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NOVEL METHOD FOR THE SYNTHESIS OF FURO[2,3-*d*]PYRIMIDINES BY CYCLIZATION OF 4-(PHENACYLOXY)PYRIMIDINE-5-CARBONITRILES

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It is known that alkylation of 4(3H)-pyrimidinones occurs with the formation of a mixture of N(1)-, N(3)-, and O-alkylation products [1, 2]. We have previously found [3, 4] that reaction of 5-cyano-2-methylsulfanyl-4(3H)-pyrimidinone (**1**) with 4-substituted ω-bromoacetophenones **2a,b** in the presence of potassium carbonate and a catalytic amount of potassium iodide in anhydrous acetonitrile medium readily gives all three of the O-, N(1)-, and N(3)- alkylations. The main reaction course (O-alkylation) gives the 2-methylsulfanyl-4-(phenacyloxy)pyrimidine-5-carbonitriles **3a,b** in preparative yields of 37-50%. In continuing our study of the alkylation of 4(3H)-pyrimidinones we report here a novel synthetic route to the furo[2,3-*d*]pyrimidine system *via* cyclization of 2-methylsulfanyl-4-(phenacyloxy)pyrimidine-5-carbonitriles **3a,b**. Interest in the method of synthesis of furo[2,3-*d*]pyrimidines is due to the wide spectrum of biological activity of these compounds [5-8].

The synthesis of the previously unknown 5-amino-6-(4'-R-benzoyl)-2-methylfulfanylfuro[2,3-*d*]pyrimidines **4a,b** from carbonitriles **3a,b** was carried out under Thorpe-Ziegler cyclization conditions using the system ethanol–sodium ethoxide. According to our data, such a transformation has only been studied for O-(β-oxo)alkyl derivatives of 3-cyano-2(1H)-pyridinone [9] (forming 3-aminofuro[2,3-*d*]pyridines) and the investigation of the routes of synthesis of furo[2,3-*b*]pyrimidines by cyclization of pyrimidines has been mainly reported in the literature through closing the side chain of 5-alkynyl derivatives [8] with only a single example of the cyclization of 5-alkoxycarbonyl [5] and 5-cyano derivatives [10].

Elemental analysis, IR, and ^{1}H and ^{13}C NMR spectra obtained for compounds were fully in agreement with the structures of the furo[2,3-*d*]pyrimidines **4a,b**. For these compound the ^{1}H NMR spectra show singlets for the protons of the 5-amino group and H-4 of the pyrimidine ring at 7.67-7.84 and 9.26-9.27 ppm respectively together with the absence of a signal for the OCH_2 group appearing in the region 5.99-6.04 ppm in the ^{1}H NMR spectra of the starting carbonitriles **3a,b**. The ^{13}C NMR spectra of the furopyrimidines **4a,b** show a shift of the carbonyl carbon atom of 10.95-12.57 ppm to higher field when compared with those in compounds **3a,b** and the C-4a signal is seen near 131.5 ppm (the corresponding C-5 signal in the spectrum of carbonitriles **3a,b**

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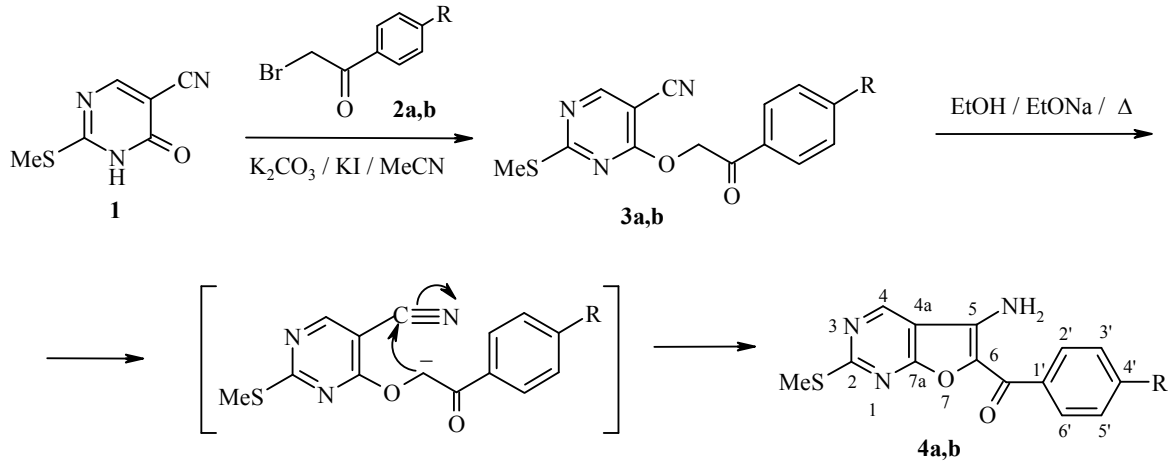
appearing at 90.9 ppm). The IR spectra show characteristic absorption bands for ν_{CO} and ν_{NH} at 1638-1622 and 3411-3200 cm^{-1} respectively together with the absence of the absorption for ν_{CN} at 2229-2226 cm^{-1} which characterizes compounds **3a,b**.



