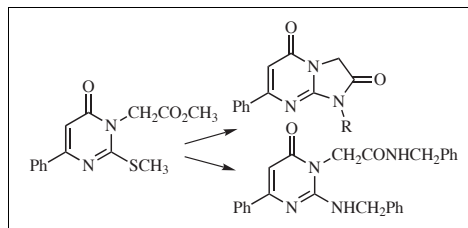


Milda M. Burbuliene*, Rita Dobrovolskaite and Povilas Vainilavicius

Department of Organic Chemistry, Faculty of Chemistry, Vilnius University, Naugarduko 24, LT-03225 Vilnius, Lithuania

E-mail: milda.burbuliene@chf.vu.lt

Received January 30, 2006



The title ester **1** reacted with hydrazine hydrate to give hydrazide **2**, which underwent intramolecular cyclization to yield 1-amino-7-phenyl-1*H*-imidazo[1,2-*a*]pyrimidine-2,5-dione (**3**) or took place in a substitution reaction with benzylamine to form *N*-benzyl-2-(2-benzylamino-4-oxo-6-phenyl-4*H*-pyrimidin-3-yl)-acetamide (**4**). The reaction of ester **1** with benzylamine gave corresponding amide **7**, disubstituted derivative **4** or 1-benzyl-7-phenyl-1*H*-imidazo[1,2-*a*]pyrimidine-2,5-dione (**8**) depending on the reaction conditions.

J. Heterocyclic Chem., **43**, 1557 (2006).

Introduction.

Pyrimidine is one of the fundamental heterocycles found in bioactive molecules. *N*-Alkyl substituted oxypyrimidines bearing functional groups in the alkyl fragment can be considered to some extent as analogs of natural nucleosides. Therefore they are expected to be pharmacologically active compounds with antiviral [1-4], blood platelet aggregation inhibitory [5] or anti-inflammatory [6] activity. We have previously reported synthesis of some pyrimidine *N*-, *O*- and *S*-alkyl derivatives and their anti-inflammatory activity [7-9]. *N*₍₁₎- and/or *N*₍₃₎-Alkyl derivatives of the uracil family are used as starting materials for the synthesis of oligonucleotides [10,11] and polymeric analogues of nucleic acids [12,13]. 6-Methyl-2-thiouracil is a useful backbone in various areas of research [7,8,14-19]. 6-Phenyl-2-thiouracil unlike its 6-methyl analogue is not yet studied sufficiently. Few recent publications, however, show 2-mercapto-6-phenyl-3*H*-pyrimidin-4-one derivatives to exhibit pharmacological properties, such as, anti-HIV-1 [16], antibacterial or antifungal [20] activity. Consequently it was expedient from this point of view to use 2-mercapto-6-phenyl-3*H*-pyrimidin-4-one as a starting material. On the other hand we have just published properties of some derivatives of 2-methylsulfanyl-3*H*-quinazolin-4-one [21]. The later can be regarded as a linear bicyclic analogue of 2-methylsulfanyl-6-phenyl-3*H*-pyrimidin-4-one.

Results and Discussion.

