

Simple and efficient synthesis of new N₍₃₎-, O- and S-substituted 2-methylthio-6-phenylpyrimidin-4(3H)-one based derivatives

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Reactions of sodium salt of 2-methylthio-6-phenylpyrimidin-4(3H)-one with chloroacetone, ω-bromoacetophenone and methyl bromoacetate in different solvents were studied. Regioselective N₍₃₎-alkylation took place in tetrachloromethane at reflux, while in dimethylformamide at ambient temperature O-acylmethyl derivatives were obtained. 2-Methylthio-6-phenylpyrimidine-4(3H)-thione reacted with chloroacetone and ω-bromoacetophenone in a sodium methoxide–methanol solution to give the corresponding S-substituted derivatives. Oxidation reactions of the resulting N₍₃₎-, O- and S-acylmethyl derivatives with hydrogen peroxide in acetic acid were discussed.

Keywords: alkylation, oxidation, pyrimidine, sulfone, thioether

INTRODUCTION

The pyrimidine moiety is an important component in natural products and it is a usual building block in the synthesis of pharmacologically active compounds [1]. Substituted pyrimidines, alkyl- and arylthiopyrimidines among them, are of great interest for antibacterial, anticancer, antitubercular etc. activity [2–6]. Therefore, the development of efficient and practical synthetic methods of pyrimidine derivatives is a significant and challenging work.

Some time ago we have reported a number of pyrimidine derivatives exhibiting biological activity [7–9]. In connection with our earlier experience in the field of alkylation reactions of pyrimidine ring [10, 11], herein we present simple and efficient synthetic procedures to new O-, N₍₃₎- and S-acylmethyl substituted pyrimidine derivatives starting with 2-methylthio-6-phenylpyrimidin-4(3H)-one. In addition, the methylthio group adjacent to the nitrogen atoms of the pyrimidine ring is readily oxidized. The corresponding pyrimidine-derived sulfoxides or sulfones can be easily substituted with a wide range of nucleophiles, and valuable synthons can be obtained in this way. Customary oxidation processes and oxidants known hitherto using halogens [12–14], peracids [14, 15], hydrogen peroxide [14,

16–19] etc. have been applied to the reactions of thioethers. Hydrogen peroxide is the most attractive environment-friendly oxidizing agent. In this paper the results of reaction of new O-, N₍₃₎- and S-acylmethyl substituted 2-methylthio-6-phenylpyrimidine derivatives with hydrogen peroxide will be discussed.

EXPERIMENTAL

Melting points were determined in open capillaries with a digital melting point IA9100 series apparatus (Thermo Fisher Scientific) and are uncorrected. The IR spectra were recorded on a FTIR spectrophotometer Spectrum BX II (Perkin-Elmer). ¹H and ¹³C NMR spectra were recorded on a Varian INOVA (300 and 75 MHz, respectively) or Bruker Ascend 400 (400 and 100 MHz, respectively) spectrometers, using residual solvent peaks as an internal standard. All reactions and purity of the synthesized compounds were monitored by TLC on Silica Gel 60 F₂₅₄ aluminium plates (Merck). Visualization was accomplished by UV light. Elemental analyses were performed at the Microanalysis Laboratory of the Department. Reagents were purchased from commercial sources. The solvents used were dried and purified by the routine laboratory methods.

2-Methylthio-6-phenylpyrimidin-4(3H)-one (**1**), methyl (2-methylthio-4-oxo-6-phenylpyrimidin-3(4H)-yl)acetate (**4c**) were synthesized according to refs. [20, 10].

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2-Methylthio-6-phenylpyrimidine-4(3H)-thione (2)

A mixture of Lawesson's reagent (3.64 g, 9.0 mmol) and pyrimidinone **1** (1.96 g, 9 mmol) in dry toluene (~40 ml) was refluxed for 3 hours. The hot reaction mixture was then filtered. The filtrate was cooled to room temperature, the solid was filtered off and recrystallized from methanol to give yellow crystals of **2**, yield 67%, 1.41 g, m. p. 220–222 °C; IR (ν_{\max} , cm^{-1}): 3120 (NH). ^1H NMR (300 MHz, DMSO- d_6): δ_{H} 2.60 (s, 3H, SCH₃), 7.53–7.64 (m, 3H, C₆H₅), 7.80 (s, 1H, C(5)-H), 8.10–8.13 (m, 2H, C₆H₅) ppm. ^{13}C NMR (75 MHz, DMSO- d_6): δ_{C} 13.8, 118.5, 128.0, 129.6, 132.0, 135.7, 155.6, 163.1, 185.0 ppm. Anal. calcd. for C₁₁H₁₀N₂S₂ (234.34): C, 56.38; H, 4.30; N, 11.95%. Found: C, 56.76; H, 4.44; N, 11.59%.