2–4 **a** R = MeO, **b** R = Cl

The IR spectra were taken on a Perkin-Elmer BX-II FT-IR spectrophotometer for KBr tablets. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA spectrometer (300 and 75 MHz respectively) using DMSO-d_6 and with TMS as internal standard. Monitoring of the course of the reaction and the purity of the compounds obtained was carried out by TLC on Silica Gel 60 F254 glass plates (Sigma-Aldrich) using the system chloroform–ethyl acetate (4:1) and were revealed using UV light.

The starting 2-methylsulfanyl-4-(phenacyloxy)pyrimidine-5-carbonitriles **3a,b** were prepared by method [4].

Compounds 4a,b (General Method). The corresponding 5-carbonitrile **3a,b** (1.0 mmol) was added to a solution of sodium ethoxide (1 mmol) prepared from metallic sodium (0.023 g, 1.0 mmol) in absolute ethanol (10 ml) and the product was refluxed with stirring for 6-8 h using TLC to monitor the reaction course. The hot reaction mixture was filtered and the precipitate on the filter was washed with refluxing ethanol (2×2.5 ml), and recrystallized. The cooled mother liquor gave an additional amount of the furo[2,3-*d*]pyrimidines **4a,b**.

5-Amino-2-methylsulfanyl-6-(4'-methoxybenzoyl)furo[2,3-*d*]pyrimidine (4a). Yield 63%; mp 238-240ºC (ethanol), R_f 0.43. IR spectrum, ν, cm^{-1}: 3384, 3299, 3200 (NH), 1638 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.60 (3H, s, SCH_3); 3.88 (3H, s, OCH_3); 7.13 (2H, d, *J* = 9.0, H-3',5'); 7.67 (2H, s, NH_2); 8.09 (2H, d, *J* = 9.0, H-2',6'); 9.26 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 14.65 (SCH_3), 56.15 (OCH_3); 109.33 (C-5); 114.48 (C-3',5'); 130.55 (C-1'); 131.42 (C-2',6'); 131.50 (C-4a); 154.47 (C-6); 162.89 (C-4'); 165.02 (C-7a), 172.92 (C-2); 180.31 (CO). Found, %: C 57.07; H 4.13; N 13.41. $C_{15}H_{13}N_3O_3S$. Calculated, %: C 57.13; H 4.15; N 13.32.

5-Amino-(4'-chlorobenzoyl)-2-methylsulfanyl-6-furo[2,3-*d*]pyrimidine (4b). Yield 50%; mp 246-249ºC (ethanol), R_f 0.39. IR spectrum, ν, cm^{-1}: 3411, 3296 (NH), 1622 (C=O ketone). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.59 (3H, s, SCH_3); 7.65 (2H, d, *J* = 8.7, H-3',5'); 7.84 (2H, s, NH_2); 8.05 (2H, d, *J* = 8.7, H-2',6'); 9.27 (1H, s, H-4); ^{13}C NMR spectrum, δ, ppm: 14.66 (SCH_3); 109.12 (C-5); 129.28 (C-3',5'); 131.03 (C-2',6'); 131.36 (C-4a); 136.65 (C-1'); 137.35 (C-4'); 141.95 (C-4); 154.72 (C-6); 165.18 (C-7a); 173.45 (C-2); 179.71 (CO). Found, %: C 52.46; H 3.23; N 13.02. $C_{14}H_{10}ClN_3O_2S$. Calculated, %: C 52.59; H 3.15; N 13.14.

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