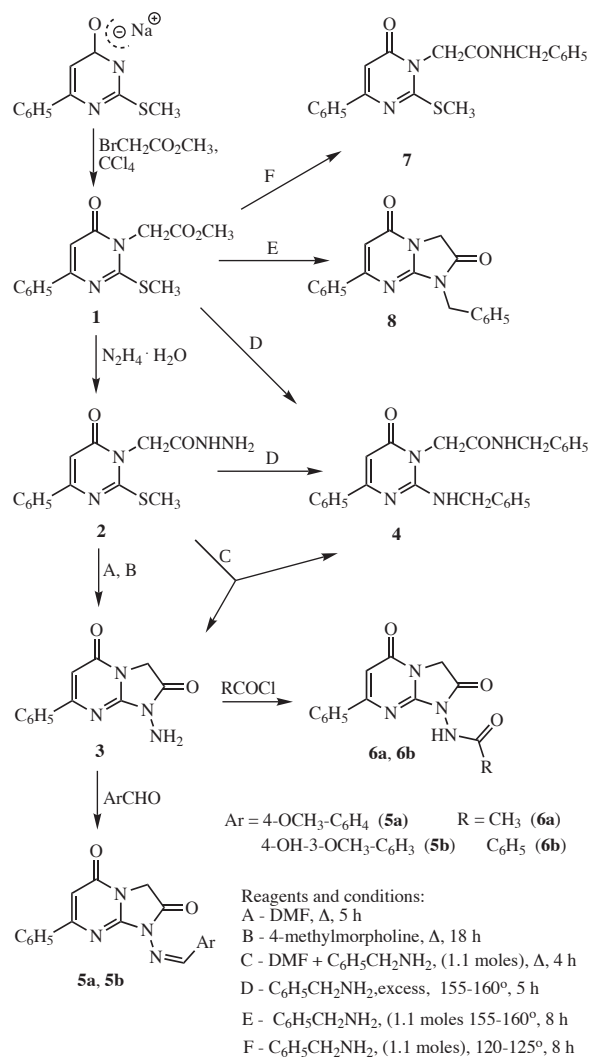
On the basis of our earlier findings concerning regioselective alkylation of 2-alkylthio-pyrimidin-4-

ones [19], we have developed a simple and highly efficient synthetic approach to the starting *N*₍₃₎-substituted ester **1**.

Alkylation of ambident anion of 2-methylsulfanyl-6-phenyl-3*H*-pyrimidin-4-one with methyl bromoacetate was accomplished in aprotic nonpolar solvent – tetrachloromethane (Scheme 1). The reaction was monitored by tlc and formation of the *O*-isomer was not detected. Ester **1** was obtained in 91% yield. The ¹H nmr spectra showed characteristic for ester **1** singlet of NCH₂ group protons at 4.85 ppm, also resonances of methylsulfanyl and methoxy group protons in the region of 2.70 and 3.75 ppm respectively, as well as a singlet of the 5th position proton of the pyrimidine ring and two multiplets of aromatic protons. The ir spectra of ester **1** displayed two intensive peaks due to the carbonyl group absorption in the region of 1742 cm⁻¹ (ester) and 1672 cm⁻¹ (lactam).

Ester **1** reacted with hydrazine hydrate at room temperature to yield hydrazide **2**. The structure of **2** was confirmed by the ¹H nmr, which, compared to that of ester **1**, did not show signal of methoxy group protons. Instead, the broad peak arising from NH₂ group protons and a singlet of NH proton were observed at 4.31 and 9.39 ppm respectively. In the ir spectra absorption bands characteristic for hydrazine NH and CONH fragments [22] were observed in the region of 3459, 3292 cm⁻¹ and 1659, 1615, 1564 and 1269 cm⁻¹ respectively, whereas the absorption of ester CO group at 1742 cm⁻¹ was absent.

Scheme 1



Heterocyclic structures bearing good leaving group, as 2-methylsulfanyl, adjacent to nucleophilic substituent under treatment with nucleophilic reagents undergo cyclization [21,23,24].

It has been demonstrated, that 6-methyl substituted analogue of hydrazide **2** has cyclized to the corresponding 8-methyl-1,2-dihydro-pyrimido[2,1-*c*][1,2,4]triazine-3,6-dione [24], whereas linear bicyclic analogue of **2** - (2-methylsulfanyl-4-oxo-4*H*-quinazolin-3-yl)-acetohydrazide - in similar conditions has cyclized to 1-amino-1*H*-imidazo[2,1-*a*]quinazoline-2,5-dione [21].

Based on our previous experience we have studied the reactivity of hydrazide **2** under the influence of solvents with different basicity. Conditions and reaction products are given in Table 1.

Hydrazide **2**, when heated in abs. dimethylformamide, has cyclized into 1-aminoimidazo derivative **3**, the same as the analogous hydrazide of quinazolin-4-one [21].