1-[(2-Methylthio-6-phenylpyrimidin-4-yl)oxy]acetone (3a)

A mixture of pyrimidinone **1** (2.1 mmol, 0.46 g) and sodium methoxide (2.1 mmol, 0.048 g of sodium, dissolved in ~8 ml of methanol) was refluxed for 10 min. The solvent was evaporated to dryness, the residue sodium salt was dried perfectly and then was dissolved in dimethylformamide (10 ml). Chloroacetone (2.2 mmol, 0.21 g, 0.19 ml) was added dropwise under stirring to this solution and the reaction mixture was maintained at room temperature for 5 h. Then water (20 ml) was added and the mixture was left for 1 hour at ambient temperature. The resulting solid was filtered off and recrystallized from 2-propanol to yield **3a**, 88%, 0.51 g, m. p. 115–116 °C; IR (ν_{\max} , cm^{-1}): 1732 (C=O). ^1H NMR (300 MHz, CDCl₃): δ_{H} 2.27 (s, 3H, CH₃), 2.62 (s, 3H, SCH₃), 5.01 (s, 2H, OCH₂), 6.97 (s, 1H, C(5)-H), 7.50–7.53 (m, 3H, C₆H₅), 8.07–8.10 (m, 2H, C₆H₅) ppm. ^{13}C NMR (75 MHz, DMSO- d_6): δ_{C} 14.4, 26.6, 70.5, 98.8, 127.4, 129.0, 131.1, 136.7, 165.6, 168.9, 172.0, 203.3 ppm. Anal. calcd. for C₁₄H₁₄N₂O₂S (274.34): C, 61.29; H, 5.14; N, 10.21%. Found: C, 61.56; H, 5.47; N, 10.34%.

2-[(2-Methylthio-6-phenylpyrimidin-4-yl)oxy]-1-phenylethanone (3b)

The dry sodium salt of pyrimidinone **1** prepared as described for **3a** from pyrimidinone **1** (2.1 mmol, 0.46 g) and sodium (2.1 mmol, 0.048 g) was dissolved in dimethylformamide (10 ml). ω -Bromoacetophenone (0.42 g, 2.15 mmol) was added in portions under stirring to this solution. The reaction mixture was stirred at room temperature for 3 h. The precipitate formed was filtered off. An additional amount of product was obtained by adding water to the filtrate. The solids were combined and recrystallized from 2-propanol to yield **3b**, 89%, 0.63 g, m. p. 165–166 °C; IR (ν_{\max} , cm^{-1}): 1696 (C=O). ^1H NMR (300 MHz, CDCl₃): δ_{H} 2.49 (s, 3H, SCH₃), 5.71 (s, 2H, OCH₂), 7.03 (s, 1H, C(5)-H), 7.50–7.56 (m, 5H, C₆H₅), 7.58–8.11 (m, 5H, C₆H₅) ppm. ^{13}C NMR (75 MHz, CDCl₃): δ_{C} 14.4, 68.1, 99.0, 127.4, 128.1, 129.0, 129.2, 131.0, 134.1, 134.8, 136.8, 165.5, 169.1, 171.9, 193.4 ppm. Anal. calcd. for C₁₉H₁₆N₂O₂S (336.41): C, 67.84; H, 4.79; N, 8.33%. Found: C, 68.44; H, 5.05; N, 8.47%.

Methyl [(2-methylthio-6-phenylpyrimidin-4-yl)oxy]acetate (3c)

The dry sodium salt of pyrimidinone **1** prepared as described for **3a** from pyrimidinone **1** (2.1 mmol, 0.46 g) and sodium (2.1 mmol, 0.048 g) was dissolved in dimethylformamide (10 ml). Ethyl bromoacetate (2.3 mmol, 0.38 g, 0.25 ml) was added dropwise to a stirred solution at room temperature. The mixture was maintained in this condition for 1 hour, then water (15 ml) was added and still left for 1 hour. The resulting solid was filtered off and recrystallized from 2-propanol to yield **3c**, 88%, 0.54 g, m. p. 85–86 °C; IR (ν_{\max} , cm^{-1}): 1746 (C=O). ^1H NMR (300 MHz, CDCl₃): δ_{H} 2.61 (s, 3H, SCH₃), 3.83 (s, 3H, OCH₃), 5.01 (s, 2H, OCH₂), 6.97 (s, 1H, C(5)-H), 7.50–7.52 (m, 3H, C₆H₅), 8.06–8.09 (m, 2H, C₆H₅) ppm. ^{13}C NMR (75 MHz, CDCl₃): δ_{C} 14.4, 52.5, 62.9, 98.9, 127.4, 129.0, 131.1, 136.7, 165.7, 168.9, 169.1, 172.0 ppm. Anal. calcd. for C₁₄H₁₄N₂O₃S (290.34): C, 57.92; H, 4.86; N, 9.65%. Found: C, 57.91; H, 4.81; N, 9.45%.

