and **6b**.

* Communication 8, see ref. [1].

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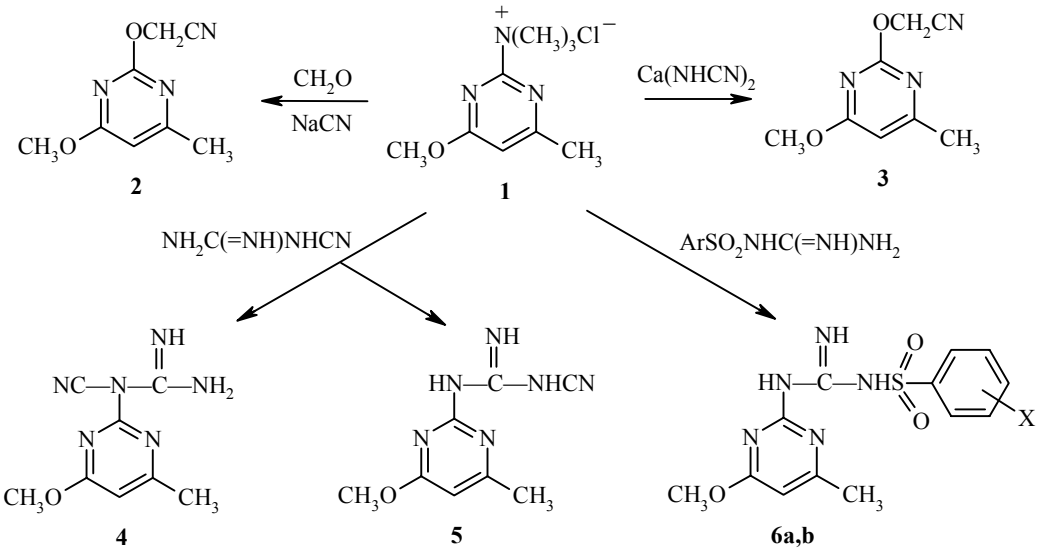
Scheme 1



6 a X = 4-CH_3; **b** X = 2-Cl

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for vaseline mulls, while the ^{1}H NMR spectra were taken on a Mercury-300 spectrometer in acetone-d_6 and DMSO-d_6.

2-Cyanomethoxy-6-methoxy-4-methylpyrimidine (2). Compound **1** (2.2 g, 0.01 mol) [3] was added in portions to a cyanomethylating mixture obtained from sodium cyanide (0.54 g, 0.011 mol) and 36% formalin (1.0 ml, 0.011 mol) at 0°C. The mixture was stirred for 30 min at 0°C and for 1 h at 15-20°C. Then, ice water (8 ml) was added and the product was filtered off. Yield of compound **2** 1.5 g (83%); mp 65-67°C, R_f 0.42 (1:1 acetone–hexane). IR spectrum: 2260 (C≡N); 1585, 1560, 1505 (C=N, C=C); 1165, 1120 cm^{-1} (C–O–C). ^{1}H NMR spectrum (acetone-d_6): 2.2 (3H, s, CH_3); 3.8 (3H, s, OCH_3); 4.45 (2H, t, OCH_2); 6.2 ppm (1H, s, CH). Found, %: C 53.79; H 5.27; N 23.64. $C_8H_9N_3O_2$. Calculated, %: C 53.63; H 5.03; N 23.46.

2-Cyanamino-6-methoxy-4-methylpyrimidine (3). A suspension of technical-grade potassium cyanamide (containing 55% major product) (3.7 g, 0.046 mol) in water (20 ml) was stirred for 3 h at 30-35°C and filtered. Compound **1** (2.2 g, 0.01 mol) was added in portions to the filtrate (containing acid potassium cyanamide) at 5-10°C. The reaction mixture was maintained for 24 h at 15-20°C and filtered to remove turbidity. The filtrate was brought to pH 4 by adding hydrochloric acid. Filtration gave the product **3**, which was washed with water (5 ml). Yield of **3** 1.1 g (67%); mp 246-248°C (dec.). IR spectrum: 2250 (C≡N); 1560, 1545, 1510 (C=N, C=C); 1180, 1115 (C–O–C); 3200-3350 cm^{-1} (NH). ^{1}H NMR spectrum (DMSO-d_6): 2.2 (3H, s, CH_3); 3.8 (3H, s, OCH_3); 5.9 (1H, s, CH); 11.1 ppm (1H, br. s, NH). Found, %: C 51.40; H 5.04; N 34.41. $C_7H_8N_4O$. Calculated, %: C 51.22; H 4.88; N 34.15.