Replacement of dimethylformamide with 4-methylmorpholine (as a solvent and a catalyst) lowered the yield of cyclization product **3** to 25%. Instead 59% of unreacted hydrazide **2** was isolated. Under reflux of hydrazide **2** in dimethylformamide with a molar amount of benzylamine, along with the imidazo derivative **3**, the disubstituted **4** was isolated from the reaction mixture too. The later **4** was obtained in 42% yield under heating of hydrazide **2** in an excess of benzylamine (as a solvent and a more basic catalyst). It was somewhat unexpected. Under the similar conditions the analogous (quinazolin-3-yl)-acetohydrazide proceeded cyclization, but not substitution reaction [21].

Table 1
Transformations of hydrazide **2** in different solvents.

Entry	Solvent	Temperature	Time, h	Product (yield, %)
1	DMF	reflux	5	3 (74)
2	4-Methylmorpholine	reflux	18	3 (25) 2 (59)
3	DMF+Benzylamine (1.1 mmol)	reflux	4	3 (50) 4 (16)
4	Benzylamine	155-160°	5	4 (42)

The structure of **4** was confirmed by the data of ¹H nmr spectra: two dublets (arising from two adjacent amino groups) of two methylene group protons at 4.36 and 4.69 ppm, as well as downfield signals of two amino group protons at 8.72 and 7.96 ppm and multiplets of 15 aromatic protons were observed. The 5th position proton of pyrimidine ring resonate upfield for 0.4-0.5 ppm compared to that of compounds **3** and **2**. The structure of **3** is in accordance with its ¹H nmr and ir spectra. Besides, the structure **3** was proved by the reaction of the later with aromatic aldehydes to form hydrazones **5a**, **5b** and acylation reaction - to give compounds **6a**, **6b**. Two absorption bands in the region of 1775-1781 cm⁻¹ (C₂=O) and 1686-1670 cm⁻¹ (C₅=O) characteristic for imidazo-[1,2-*a*]pyrimidine-2,5-diones in their ir spectra support the structural determination.

The diverse transformations of hydrazide **2** prompted us to study reaction of ester **1** with benzylamine. The ester **1** was treated with benzylamine (1:1.05 moles) under various conditions. The data are listed in the Table 2.

Treatment of ester **1** with benzylamine in methanol at reflux was effectless. When dry dimethylformamide as a solvent was used at 120-125° temperature amide **7** was isolated in 12% yield. No significant advance was achieved when the reaction was carried out at the same temperature without a solvent (**7** was obtained in 18% yield). Major improvement was observed when the reaction time was prolonged to 8 hours. In this manner

from the reaction mixture amide **7** was isolated in 47% yield, and there were less unreacted ester **1**. Interestingly, from the remainder of reaction mixture traces of cyclic compound **8** were observed by tlc and ^1H nmr. Increase of the reaction temperature to 155-160° gave viscous mixture of compounds from which unfortunately the only cyclic **8** was isolated in 35% yield. When the reaction time was prolonged to 8 hours the yield of **8** was increased to 52%. Treatment of ester **1** at 155-160° temperature with an excess of benzylamine gave rise to the disubstituted compound **4** formation.

Table 2
Reaction of ester **1** with benzylamine

Entry	Solvent	Temperature, °C	Time, h	Product (yield, %)
1	CH ₃ OH	reflux	5	1 (100)
2	DMF	120-125	5	1 (66), 7 (12)
3	-	120-125	3	1 (61), 7 (18)
4	-	120-125	8	7 (47), 1 (7), 8 *
5	-	155-160	4	8 (35)
6	-	155-160	8	8 (52)
7	C ₆ H ₅ CH ₂ NH ₂	155-160	5	4 (67)

*Traces

In the ^1H nmr spectra of **7** two methylene group signals were observed at 4.74 (singlet) and 4.35 ppm (doublet due to the adjacent NH group) as well as a singlet of methylsulfanyl group protons. In the ^1H nmr spectra of **8** characteristic two methylene group protons were observed as singlets at 4.62 (exocyclic) and 4.94 ppm (endocyclic) and ir spectra displayed two carbonyl group absorption bands in the region of 1758 (C₂=O) and 1677 cm⁻¹ (C₅=O).