2-Methylthio-3-(2-oxopropyl)-6-phenylpyrimidin-4(3H)-one (4a)

The dry sodium salt of pyrimidinone **1** prepared as described for **3a** from pyrimidinone **1** (2.1 mmol, 0.46 g) and sodium (2.1 mmol, 0.048 g) was dissolved in tetrachloromethane (10 ml). Chloroacetone (2.2 mmol, 0.21 g, 0.19 ml) was added dropwise. The reaction mixture was refluxed under stirring for 4 hours. The precipitate was filtered off and recrystallized from methanol–water (1:1) to give **4a**, 86%, 1.94 g, m. p. 125–126 °C; IR (ν_{\max} , cm^{-1}): 1727, 1673 (C=O). ^1H NMR (300 MHz, CDCl₃): δ_{H} 2.33 (s, 3H, CH₃), 2.74 (s, 3H, SCH₃), 4.96 (s, 2H, NCH₂), 6.73 (s, 1H, C(5)-H), 7.49–7.52 (m, 3H, C₆H₅), 8.02–8.05 (m, 2H, C₆H₅) ppm. ^{13}C NMR (75 MHz, CDCl₃): δ_{C} 15.6, 27.6, 52.8, 104.3, 127.3, 129.0, 131.0, 136.4, 159.6, 162.6, 162.0, 199.6 ppm. Anal. calcd. for C₁₄H₁₄N₂O₂S (274.34): C, 61.29; H, 5.14; N, 10.21%. Found: C, 61.58; H, 5.14; N, 10.49%.

2-Methylthio-3-(2-oxo-2-phenylethyl)-6-phenylpyrimidin-4(3H)-one (4b)

The dry sodium salt of pyrimidinone **1** prepared as described for **3a** from pyrimidinone **1** (2.1 mmol, 0.46 g) and sodium (2.1 mmol, 0.048 g) was dissolved in tetrachloromethane (10 ml). Then ω -bromoacetophenone (2.15 mmol, 0.42 g) was added in portions and the reaction mixture was heated at reflux for 5 hours. The precipitate was filtered off to yield 88%, 0.62 g, m. p. 185–186 °C (from 2-propanol); IR (ν_{\max} , cm^{-1}): 1707, 1667 (C=O). ^1H NMR (300 MHz, DMSO- d_6): δ_{H} 2.70 (s, 3H, SCH₃), 5.68 (s, 2H, NCH₂), 6.91 (s, 1H, C(5)-H), 7.55–7.57 (m, 3H, C₆H₅), 7.63–7.68 (m, 2H, C₆H₅), 7.79–7.81 (m, 1H, C₆H₅), 8.15–8.21 (m, 4H, C₆H₅) ppm. ^{13}C NMR (75 MHz, DMSO- d_6): δ_{C} 15.6, 50.8, 104.0, 127.7, 128.9, 129.6, 129.8, 131.6, 134.9, 135.2, 136.4, 158.9, 162.2, 163.3, 192.2 ppm. Anal. calcd. for C₁₉H₁₆N₂O₂S (336.41): C, 67.84; H, 4.79; N, 8.33%. Found: C, 68.22; H, 4.63; N, 8.31%.

1-[(2-Methylthio-6-phenylpyrimidin-4-yl)thio]acetone (5a)

To a mixture of thione **2** (2.0 mmol, 0.47 g) and sodium methoxide solution (2 mmol, 0.046 g of sodium dissolved in 10 ml methanol) chloroacetone (2.1 mmol, 0.20 g, 0.18 ml) was added dropwise. The reaction mixture was heated at reflux for 30 min and cooled to room temperature. The solid was filtered off and recrystallized from 2-propanol to give **5a**, 71%, 0.41 g, m. p. 105–107 °C; IR (ν_{\max} , cm^{-1}): 1727 (C=O). ^1H NMR (400 MHz, CDCl_3): δ_{H} 2.38 (s, 3H, SCH_3), 2.61 (s, 3H, CH_3), 4.03 (s, 2H, SCH_2), 7.30 (s, 1H, C(5)-H), 7.48–7.49 (m, 3H, C_6H_5), 8.03–8.05 (m, 2H, C_6H_5) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 14.1, 28.9, 39.6, 109.5, 127.2, 128.9, 131.1, 136.1, 161.9, 168.1, 172.1, 202.4 ppm. Anal. calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{OS}_2$ (290.41): C, 57.90; H, 4.86; N, 9.65%. Found: C, 57.84; H, 4.81; N, 9.61%.