N-Cyano-N-(6-methoxy-4-methyl-2-pyrimidinyl)guanidines (4, 5). A suspension of NaOH (0.44 g, 0.01 mol) and dicyandiamide (0.84 g, 0.01 mol) in acetone (15 ml) was stirred for 15 min at 0°C and, then, compound **1** (2.2 g, 0.01 mol) was added in portions to the suspension at 0°C. The mixture was stirred for 2-14 h at 20°C until no further amine was released and, then, filtered. The filter was treated with water (5 ml) and the precipitate was filtered off to give 1.5 g (72%) of compound **4**; mp 233-235°C. IR spectrum: 1590, 1545 (C=N, C=C); 1625 (C=NH); 2180 (C≡N); 3300 cm^{-1} (NH_2). ^{1}H NMR spectrum (DMSO-d_6): 2.2 (3H, s, CH_3); 3.85 (3H,

s, OCH_3); 5.8 (1H, s, CH); 6.6 (2H, s, NH_2); 11.3 ppm (1H, br. s, NH). Found, %: C 46.91; H 5.12; N 41.00. $C_8H_{10}N_6O$. Calculated, %: C 46.60; H 4.85; N 40.78. The acetone filtrate was evaporated and the residue was treated with water. The precipitate was filtered off to give 0.25 g (12%) of compound **5**; mp 214-216°C.

N-Arylsulfonyl-N'-(6-methoxy-4-methyl-2-pyrimidinyl)guanidines (6a,b). Guanidine **6a** (X = 4-CH_3). Compound **1** (2.2 g, 0.01 mol) was added in portions to a suspension of NaOH (0.44 g, 0.01 mol) and *p*-toluenesulfoguanidine (2.1 g, 0.01 mol) in acetone (15 ml) at 0°C. The mixture was stirred for 48 h at 20°C until no further amine was released and filtered. The filtrate was evaporated. The residue was treated with water (5 ml) and filtered to give compound **6a** (2.6 g, 78%); mp 168-169°C (dec.). IR spectrum: 1180-1140 (S=O); 1550, 1600 (C=N, C=C); 1620 (C=NH); 3200, 3400 cm^{-1} (NH). ^1H NMR spectrum (DMSO-d_6): 2.25 (3H, s, CH_3); 2.42 (3H, s, CH_3–Ar); 3.80 (3H, s, OCH_3); 5.82 (1H, s, CH); 6.8 (1H, br. s, =NH); 7.28-7.8 (4H, m, Ar); 9.3 ppm (2H, br. s, 2NH). Found, %: N 21.12; S 9.33. $C_{14}H_{17}N_5O_3S$. Calculated, %: N 20.90; S 9.55.

Guanidine **6b** (X = 2-Cl) was obtained analogously in 79% yield; mp 177-179°C (dec.). IR spectrum: 1550, 1590 (C=N, C=C); 1625 (C=NH); 3200, 3380 cm^{-1} (NH). ^1H NMR spectrum (DMSO-d_6): 2.2 (3H, s, CH_3); 5.8 (1H, s, CH); 6.8 (1H, br. s, =NH); 7.35-7.85 (4H, m, Ar); 9.25 ppm (2H, br. s, 2NH). Found, %: Cl 9.68; N 19.92; S 9.34. $C_{13}H_{14}ClN_5O_3S$. Calculated, %: Cl 9.99; N 19.69; S 9.00.

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