Synthesis of ethyl N-(6-substituted 5-cyano-2-methylthiopyrimidin-4-yl)glycinates and their cyclisation to pyrrolo[2,3-d]pyrimidines

INTRODUCTION
Unsubstituted in the position 7 pyrrolo[2,3-d]pyrimidines are usually obtained by cyclisation reactions of suitably substituted pyrroles [1–3] or 6-aminopyrimidines substituted in the position 5 of the ring [4–9]. Recently it has been shown that alkyl N-methyl-N-(5-cyanopyrimidin-4-yl)glycinates in the presence of bases easily undergo cyclisation reaction to give the corresponding 7-methylpyrrolo[2,3-d]pyrimidines [10, 11]. However methyl group is not a suitable substituent to perform various transformations at the N7 atom of pyrrolo[2,3-d]pyrimidine. Therefore, synthesis of pyrrolo[2,3-d]pyrimidines with the unoccupied position 7 is of considerable interest in respect of further transformations and synthesis of various 7-substituted pyrrolopyrimidines. In this connection, we present herein results of a study of the protection of NH group in (pyrimidin-4-yl)glycinates and the use of the obtained compounds for synthesis of pyrrolo[2,3-d]pyrimidine derivatives.

RESULTS AND DISCUSSION
Ethyl N-(6-substituted 5-cyano-2-methylthiopyrimidin-4-yl)glycinates (II a, b) were synthesised by reaction of easily obtainable 4,6-dichloro- or 6-amino-4-chloro-2-methylthiopyrimidine-5-carbonitriles (I a, b) [12, 13] with ethyl glycinate in the presence of triethylamine. Compounds II a, b when treated with sodium hydride in dimethylformamide did not give the expected pyrrolo[2,3-d]pyrimidines. The reason for such a behavior can be a comparatively high acidity of the NH group of a glycine moiety, because of which sodium hydride firstly reacts with NH group to form a salt inactive in the further cyclisation reaction. In order to protect the NH group of a glycine moiety ethyl chloroformate, di(tert-butyl)dicarbonate (Boc2O) and methanesulfonyl chloride (MsCl) were chosen as reagents suitable for this purpose [14]. A preliminary study of the reactivity of IIa towards ethyl chloroformate showed that compound IIa in tetrahydrofurane using pyridine, ethyldiisopropylamine or 4-dimethylaminopyridine (DMAP) as bases did not give satisfactory results: complex mixtures were formed and the target compound IIIa was not isolated from the reaction mixture in a pure form. Compound IIIa was obtained in a 31% yield when the reaction had been carried out in a mixture of tetrahydrofurane and dimethylformamide using an excess of sodium hydride (Scheme 1). Treatment of compound IIa with Boc2O in tetrahydrofurane in the presence of triethylamine and DMAP led to the formation of the corresponding N-(tert-butoxycarbonyl) derivative IIIb in a 47% yield. Compound IIIb reacted with 4.5 equivalents of Boc2O at room temperature to give compound IV in a 91% yield, which was pure enough to use in the subsequent reactions. Compound V was synthesised in a reasonable yield (60%) when the reaction of IIa with MsCl had been carried out in acetonitrile using a slight excess of sodium hydride.

Study of the cyclisation of compounds III, IV into pyrrolo[2,3-d]pyrimidines showed that such bases as potassium carbonate, ethyldiisopropylamine, triethylamine in dimethylformamide, tetrahydrofurane or acetonitrile caused the formation of inseparable by column chromatography mixtures. However, when an equivalent amount of sodium ethoxide in ethanol was
used, cyclisation of \( \text{IIIb} \) proceeded at room temperature to form a mixture of pyrrolopyrimidines \( \text{VI} \) and \( \text{VI} \) (data of the \( ^1H \) NMR spectra) (Scheme 2). However, from the reaction mixture only compound \( \text{VI} \) was separated by column chromatography. In order to obtain pyrrolopyrimidine \( \text{VII} \), the reaction was repeated and when the cyclisation had completed a dilute hydrochloric acid was added to remove the tert-butoxycarbonyl group. Compound \( \text{VII} \) was isolated in a 60% yield. Reaction of compound \( \text{IV} \) with sodium ethoxide at room temperature also proceeded with the formation of several compounds. We succeeded in isolating two compounds whose structures according to spectral and elemental analyses data corresponded to pyrrolopyrimidines \( \text{VIII}, \text{IX} \). Heating compound \( \text{V} \) with triethylamine in ethanol furnished pyrrolopyrimidine \( \text{X} \). In the latter reaction, removing of the methanesulfonyl group occurred together with the cyclisation reaction.

Compound \( \text{X} \) was also obtained by treating \( \text{IIa} \) with MeSCl in acetonitrile in the presence of sodium hydride and subsequent work-up of the reaction mixture with water.