2-[(2-Methylthio-6-phenylpyrimidin-4-yl)thio]-1-phenylethanone (5b)

To a solution of thione **2** (2 mmol, 0.47 g) and sodium methoxide (2 mmol, 0.046 g of sodium, dissolved in 15 ml of methanol) ω -bromoacetophenone (2.15 mmol, 0.42 g) was added. The mixture was stirred at reflux for 15 min, then cooled to room temperature. The resulting precipitate was filtered and recrystallized from 2-propanol to yield **5b**, 70%, 0.49 g, m. p. 122–123 °C; IR (ν_{\max} , cm^{-1}): 1694 (C=O). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 2.31 (s, 3H, SCH_3), 4.95 (s, 2H, SCH_2), 7.50–7.60 (m, 5H, C_6H_5), 7.68–7.72 (m, 1H, C_6H_5), 7.81 (s, 1H, 5-CH), 8.09–8.17 (m, 4H, C_6H_5) ppm. ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 13.8, 37.5, 109.8, 127.6, 128.8, 129.3, 129.4, 131.8, 134.1, 135.9, 136.2, 161.5, 169.9, 171.4, 193.7 ppm. Anal. calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{OS}_2$ (352.48): C, 64.74; H, 4.58; N, 7.95%. Found: C, 64.64; H, 4.54; N, 7.87%.

General procedure for the synthesis of compounds 6a, b

To a solution of compound **3a** or **3b** (1.0 mmol) in glacial acetic acid (10 ml) 30% hydrogen peroxide (7 mmol, 0.79 g, 0.71 ml) was added at room temperature. The reaction mixture was stirred at ambient temperature for 48 hours. The solid formed was filtered off to give **6a** or **6b**. From the filtrate by adding water 6-phenyluracil 7 mp 270 °C [21] (~0.11 g) was isolated.

1-[(2-Methylsulfonyl-6-phenylpyrimidin-4-yl)oxy]acetone (6a). Yield 85%, 0.26 g, m. p. 125–126 °C; IR (ν_{\max} , cm^{-1}): 1734 (C=O). ^1H NMR (300 MHz, CDCl_3): δ_{H} 2.33 (s, 3H, CH_3), 3.41 (s, 3H, SO_2CH_3), 5.18 (s, 2H, OCH_2), 7.44 (s, 1H, C(5)-H), 7.58–7.60 (m, 3H, C_6H_5), 8.10–8.13 (m, 2H, C_6H_5) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 26.6, 39.3, 71.1, 105.8, 127.7, 129.4, 132.3, 134.9, 165.3, 166.8, 170.8, 201.3 ppm. Anal. calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$ (306.34): C, 54.89; H, 4.61; N, 9.14%. Found: C, 54.51; H, 4.57; N, 9.32%.

2-[(2-Methylsulfonyl-6-phenylpyrimidin-4-yl)oxy]-1-phenylethanone (6b). Yield 50%, 0.18 g, m. p. 190–192 °C;

IR (ν_{\max} , cm^{-1}): 1701 (C=O). ^1H NMR (300 MHz, CDCl_3): δ_{H} 3.29 (s, 3H, SO_2CH_3), 5.85 (s, 2H, OCH_2), 7.50 (s, 1H, C(5)-H), 7.54–7.57 (m, 5H, C_6H_5), 7.58–8.03 (m, 3H, C_6H_5), 8.12–8.15 (m, 2H, C_6H_5) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 39.2, 69.0, 106.0, 127.7, 128.1, 129.1, 129.3, 129.8, 132.2, 134.5, 135.0, 165.2, 166.8, 170.9, 192.3 ppm. Anal. calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$ (368.41): C, 61.94; H, 4.38; N, 7.60%. Found: C, 62.29; H, 4.45; N, 7.64%.

Methyl [(2-methylsulfonyl-6-phenylpyrimidin-4-yl)oxy]acetate (6c)

To a stirred solution of compound **3c** (1.0 mmol, 0.29 g) in glacial acetic acid (10 ml) 30% hydrogen peroxide (7 mmol, 0.79 g, 0.71 ml) was added at room temperature. The reaction mixture was stirred at room temperature for 28 hours, poured into ice water (~45 ml) and left for 1 hour. The precipitate was filtered off and recrystallized from ethanol to yield **6c**, 37%, 0.12 g, m. p. 135–136 °C; IR (ν_{\max} , cm^{-1}): 1744 (C=O). ^1H NMR (300 MHz, CDCl_3): δ_{H} 3.41 (s, 3H, SO_2CH_3), 3.85 (s, 3H, OCH_3), 5.13 (s, 2H, OCH_2), 7.44 (s, 1H, C(5)-H), 7.56–7.58 (m, 3H, C_6H_5), 8.11–8.14 (m, 2H, C_6H_5) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 39.3, 52.8, 63.8, 105.9, 127.8, 129.4, 132.3, 134.9, 165.3, 166.9, 168.2, 170.7 ppm. Anal. calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_5\text{S}$ (322.34): C, 52.17; H, 4.38; N, 8.69%. Found: C, 52.35; H, 4.30; N, 8.81%.

