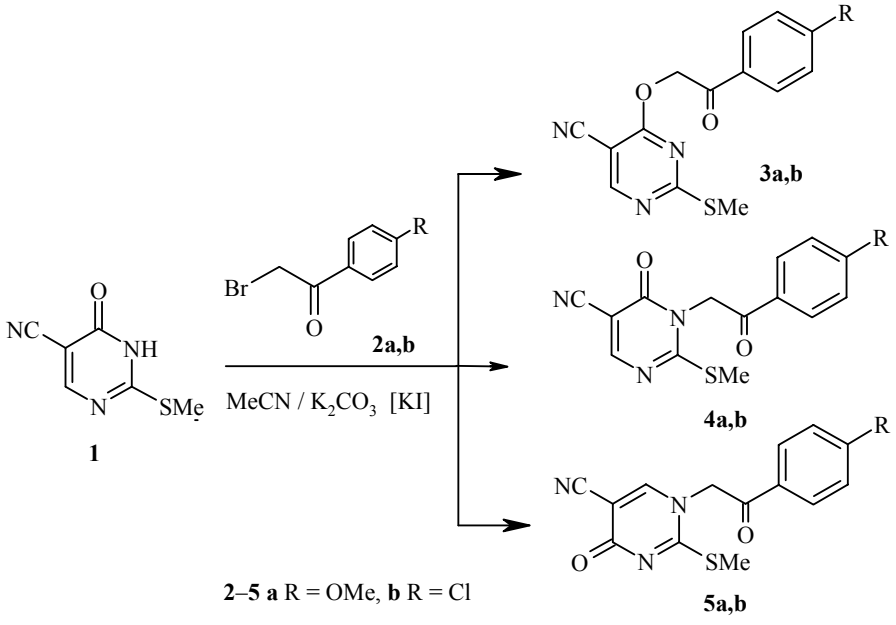
N(1)-, N(3)-, AND O-ALKYLATION OF 5-CYANO-2-METHYLSULFANYL-4(3H)-PYRIMIDINONE BY 4-SUBSTITUTED ω-BROMOACETOPHENONES IN THE SYSTEM ACETONITRILE-K_2CO_3

V. Gefenas[1]*, Z. Stankeviciute[1,2], and A. Malinauskas[2]

Keywords: ω-Bromoacetophenones, potassium carbonate, 5-cyano-2-methylsulfanyl-4(3H)-pyrimidinone, N(1)-, N(3)-, and O-alkylation, acetonitrile.

Alkylation of 4(3H)-pyrimidinones occurs to give a mixture of N(1)-, N(3)-, and O-alkylation products [1]. Analysis of literature data shows that alkylation with haloacetic esters, chloroacetonitrile, N-benzylhaloacylamides, 3-bromopropan-1-ol, or ω-bromoacetophenone generally gives just the O- and N(3)-alkylation products. According to our results N(1)-alkylation products have hardly been studied and only discovered and separated with the use of haloalkanes and benzyl halides as alkylating agent [1-4].



* To whom correspondence should be addressed, e-mail: vladasg@vpu.lt.

[1]Faculty of Natural Sciences, Vilnius Pedagogical University, Vilnius LT-08106, Lithuania.
[2]Institute of Chemistry, Vilnius LT-01108, Lithuania.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1754-1756, November, 2009. Original article submitted October 12, 2009.

We have found that treatment of 5-cyano-2-methylsulfanyl-4(3H)-pyrimidinone (**1**) with the 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 O-, N(3)-, and N(1)-alkylation products **3a-b** to **5a-b**. According to ^{1}H NMR spectroscopic data for the reaction mixtures side products are not formed under these conditions.

The main reaction product is the O-alkylated isomer **3a,b** with the N(3)- and N(1)-alkylation products **4a,b** and **5a,b** respectively separated as minor components by fractional crystallization or by column chromatography. (the overall alkylation yield being 70-74%). Elemental analysis, IR , ^{1}H and ^{13}C NMR spectra for the compounds prepared were fully in agreement with their structures as alkylated derivatives of the 5-cyano-2-methylsulfanyl-4(3H)-pyrimidinone.