As shown in Table 2 from the reaction of ester **1** with benzylamine depending on the conditions compounds **7**, **8** or **4** could be obtained.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Unity Varian INOVA spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C using dimethyl sulfoxide-*d*₆ as a solvent. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard. The ir spectra were recorded on a Spectrum BX FT-IR (Perkin-Elmer, Sweden) as potassium bromide pellets. The reactions and purity of compounds was controlled by tlc on Silufol UV 254 plates (KAVALIER, Czech Rep.) Elemental analyses were performed at the Microanalyses Laboratory of the Department. All solvents were dried and distilled before use.

2-Methylsulfanyl-6-phenyl-3*H*-pyrimidin-4-one and 2-mercapto-6-phenyl-3*H*-pyrimidin-4-one were synthesized as reported in references [20, 25].

(2-Methylsulfanyl-4-oxo-6-phenyl-4*H*-pyrimidin-3-yl)-acetic acid methyl ester (**1**).

A mixture of 2-methylsulfanyl-6-phenyl-3*H*-pyrimidin-4-one (2.18 g, 10 mmoles) and sodium methoxide, prepared of sodium (0.23 g, 10 mmoles) dissolved in methanol (15 ml), was refluxed for 15 minutes. The solvent was evaporated to dryness and the residue sodium salt was dried perfectly. Then to a stirred mixture of this salt in tetrachloromethane (25 ml), methyl bromoacetate (1.53 g, 0.95 ml, 10 mmoles) was added dropwise. The reaction mixture was refluxed for 3 hours, cooled and filtered. Water was poured onto the solid and the resulting mixture was extracted with chloroform, dried over sodium sulphate and evaporated to dryness. The remainder was crystallized from ethyl acetate to yield **1** as colorless crystals, 2.64 g (91%), mp 130-131°; ir 1742 (C=O), 1672 (C₄=O) cm⁻¹; ^1H nmr (DMSO-*d*₆): δ 2.70 (s, 3H, SCH₃), 3.75 (s, 3H, OCH₃), 4.85 (s, 2H, N-CH₂), 6.87 (s, 1H, CH-5), 7.51-7.53, 8.13-8.16 (2m, 3H, 2H, Ph-H) ppm.

Anal. Calcd. for C₁₄H₁₄N₂O₃S (290.34): C, 57.92; H, 4.86; N, 9.65. Found: C, 57.88; H, 4.81; N, 9.71.

(2-Methylsulfanyl-4-oxo-6-phenyl-4*H*-pyrimidin-3-yl)-acetic acid hydrazide (**2**).

To a solution of ester **1** (2.9 g, 10 mmoles) in methanol (10 ml) 85% hydrazine hydrate (2 g, 40 mmoles) was added and the reaction mixture was stirred at room temperature for 2 hours. The precipitate was then collected by filtration, washed with methanol and crystallized from dimethylformamide-water to give 2.52 g (87%) of hydrazide **2**, mp 223-225°; ir 3459, 3292 (NH), 1659 (C₄=O), 1615 (amide I), 1564 (amide II), 1269 (amide III) cm⁻¹; ^1H nmr (DMSO-*d*₆): δ 2.68 (s, 3H, SCH₃), 4.31 (br s, 2H, NH₂), 4.63 (s, 2H, N-CH₂), 6.81 (s, 1H, CH-5), 7.51-7.53, 8.13-8.16 (2m, 3H, 2H, Ph-H), 9.39 (s, 1H, NH) ppm.

Anal. Calcd. for C₁₃H₁₄N₄O₂S (290.34): C, 53.78; H, 4.86; N, 19.30. Found: C, 53.52; H, 4.94; N, 19.17.

1-Amino-7-phenyl-1*H*-imidazo[1,2-*a*]pyrimidine-2,5-dione (**3**).