General procedure for the synthesis of compounds 8a–c

To a stirred solution of compound **4a** (**4b** or **4c**) (1.0 mmol) in glacial acetic acid (10 ml) 30% hydrogen peroxide (7 mmol, 0.79 g, 0.71 ml) was added at room temperature. The reaction mixture was stirred at room temperature for 48 hours (comp. **4a**, **4c**) or ~120 hours (comp. **4b**). The resulting precipitate was filtered off. Additional amount of product was obtained by adding water to the filtrate. The solids were combined and recrystallized from 2-propanol to give each of **8a**, **8b** or **8c**.

3-(2-Oxopropyl)-6-phenylpyrimidine-2,4(1H,3H)-dione (8a). Yield 67%, 0.16 g, m. p. 244–246 °C; IR (ν_{\max} , cm^{-1}): 3103 (NH), 1716, 1706, 1638 (C=O). ^1H NMR (300 MHz, CDCl_3): δ_{H} 2.29 (s, 3H, CH_3), 4.79 (s, 2H, NCH_2), 6.07 (s, 1H, C(5)-H), 7.52–7.66 (m, 5H, C_6H_5), 9.74 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 27.5, 49.5, 98.8, 126.6, 129.6, 131.6, 132.0, 151.1, 152.9, 162.9, 200.4 ppm. Anal. calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3$ (244.25): C, 63.93; H, 4.95; N, 11.47%. Found: C, 64.12; H, 5.18; N, 11.13%.

3-(2-Oxo-2-phenylethyl)-6-phenylpyrimidine-2,4(1H,3H)-dione (8b). Yield 82%, 0.25 g, m. p. 268–270 °C; IR (ν_{\max} , cm^{-1}): 3212 (NH), 1722, 1699, 1639 (C=O). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ_{H} 5.38 (s, 2H, NCH_2), 6.09 (s, 1H, C(5)-H), 7.54–7.65 (m, 5H, C_6H_5), 7.73–7.84 (m, 3H, C_6H_5), 8.11–8.13 (m, 2H, C_6H_5), 11.64 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ_{C} 47.1, 98.0, 127.8, 128.7, 129.6, 129.7, 130.0, 134.8, 135.2, 152.2, 162.3, 193.4 ppm. Anal. calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_3$ (306.3): C, 70.58; H, 4.61; N, 9.15%. Found: C, 70.42; H, 4.67; N, 9.37%.

Methyl (2,4-dioxo-6-phenyl-1,4-dihydropyrimidin-3(1H)-yl)acetate (8c). Yield 80%, 0.21 g, m. p. 240–242 °C; IR (ν_{\max} , cm^{-1}): 3100 (NH), 1748, 1714, 1644 (C=O). ^1H NMR (300 MHz, CDCl_3): δ_{H} 3.78 (s, 3H, OCH_3), 4.75 (s, 2H, NCH_2), 6.11 (s, 1H, C(5)-H), 7.52–7.60 (m, 3H, C_6H_5), 7.68–7.72 (m, 2H, C_6H_5), 10.26 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ_{C} 41.5, 52.8, 98.8, 126.6, 129.6, 131.4, 132.1, 151.1, 153.0, 162.9, 168.4 ppm. Anal. calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_4$ (260.25): C, 60.00; H, 4.65; N, 10.76%. Found: C, 60.08; H, 4.56; N, 10.92%.

1-[(2-Methylsulfonyl-6-phenylpyrimidin-4-yl)sulfonyl]acetone (9a)