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

Starting 5-Cyano-2-methylsulfanyl-4(3H)-pyrimidinone (1) was prepared by method [5].

Compounds 3a,b-5a,b (General Method). A mixture of compound **1** (2 g, 12.0 mmol) and anhydrous K_2CO_3 (0.84 g, 6.0 mmol) was refluxed with stirring in anhydrous MeCN (30 ml) for 1 h. Potassium iodide (0.2 g, 1.2 mmol) was then added to the refluxing reaction mixture followed by dropwise addition over 1 h of a solution of the ω-bromoacetophenone **2a,b** (2.38 g, 12.0 mmol) in anhydrous acetonitrile (30 ml) and further refluxing for 2 h. The hot reaction mixture was filtered, the inorganic residue was washed with refluxing acetonitrile, and the filtrate obtained crystallized successfully at -15 and 0ºC. The filtrate was evaporated to a dry residue which was treated successively with benzene and acetonitrile. The obtained fractions were recrystallized or separated by column chromatography (Silica Gel S, chloroform-ethyl acetate, 4:1).

4-(4'-Methoxyphenacyloxy)-2-methylsulfanylpyrimidine-5-carbonitrile (3a). Yield 50%; mp 140-142ºC (benzene), R_f 0.74. IR spectrum, ν, cm^{-1}: 1686 (ketone C=O), 2226 (CN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, SCH_3); 3.89 (3H, s, OCH_3); 5.99 (2H, s, OCH_2); 7.12 (2H, d, *J* = 9.0, H-3',5'); 8.01 (2H, d, *J* = 9.0, H-2',6'); 8.93 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 14.41 (SCH_3); 56.38 (OCH_3); 70.00 (OCH_2); 90.91 (C-5); 114.56 (CN); 114.98 (C-3',5'); 127.24 (C-1'); 130.92 (C-2',6'); 162.84 (C-6); 164.56 (C-4'); 167.57 (C-4); 176.50 (C-2); 191.26 (CO). Found, %: C 57.15; H 4.23; N 13.61. $C_{15}H_{13}N_3O_3S$. Calculated, %: C 57.13; H 4.15; N 13.32.

3-(4'-Methoxyphenacyl)-2-methylsulfanyl-4-oxo-3,4-dihydropyrimidine-5-carbonitrile (4a). Yield 3%, mp 183-185ºC (from 2-propanol); R_f 0.54. IR Spectrum, ν, cm^{-1}: 1680 (lactam and ketone C=O), 2232 (CN). ^{1}H NMR Spectrum, δ, ppm (*J*, Hz): 2.63 (3H, s, SCH_3); 3.90 (3H, s, OCH_3); 5.66 (2H, s, NCH_2); 7.15 (2H, d, *J* = 9.0, H-3',5'); 8.11 (2H, d, *J* = 9.0, H-2',6'); 8.67 (1H, s, H-6). ^{13}C NMR Spectrum, δ, ppm: 16.00 (SCH_3); 51.45 (NCH_2); 56.47 (OCH_3); 96.60 (C-5); 115.08 (C-3',5'); 115.40 (CN); 127.44 (C-1'); 131.50 (C-2',6'); 158.91 (C-6); 160.38 (C-2); 164.97 (C-4'); 170.72 (C-4); 189.28 (CO). Found, %: C 57.29; H 4.23; N 13.26. $C_{15}H_{13}N_3O_3S$. Calculated, %: C 57.13; H 4.15; N 13.32.