Method 1. A mixture of hydrazide **2** (0.29 g, 1 mmole) and dimethylformamide (7 ml) was heated at reflux for 5 hours then the solvent was distilled under reduced pressure. The solid was crystallized from acetic acid to give **3** as a white solid, 0.18 g (74%), mp 248-250°; ir: 3056 (NH), 1753 (C₂=O), 1677 (C₅=O) cm⁻¹; ^1H nmr (DMSO-*d*₆): δ 4.50 (s, 2H, N-CH₂), 5.26 (br s, 2H, NH₂), 6.72 (s, 1H, CH-5), 7.50-7.52, 8.11-8.13 (2m, 3H, 2H, Ph-H) ppm.

Anal. Calcd. for C₁₂H₁₄N₄O₂ (242.23): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.47; H, 4.23; N, 23.23.

Method 2. A mixture of hydrazide **2** (0.29 g, 1 mmole) and 4-methylmorpholine (10 ml) was heated at reflux for 18 hours. Then the mixture was left to cool to room temperature and the precipitate as unreacted hydrazide **2** was collected by filtration, 0.17 g (59%), mp 223-225°. The filtrate was distilled under reduced pressure to dryness, the residue was washed with methanol and filtered to yield compound **3**, 0.06 g (25%), mp 248-250°.

Method 3. A mixture of hydrazide **2** (0.58 g, 2 mmoles) and benzylamine (0.23 g, 2.1 mmoles) in dimethylformamide (15

ml) was heated at reflux for 4 hours. The solvent was removed under reduced pressure, the residue was triturated with methanol and collected by filtration to give brownish powder, which was crystallized from acetic acid as white crystals of **3**, 0.24 g (50%), 248-250°. The residue was crystallized from ethoxyethane to give dusty **4**, 0.136 g (16%), mp 228-230°.

N-Benzyl-2-(2-benzylamino-4-oxo-6-phenyl-4*H*-pyrimidin-3-yl)-acetamide (**4**).

Method 1. A mixture of hydrazide **2** (0.29 g, 1 mmole) and benzylamine (7 ml) was maintained at 155-160° for 5 hours and left to cool to room temperature. The solid was filtered, washed with methanol and crystallized from ethoxyethane to give **4**, 0.18 g (42%), mp 228-230°; ir: 3444, 3254 (NH), 1668 (C₄=O), 1648 (CONH) cm⁻¹; ¹H nmr (DMSO-d₆): δ 4.36 (d, 2H, CONHCH₂, J = 6.0 Hz), 4.69 (d, 2H, NHCH₂, J = 5.03 Hz), 4.74 (s, 2H, N-CH₂), 6.30 (s, 1H, CH-5), 7.23-7.44, (m, 13H, Ph-H), 7.95-7.97 (m, 3H, Ph-H+NH), 8.72 (t, 1H, CONH, J = 6.0 Hz) ppm.

Anal. Calcd. for C₂₆H₂₄N₄O₂ (424.50): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.29; H, 5.54; N, 13.45.

Method 2. A mixture of ester **1** (0.29 g, 1 mmole) and benzylamine (7 ml) was maintained at 155-160° for 5 hours and worked as above to yield **4**, mp 228-230°, 0.28 g (67%).

General Procedure for the Synthesis of 1-[(Benzylidene)-amino]-7-phenyl-1*H*-imidazo[1,2-*a*]pyrimidine-2,5-dione (**5a**, **5b**).

A mixture of compound **3** (0.48 g, 2 mmoles) and aromatic aldehyde (2 mmoles) in acetic acid (15 ml) was heated at reflux for 15 min. An excess of solvent was removed under reduced pressure, the resulting precipitate was collected by filtration, washed with methanol and crystallized from acetic acid to give **5a** or **5b**.

1-[(4-Methoxy-benzylidene)-amino]-7-phenyl-1*H*-imidazo[1,2-*a*]pyrimidine-2,5-dione (**5a**).