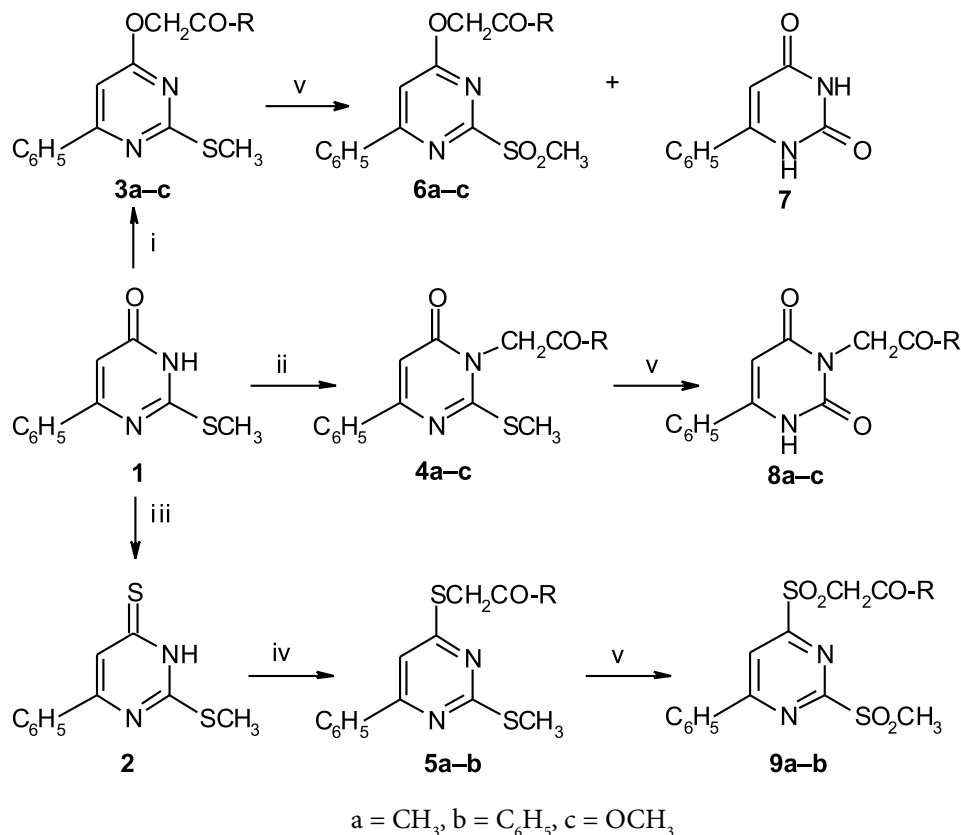
To a solution of compound **5a** (0.29 g, 1.0 mmol) in glacial acetic acid (10 ml), 30% hydrogen peroxide (7 mmol, 0.79 g, 0.71 ml) was added. The reaction mixture was stirred at room temperature for 20 hours, then poured into water and extracted with chloroform. The extract was dried over sodium sulphate and distilled off. The resulting oil was recrystallized from 2-propanol to give **9a**, 75%, 0.26 g, m. p. 113–115 °C; IR (ν_{\max} , cm^{-1}): 1722 (C=O). ^1H NMR (400 MHz, CDCl_3): δ_{H} 2.43 (s, 3H, OCH_3), 3.47 (s, 3H, SO_2CH_3), 4.68 (s, 2H, SO_2CH_2), 7.59–7.69 (m, 3H, C_6H_5), 8.26–8.28 (m, 2H, C_6H_5), 8.52 (s, 1H, C(5)-H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 31.5, 39.4, 59.3, 114.8, 128.3, 129.7, 133.4, 134.0, 166.3, 166.8, 169.8, 195.4 ppm. Anal. calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_5\text{S}_2$ (354.40): C, 47.45; H, 3.98; N, 7.90%. Found: C, 47.24; H, 4.0; N, 7.92%.

[(2-Methylsulfonyl-6-phenylpyrimidin-4-yl)sulfonyl]-1-phenylethanone (9b)

To a solution of compound **5b** (0.35 g, 1.0 mmol) in glacial acetic acid (10 ml), 30% hydrogen peroxide (7 mmol, 0.79 g, 0.71 ml) was added. The reaction mixture was stirred at room temperature for 48 hours. The resulting crystals were filtered off and recrystallized from 2-propanol to give **9b**, 78%, 0.32 g, m. p. 164–166 °C; IR (ν_{\max} , cm^{-1}): 1678 (C=O). ^1H NMR (400 MHz, DMSO-d_6): δ_{H} 3.56 (s, 3H, SO_2CH_3), 5.85 (s, 2H, SO_2CH_2), 7.57–7.59 (m, 2H, C_6H_5), 7.65–7.74 (m, 4H, C_6H_5), 8.01–8.03 (m, 2H, C_6H_5), 8.45–8.47 (m, 2H, C_6H_5), 8.87 (s, 1H, C(5)-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_{C} 39.5, 59.5, 116.1, 128.9, 129.4, 129.5, 130.0, 134.0, 134.1, 135.1, 135.8, 166.3, 167.4, 169.1, 189.7 ppm. Anal. calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_5\text{S}_2$ (416.47): C, 54.79; H, 3.87; N, 6.73%. Found: C, 54.79; H, 3.85; N, 6.58%.