**EXPERIMENTAL**

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls on a Perkin-Elmer FT-IR Spectrum BX II spectrophotometer. NMR spectra were recorded on a Varian INOVA spectrometer (300 MHz) using tetramethylsilane as the internal standard. Elemental analyses were performed at the Elemental Analysis Laboratory of the Department of Organic Chemistry of Vilnius University. TLC was performed with silica gel plates 60 F254 (Merck), visualization – UV light.

**Ethyl \( N \)-(6-amino-5-cyano-2-methylthiopyrimidin-4-yl)glycinate (\( \text{IIb} \)).** To a mixture of compound \( \text{Ib} \) [13] (0.44 g, 2.19 mmol), ethanol (10 ml) and ethyl ester of glycine hydrochloride (0.674 g, 4.83 mmol) triethylamyl (1.343 ml, 9.64 mmol) was added dropwise. The reaction mixture was refluxed for 1 h 45 min and then cooled to room temperature. The precipitate was filtered off, washed with water and recrystallised to give 0.396 g (68%) of compound \( \text{Ib} \) m.p. 225–226 °C (from EtOH). IR (cm\(^{-1}\)): 3381 (NH), 3119 (NH), 2204 (CN), 1724 (C = O). \( ^1H \) NMR (DMSO-d\(_6\), \( \delta \) ppm): 1.19 (t, 3H, J = 7.2 Hz, CH\(_3\)), 2.34 (s, 3H, SCH\(_3\)), 4.02 (d, 2H, J = 5.6 Hz, NCH\(_3\)), 4.12 (q, 2H, J = 7.2 Hz, OCH\(_2\)), 7.32 (s, 2H, NH\(_2\)), 7.82 (t, 1H, J = 5.6 Hz, NH\(_2\)). \( ^13C \) NMR (DMSO-d\(_6\), \( \delta \) ppm): 13.73, 14.83, 43.32, 61.09, 65.17, 116.54, 162.55, 163.93, 170.65, 173.71. Elemental analysis data: found, %: C, 45.36; H, 5.00; N, 25.88; formula C\(_{10}\)H\(_{13}\)N\(_5\)O\(_2\)S (267,309): calculated, %: C, 44.93; H, 4.90; N, 26.20.

**Ethyl \( N \)-(6-chloro-5-cyano-2-methylthiopyrimidin-4-yl)-N-(ethoxycarbonyl)glycinate (\( \text{IIa} \)).** A mixture of compound \( \text{IIa} \) [10] (0.1 g, 0.37 mmol), anhydrous dimethylformamide (2 ml) and 60% suspension of NaH (0.029 g, 0.73 mmol) in mineral oil was stirred at room temperature for 1 h under argon. The mixture was cooled to 0–5 °C and ethylchloroformate (0.053 ml, 0.55 mmol) was added dropwise. The reaction mixture was stirred for additional 1.5 h at room temperature and evaporated under reduced pressure to dryness. The residue was purified using column chromatography (eluent CH\(_2\)Cl\(_2\), R\(_f\) = 0.5) to give 0.04 g (31%) of compound \( \text{IIa} \) as an oil. IR (cm\(^{-1}\)): 2232 (CN), 1734 (C = O). \( ^1H \) NMR (CDCl\(_3\), \( \delta \) ppm): 1.31 (t, 3H, J = 7.2 Hz, CH\(_3\)), 1.39 (t, 3H, J = 7.2 Hz, CH\(_3\)), 2.54 (s, 3H, SCH\(_3\)), 4.25 (q, 2H, J = 7.2 Hz, OCH\(_2\)), 4.43 (q, 2H, J = 7.2 Hz, OCH\(_2\)), 4.63 (s, 2H, NCH\(_3\)). \( ^13C \) NMR (CDCl\(_3\), \( \delta \) ppm): 14.4, 14.7, 49.5, 62.0, 64.7, 98.9, 112.8, 153.1, 163.1, 168.4, 176.1. Elemental analysis data: found, %: C, 43.21; H, 4.63; N, 15.62.