This compound was obtained as colorless crystals, yield 0.62 g, (86%), mp 210-212°; ir: 1775 (C₂=O), 1686 (C₅=O) cm⁻¹; ¹H nmr (DMSO-d₆): δ 3.88 (s, 3H, OCH₃), 4.61 (s, 2H, N-CH₂), 6.84 (s, 1H, CH-5), 7.15 (d, 2H, Ar-H, J = 9 Hz), 7.52-7.54 (m, 3H, Ar-H), 7.93 (d, 2H, Ar-H, J = 9 Hz), 8.07-8.11 (m, 2H, Ar-H), 9.35 (s, 1H, CH) ppm.

Anal. Calcd. for C₂₀H₁₆N₄O₃ (360.37): C, 66.66; H, 4.48; N, 15.55. Found: C, 66.54; H, 4.31; N, 15.49.

1-[(4-Hydroxy-3-methoxy-benzylidene)-amino]-7-phenyl-1*H*-imidazo[1,2-*a*]pyrimidine-2,5-dione (**5b**).

This compound was obtained as a white solid, 0.52 g (69%), mp > 300°; ir: 3444 (OH), 1781 (C₂=O), 1670 (C₅=O) cm⁻¹; ¹H nmr (DMSO-d₆): δ 3.88 (s, 3H, OCH₃), 4.61 (s, 2H, N-CH₂), 6.82 (s, 1H, CH-5), 6.96 (d, 1H, Ph-H, J = 8.1 Hz), 7.38 (d, 1H, Ph-H, J = 8.1 Hz), 7.51-7.53 (m, 4H, Ph-H), 8.06-8.09 (m, 2H, Ph-H), 9.20 (s, 1H, CH), 9.99 (br s, 1H, OH) ppm.

Anal. Calcd. for C₂₀H₁₆N₄O₄ (376.37): C, 63.82; H, 4.28; N, 14.89. Found: C, 63.75; H, 4.33; N, 15.01.

N-(2,5-Dioxo-7-phenyl-2,3-dihydro-5*H*-imidazo[1,2-*a*]pyrimidin-1-yl)-acetamide (**6a**).

A mixture of compound **3** (0.48 g, 2 mmoles) and acetic anhydride (0.31 g, 3 mmoles) in acetic acid was heated at reflux

for 15 min. After being cooled to room temperature, the solid was collected by filtration, washed with methanol and crystallized from tetrahydrofuran to yield 0.43 g (76%), mp 154-156°; ir: 1782 (C₂=O), 1714 (NHCO) 1673 (C₅=O) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.12 (s, 3H, CH₃), 4.78 (s, 2H, N-CH₂), 6.82 (s, 1H, CH-5), 7.51-7.53 (m, 3H, Ph-H), 8.03-8.06 (m, 2H, Ph-H), 11.02 (s, 1H, NH) ppm.

Anal. Calcd. for C₁₄H₁₂N₄O₃ (284.28): C, 59.15; H, 4.25; N, 19.71. Found: C, 59.45; H, 4.27; N, 19.66.

N-(2,5-Dioxo-7-phenyl-2,3-dihydro-5*H*-imidazo[1,2-*a*]pyrimidin-1-yl)-2-benzamide (**6b**).

A mixture of compound **3** (0.48 g, 2 mmoles) and benzoyl chloride (0.28 g, 2 mmoles) in pyridine (15 ml) was refluxed for 2 hours. Pyridine was removed under reduced pressure, the residue was diluted with water, neutralized with acetic acid, filtered and crystallized from methanol to give **6b** as white plates, 0.85 g (59%), mp 168-170°; ir: 3163 (NH), 1782 (C₂=O), 1713 (NHCO), 1670 (C₅=O) cm⁻¹; ¹H nmr (DMSO-d₆): δ 4.91 (s, 2H, N-CH₂), 6.86 (s, 1H, CH-5), 7.47-8.05 (m, 10H, Ph-H), 11.72 (s, 1H, NH) ppm.

Anal. Calcd. for C₁₉H₁₄N₄O₃ (346.34): C, 65.89; H, 4.07; N, 16.18. Found: C, 65.99; H, 4.14; N, 16.01.

N-Benzyl-2-(2-methylsulfanyl-4-oxo-6-phenyl-4*H*-pyrimidin-3-yl)-acetamide (**7**).