RESULTS AND DISCUSSION

The new pyrimidine derivatives were prepared following the reaction sequence depicted in the Scheme. Regioselective alkylation of sodium salt of the starting 2-methylthio-6-phenylpyrimidin-4-one (**1**) with chloroacetone, ω -bromoacetophenone or methyl chloroacetate was achieved using suitable solvents. First, it should be mentioned that performing reactions in methanol, despite of the alkylating agent used, the alkylation occurred at both centers of the ambidentic



Scheme. Reagents and conditions: (i) CH_3OH , Na; DMF, $\text{X-CH}_2\text{-CO-R}$, r. t., 1–5 h; (ii) CH_3OH , Na; CCl_4 , $\text{X-CH}_2\text{-CO-R}$, reflux, 3–5 h; (iii) LR, toluene, reflux, 3 h; (iv) CH_3OH , Na, $\text{X-CH}_2\text{-CO-R}$, reflux, 15–30 min; (v) 30% H_2O_2 , acetic acid, r. t., 20–48 h

system. According to the data of ^1H NMR the ratio of $\text{N}_{(3)}$ - and O-isomers was equal to 1:1. The O-substituted derivatives **3a–c** were isolated in high yields (~88%) when reactions were carried out in dimethylformamide at room temperature. The optimal reaction conditions, however, required very slow adding of an alkylating reactant to avoid an excess in the reaction mixture. Otherwise, traces of N-isomer may occur. Reactions in nonpolar tetrachloromethane yielded 86–91% of $\text{N}_{(3)}$ -acyl substituted pyrimidines **4a–c**. In this case, to prevent O-isomer formation alkylating agents were added in portions to the reaction mixtures under reflux. The optimal conversion was reached by heating the reaction mixtures at reflux for 3–5 hours. Assignment to $\text{N}_{(3)}$ - or O-substitution was easily made by IR spectra. The $\text{N}_{(3)}$ -derivatives **4a, b** showed two absorption bands characteristic of C=O of lactam at 1673–1667 cm^{-1} and side chain substituents – in the range 1727–1707 cm^{-1} , while O-substituted **3a–c** showed only peaks indicating side chain acyl group absorption in the area 1746–1696 cm^{-1} . Also, some regularities were determined in the examination of NMR spectra. To compare, in ^{13}C NMR of O-substituted derivatives **3a–c** peaks for $\text{C}_{(5)}$ were observed at ~99 ppm, the same peaks for $\text{N}_{(3)}$ -isomers were observed at ~104 ppm. The carbon signals of the CH_2 group of $\text{N}_{(3)}$ -substituted **4a–c** are shifted downfield within 17.7 ppm with respect to that of O-analogues **3a–c**.

Treatment of starting pyrimidine-4-one **1** with Lawesson's reagent in xylene at reflux afforded 4-thioxopyrimidine **2**. The latter was allowed to react with halo acyl derivatives in abs. methanol–sodium methoxide solution to give S-substituted derivatives **5a, b**.

The sulfur atom in thioethers gives a possibility for modification of the ligand structure [12, 14]. Thus, further we investigated the reactivity of thioethers **3, 4** and **5** towards hydrogen peroxide. Oxidation of the 2-methylthio group of pyrimidines can be a simple way to synthesize sulfoxides and sulfones [12, 22, 23], which, in turn, are sensitive leaving groups in nucleophilic substitution.

As a model compound [(2-methylthio-6-phenylpyrimidin-4-yl)oxy]acetone (**3a**) was used. Optimal reaction conditions for oxidation of compound **3a** with hydrogen peroxide were determined by a series of experiments. Reactions were performed in acetic acid using 30% hydrogen peroxide. Reactions were monitored by TLC. It was found that upon the use of the stoichiometric ratio of reactants even at high temperature only the starting compound **3a** was isolated. With a fourfold excess of hydrogen peroxide at ambient temperature full conversion of the starting thioether **3a** was not achieved. Raising the temperature to ~50 °C led to a complex mixture although the conversion was incomplete. Finally, addition of sevenfold excess of hydrogen peroxide and providing reaction at ambient temperature for 48 hours led to full conversion of the starting **3a**. Isolation of sulfone **6a** was simple as it precipitated over the course of the reaction from the reaction solution. By adding water to the remaining solution a small amount of side-product **7** was obtained. Sulfones **6b, c** were synthesized analogously (in the case of **6c** compound **7**

was easily separated by crystallization). The microanalysis and spectroscopic data of by-product **7** (absorption bands at 1698 and 1645 cm^{-1} correspondent to $\text{C}_{(4)}=\text{O}$ and $\text{C}_{(2)}=\text{O}$ and at 3212–3106 cm^{-1} due to NH function) conform to the given structure. The melting point of **7** is in accordance with that of 6-phenyluracil [21]. In the IR spectra of compounds **6a–c** absorption peaks arising from the side chain C=O stretching were observed in the region 1744–1701 cm^{-1} . Oxidation of the methylthio group to sulfone was proved by NMR data. Due to the electron-withdrawing SO_2 group in **6a–c** peaks of some protons are shifted downfield in comparison to those of starting thioethers **3a–c**. For example, from ^1H NMR data the protons of the SO_2CH_3 group are shifted within ~0.8 ppm and the proton of the 5th position of the pyrimidine ring by 0.47 ppm. The significant differences were observed for carbon shifts in ^{13}C NMR spectra.