1-(4'-Methoxyphenacyl)-2-methylsulfanyl-4-oxo-1,4-dihydropyrimidine-5-carbonitrile (5a). Yield 11%; mp 242-245ºC (acetonitrile); R_f 0.23. IR spectrum, ν, cm^{-1}: 1651 (C=O ring), 1684 (C=O ketone), 2225 (CN). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.50 (3H, s, SCH_3); 3.91 (3H, s, OCH_3); 5.68 (2H, s, NCH_2); 7.16 (2H, d, *J* = 9.0, H-3',5'); 8.08 (2H, d, *J* = 9.0, H-2',6'); 8.61 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 15.09 (SCH_3); 56.51 (OCH_3); 58.89 (NCH_2); 94.93 (C-5); 115.14 (C-3',5'); 115.40 (CN); 127.08 (C-1'); 131.45 (C-2',6'); 154.81 (C-2); 163.12 (C-4); 165.06 (C-4'); 166.65 (C-6); 190.09 (CO). Found, %: C 57.42; H 4.31; N 13.10. $C_{15}H_{13}N_3O_3S$. Calculated, %: C 57.13; H 4.15; N 13.32

4-(4'-Chlorophenacyloxy)-2-methylsulfanylpyrimidine-5-carbonitrile (3b). Yield 37%; mp 173-175ºC (benzene); R_f 0.81. IR spectrum, ν, cm^{-1}: 1699 (C=O ketone), 2229 (CN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz):

2.33 (3H, s, SCH_3); 6.04 (2H, s, OCH_2); 7.69 (2H, d, J = 8.7, H-3',5'); 8.05 (2H, d, J = 8.7, H-2',6'); 8.95 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 14.42 (SCH_3); 70.19 (OCH_2); 90.94 (C-5); 114.48 (CN); 129.92 (C-3',5'); 130.51 (C-2',6'); 133.11 (C-1'); 139.84 (C-4'); 162.91 (C-6); 167.43 (C-4); 176.53 (C-2); 192.28 (CO). Found, %: C 52.61; H 3.23; N 13.21. $C_{14}H_{10}ClN_3O_2S$. Calculated, %: C 52.59; H 3.15; N 13.14.

3-(4'-Chlorophenacyl)-2-methylsulfanyl-4-oxo--3,4-dihydropyrimidine-5-carbonitrile (4b). Yield 1.6%; mp 186-188ºC (2-propanol); R_f 0.61. IR spectrum, ν, cm^{-1}: 1683 (C=O lactam), 1690 (C=O ketone), 2224 (CN). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.64 (3H, s, SCH_3); 5.73 (2H, s, NCH_2); 7.72 (2H, d, J = 9.0, H-3',5'); 8.16 (2H, d, J = 8.7, H-2',6'); 8.68 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 16.03 (SCH_3); 51.79 (NCH_2); 96.66 (C-5); 115.30 (CN); 129.98 (C-3',5'); 131.01 (C-2',6'); 133.23 (C-1'); 140.40 (C-4'); 158.84 (C-6); 160.45 (C-2); 170.65 (C-4); 190.56 (CO). Found, %: C 52.72; H 3.20; N 13.28. $C_{14}H_{10}ClN_3O_2S$. Calculated, %: C 52.59; H 3.15; N 13.14.

1-(4'-Chlorophenacyl)-2-methylsulfanyl-4-oxo--1,4-dihydropyrimidin-5-carbonitrile (5b). Yield 12%; mp 244-247ºC (acetonitrile); R_f 0.23. IR spectrum, ν, cm^{-1}: 1651 (C=O ring), 1689 (C=O ketone), 2227 (CN). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.51 (3H, s, SCH_3); 5.76 (2H, s, NCH_2); 7.74 (2H, d, J = 8.4, H-3',5'); 8.12 (2H, d, J = 8.7, H-2',6'); 8.59 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 15.12 (SCH_3); 59.19 (NCH_2); 95.02 (C-5); 115.34 (CN); 130.06 (C-3',5'); 130.92 (C-2',6'); 132.91 (C-1'); 140.48 (C-4'); 154.73 (C-2); 163.04 (C-4); 166.65 (C-6); 191.22 (CO). Found, %: C 52.19; H 3.58; N 13.00. $C_{14}H_{10}ClN_3O_2S$. Calculated, %: C 52.59; H 3.15; N 13.14.

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