Method 1. A mixture of ester **1** (0.58 g, 2 mmoles) and benzylamine (0.23 g, 2.1 mmoles) was maintained at 120-125° temperature for 8 hours. The reaction mixture then was cooled, triturated with acidified water, extracted with chloroform. The chloroform solution was dried over sodium sulfate, filtered and evaporated to give the unreacted ester **1**, 0.04 g (7%), mp 130-131°. The residual after extraction was crystallized from isopropanol to give **7** as colorless crystals, 0.34 g (47%), mp 205-207°; ir: 3466, 3280 (NH), 1677 (C₄=O), 1657 (CONH) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.70 (s, 3H, SCH₃), 4.35 (d, 2H, NHCH₂, J = 6.0 Hz), 4.74 (s, 2H, N-CH₂), 6.85 (s, 1H, CH-5), 7.30-7.36 (m, 5H, Ph-H), 7.52-7.54 (m, 3H, Ph-H), 8.14-8.16 (m, 2H, Ph-H), 8.82 (t, 1H, NH, J = 6.0 Hz) ppm.

Anal. Calcd. for C₂₀H₁₉N₃O₂S (365.45): C, 65.73; H, 5.24; N, 11.50. Found: C, 65.49; H, 5.19; N, 11.64.

Method 2. A mixture of ester **1** (0.58 g, 2 mmoles) and benzylamine (0.23 g, 2.1 mmoles) was maintained at 120-125° temperature for 3 hours and worked as above to give **7**, 0.13 g (18%), mp 205-207° and unreacted **1**, 0.35 g (61%), mp 130-131°.

Method 3. A mixture of ester **1** (0.58, 2 mmoles), benzylamine (0.23 g, 2.1 mmoles) and dry dimethylformamide (10 ml) was maintained at 120-125° temperature for 5 hours. After the solvent was removed under reduced pressure, the remainder was worked as above to yield **7**, 0.09 g (12%), mp 205-207° and unreacted ester **1**, 0.38 g (66%).

1-Benzyl-7-phenyl-1*H*-imidazo[1,2-*a*]pyrimidine-2,5-dione (**8**).

Method 1. A mixture of ester **1** (0.58, 2 mmoles) and benzylamine (0.23 g, 2.1 mmoles) was maintained at 155-160° temperature for 8 hours, then cooled, triturated with methanol, the precipitate formed was filtered and crystallized from isopropanol to yield **8** as a white powder, 0.33 g (52%), mp 177-179°; ir: 1758 (C₂=O), 1677 (C₇=O) cm⁻¹; ¹H nmr δ (DMSO-d₆): 4.62 (s, 2H, N-CH₂), 4.94 (s, 2H, N-CH₂), 6.76 (s, 1H, CH-5),

7.38-7.48 (m, 3H, Ar-H), 7.50-7.53 (m, 5H, Ar-H), 8.06-8.08 (m, 2H, Ar-H) ppm.

Anal. Calcd. for $C_{19}H_{15}N_3O_2$ (317.34): C, 71.91; H, 4.76; N, 13.24. Found: C, 71.87; H, 4.76; N, 13.11.

Method 2. A mixture of ester **1** (0.58, 2 mmoles) and benzylamine (0.23 g, 2.1 mmoles) was maintained at 155-160° temperature for 4 hours and then worked as above to yield **8**, 0.22 g (35%), mp 177-179°.