In a similar way N-substituted pyrimidines **4a–c** were allowed to react with hydrogen peroxide. However, instead of 2-methylthio group oxidation to sulfone, 2,4-dioxopyrimidines **8a–c** were isolated in a moderate to good yield. It can be considered that formation of 2-methylsulfonyl derivative and simultaneous nucleophilic substitution with a hydroxy group took place. Comparing the ^1H NMR spectroscopic data of compounds **8a–c** with those of **4a–c** reveals the disappearance of the signal of 2-S CH_3 group protons. Instead, the one-proton singlet in the range 9.74–11.64 ppm attributable to the NH group was observed. Besides, the IR spectra displayed absorption bands at 3212–3100 cm^{-1} characteristic of the NH group and two peaks at 1644–1638 cm^{-1} indicating the presence of carbonyl $\text{C}_{(2)}=\text{O}$ and $\text{C}_{(4)}=\text{O}$ stretching.

In view of the behaviour of thioethers **3** and **4** towards hydrogen peroxide, ketones **5a, b** possessing two sulfur atoms in their structure were undertaken to react under the same conditions. It has been found that using the sevenfold excess of hydrogen peroxide at room temperature both sulfur atoms were oxidized to the sulfone function to give compounds **9a, b**. The structure was confirmed by elemental analysis and ^1H and ^{13}C NMR spectroscopy. The ^{13}C NMR spectra of **9a, b** displayed significant characteristic downfield shifts of protons close to the electron-withdrawing sulfone group, e. g. peaks of 2- SO_2CH_3 and 4- SO_2CH_2 group protons were observed in the lower field by ca 25–21 ppm in comparison with those of **5a, b**.

CONCLUSIONS

Reactions of an ambident anion of 2-methylthio-6-phenyl-4-pyrimidinone with chloroacetone, ω -bromoacetophenone or methyl chloroacetate in different solvents were studied. Regioselective $\text{N}_{(3)}$ -alkylation took place in tetrachloromethane at reflux, while in dimethylformamide O-acylmethyl derivatives were obtained. The isomeric 2-methylthio-6-phenylpyrimidine-4-thione reacted with chloroacetone and ω -bromoacetophenone in the methanol-sodium methoxide solution to give the corresponding S-substituted derivatives.

The synthesized $N_{(3)}$ -, O- and S-acylmethyl 2-methylthio-6-phenylpyrimidine derivatives were allowed to react with hydrogen peroxide in acetic acid. Different oxidation products were obtained.

Received 4 March 2016

Accepted 22 March 2016

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PAPRASTA IR EFEKTYVI NAUJŲ $N_{(3)}$ -, O- IR S-PAKEISTŲ DARINIŲ IŠ 6-FENIL-2-METILTIO-4-PIRIMIDINONO SINTEZĖ

Santrauka

Ištirtos 6-fenil-2-metiltio-4-pirimidinono regioselektyvus alkilini-
mo chloracetono, ω -bromacetofenono ir metil-bromacetatu skirtinguose tirpikliuose reakcijos. Nustatyta, kad poliniame aprotoniniame tirpiklyje – dimetilformamide – reakcijos vyksta prie ketvirto pirimidino žiedo anglies atomo ir geromis išieigomis susidaro O- pakeisti dariniai, o nepoliniame tetrachlormetane susidaro atitinkami $N_{(3)}$ -acilmetil pakeisti izomerai. 6-Fenil-2-metiltio-4-pirimidintioną alkilinant metanolio su natrio metoksidu tirpale gauti S-pakeisti pirimidino dariniai. Veikiant susintetintus $N_{(3)}$ -, O- ir S-acilmetil-pakeistus 6-fenil-2-metiltiopirimidinus vandenilio peroksidu acto rūgštyje pasirinktomis vienodomis sąlygomis susidarė skirtingi oksidacijos produktai. Reaguojant (6-fenil-2-metiltio-4-pirimidinoksi)-pakeistiems dariniams, oksiduojama pirimidino žiedo antros padėties metiltiogrupė ir geromis išieigomis gaunami atitinkami 2-metilsulfonil-dariniai, o (6-fenil-2-metiltio-4-pirimidinilio)-pakeistuose ketonuose iki sulfono grupės oksiduojami abu sieros atomai. $N_{(3)}$ -pakeistų 6-fenil-2-metiltiopirimidinių atveju kartu su 2-metiltiogrupės oksidacija vyko konkuruojanti nukleofilinio pakeitimo hidroksigrupe reakcija ir geromis išieigomis buvo išskirti $N_{(3)}$ -pakeisti 6-fenil-2,4-pirimidindionai. Visų naujų junginių struktūra patvirtinta IR, ^1H ir ^{13}C BMR spektroskopijos ir elementinės analizės duomenimis.