REFERENCES

- [1] H. Tanaka, M. Baba, H. Hayakawata, T. Sakamaki, T. Miyasaka, M. Ubasawa, H. Takashima, K. Sekiya, I. Nitta, S. Shigeta, R. T. Walker, J. Balzarini and E. De Clercq, *J. Med. Chem.*, **34**, 349 (1991).
- [2] H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, N. Inoye, M. Baba, S. Shigeta, R. T. Walker, E. De Clercq and T. Miyasaka, *J. Med. Chem.*, **38**, 2860 (1995).
- [3] K. Danel, E. Larsen, E. B. Pedersen, B. F. Vestergaard and C. Nielsen, *J. Med. Chem.*, **39**, 2427 (1996).
- [4] R. Pontikis, R. Benhida, A.-M. Aubertin, D. G. Grierson and C. Monneret, *J. Med. Chem.*, **40**, 1845 (1997).
- [5] N. A. Meanwell, US Pat. 4983610 (1991); *Chem. Abstr.* **114**, 164276 (1991).
- [6] V. P. Krivonogov, G. A. Tolstikov, Y. I. Murinov, F. S. Zarudy, D. N. Lazareva, V. A. Davidova, A. F. Ismagilova, L. V. Spirikhin and I. B. Abrachmanov, *Khim. Pharm. Z.*, **31**, 24 (1997).
- [7] V. Jakubkiene, M. M. Burbuliene, E. Udrenaite, V. Garaliene and P. Vainilavicius, *Pharmazie*, **57**, 610 (2002).
- [8] V. Jakubkiene, M. M. Burbuliene, G. Mekuskiene, E. Udrenaite, P. Gaidelis and P. Vainilavicius, *Il Farmaco*, **58**, 323 (2003).
- [9] M. M. Burbuliene, E. Udrenaite, P. Gaidelis and P. Vainilavicius, *Polish J. Chem.*, **76**, 557 (2002).
- [10] A. Leggio, A. Liguori, A. Procopio, C. Siciliano and G. Sindona, *Tetrahedron Lett.*, **37**, 1277 (1996).
- [11] H.-J. Gi, Y. Xiang, R. F. Schinazi and K. Zhao, *J. Org. Chem.*, **62**, 88 (1997).
- [12] E. Yashima, T. Tajima and N. Miyauchi, *Biopolymers*, **32**, 811 (1992).
- [13] E. Yashima, N. Suehiro, M. Akashi, T. Tajima and N. Miyauchi, *Chem. Lett.*, 1113 (1990).
- [14] E. Petricci, M. Renzulli, M. Radi, F. Corelli and M. Botta, *Tetrahedron Lett.*, **43**, 9667 (2002).
- [15] L. Paolini, E. Petricci, F. Corelli and M. Botta, *Synthesis*, **7**, 1039 (2003).
- [16] M. S. Novikov, A. A. Ozerov, O. G. Sim and R. W. Buckheit, *Chem. Heterocycl. Compds*, **40**, 37 (2004).
- [17] S. Chakraborty, R. H. Laye, P. Munshi, R. L. Paul, M. D. Ward and G. K. Lahiri, *J. Chem. Soc., Dalton Trans.*, **11**, 2348 (2002).
- [18] B. Lohse, P. S. Ramanujam, S. Hvilsted and R. H. Berg, *J. Peptide Sci.*, **11**, 499 (2005).
- [19] P. Vainilavicius and V. Sedereviciute, *Khim. Geterotsikl. Soedin.*, **12**, 1655 (1987) (Russ.); *Chem. Abstr.*, **109**, 92927c (1988).
- [20] F. A. Attaby and S. M. Eldin, *Z. Naturforsch.*, **54b**, 788 (1999).
- [21] M. M. Burbuliene, O. Bobrovas and P. Vainilavicius, *J. Heterocycl. Chem.*, **43**, 43 (2006).
- [22] V. P. Sinditskii, M. D. Dutov and A. E. Fogel'zang, *Khim. Geterotsikl. Soedin.*, **1**, 72 (1991) (Russ.); *Chem. Abstr.*, **114**, 246692q (1991).
- [23] M. Gutchow and J. S. Powers, *J. Heterocyclic Chem.*, **38**, 419 (2001).
- [24] V. Syadaryavichiute and P. Vainilavicius, *Khim. Geterotsikl. Soedin.*, **7**, 967 (1994) (Russ.); *Chem. Abstr.*, **122**, 187538j (1995).
- [25] G. W. Anderson, I. F. Halverstadt, W. H. Miller and R. O. Roblin, *J. Am. Chem. Soc.*, **67**, 2197 (1945).