**Ethyl \( N \)-(tet-butoxycarbonyl)-N-(6-chloro-5-cyano-2-methylthiopyrimidin-4-yl)glycinate (\( \text{IIb} \)).** A mixture of compound \( \text{IIa} \) [10] (1.6 g, 5.58 mmol), anhydrous
tetrahydrofurane (20 ml), triethylamine (0.981 ml, 8.69 mmol), Boc₂O (1.536 g, 6.69 mmol) and DMAP (0.144 g, 1.12 mmol) was stirred for 30 min at room temperature. evaporated under reduced pressure to dryness. The residue was purified using column chromatography (eluents CHCl₃, Rₚ = 0.5) to give 1.0 g (47%) of compound IIIa. IR (cm⁻¹): 2233 (CN), 1752 cm⁻¹ (C = O). ¹H NMR (CDCl₃, δ ppm): 1.32 (t, 3H, J = 7.2 Hz, CH₂CH₃), 1.60 (s, 9H, Boc), 2.61 (s, 3H, SCH₃), 4.26, (q, 2H, J = 7.2 Hz, OCH₂), 4.56 (s, 2H, NCH₂). ¹³C NMR (CDCl₃, δ ppm): 14.5, 14.7, 28.1, 49.5, 61.9, 85.99, 99.0, 113.3, 151.4, 162.6, 162.9, 168.7, 175.9. Elemental analysis data: found, %: C, 46.54; H, 5.07; N, 14.47; formula: C₁₁H₁₆N₄O₃S (386.5). calculated, %: C, 46.57; H, 4.95; N, 14.48.

Ethyl N-(tert-butoxycarbonyl)-N-[6-(di(tert-butoxycarbonyl)amino]-2-(methylthio)-7H-pyrrolo[2,3-d]-pyrimidine-6-carboxylate (VI).  To a solution of compound IIIb (0.1 g, 0.37 mmol), tetrahydrofurane (3 ml), Boc₂O (0.367 g, 1.68 mmol), triethylamine (0.234 ml, 1.68 mmol) and DMAP (0.018 g, 0.15 mmol) was stirred for 1 h at room temperature. Then solvents were evaporated under reduced pressure to dryness. The obtained oil was passed through a silicagel column (eluents Et₂O: CHCl₃ = 1:1) to give 0.23 g (91%) of compound VI. IR (cm⁻¹): 2229 (CN), 1749 (C = O). ¹H NMR (CDCl₃, δ ppm): 1.22 (t, 3H, J = 7.2 Hz, OCH₂), 5.48 (s, 2H, NH₂). ¹³C NMR (CDCl₃, δ ppm): 14.4, 14.7, 14.9, 28.1, 60.4, 63.5, 84.4, 95.5, 103.2, 139.3, 148.6, 154.3, 162.3, 163.9, 171.4. Elemental analysis data: found, %: C, 51.74; H, 6.27; N, 14.12; formula C₁₇H₂₄N₄O₅S (396.462). calculated, %: C, 51.50; H, 6.10; N, 14.13.

Ethyl 5-amino-4-ethoxy-2-methylthio-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate (VII). To a solution of sodium ethoxide, prepared from sodium (0.006 g, 0.26 mmol) and anhydrous ethanol (2 ml) was added compound IIIb (0.1 g, 0.26 mmol). The reaction mixture was stirred for 1 h at room temperature and evaporated under reduced pressure to dryness. The residue was dissolved in ethyl acetate or chloroform (2 ml). The obtained solution was acidified with 3.5% HCl (0.5 ml) and stirred for 1 h at room temperature. Then solvents were distilled off under reduced pressure, diethyl ether was added. The precipitate was filtered off and recrystallised to give 0.03 g (3%) of compound VII. m.p. 80–82 °C (from a mixture of 2-propanol-water). IR (cm⁻¹): 3492 (NH₂), 3260 (NH), 1676 (C = O), 1735 (C = O), 3352, 3428 (NH₂). ¹H NMR (CDCl₃, δ ppm): 4.38 (q, 2H, J = 7.2 Hz, OCH₂), 5.48 (s, 2H, NH₂). ¹³C NMR (CDCl₃, δ ppm): 14.7, 14.8, 28.1, 60.4, 63.5, 84.4, 95.5, 103.2, 139.3, 148.6, 154.3, 162.3, 163.9, 171.4. Elemental analysis data: found, %: C, 48.43; H, 5.25; N, 19.02; formula: C₁₂H₁₅N₂O₃S (306.3). calculated, %: C, 48.64; H, 5.44; N, 18.91.

Ethyl 5-amino-7-(tert-butoxycarbonyl)-4-[di(tert-butoxycarbonyl)amino]-2-methylthio-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate (VIII). To a solution of sodium ethoxide, prepared from sodium (0.016 g, 0.69 mmol) and anhydrous ethanol (5 ml) was added compound IIIb (0.230 g, 0.34 mmol) in anhydrous ethanol (2 ml). The reaction mixture was stirred for 1 h at room temperature and evaporated under reduced pressure to dryness. The residue was dissolved in ethyl acetate or chloroform (2 ml). The obtained solution was acidified with 3.5% HCl (0.5 ml) and stirred for 1 h at room temperature. Then solvents were distilled off under reduced pressure, diethyl ether was added. The precipitate was filtered off and recrystallised to give 0.03 g (3%) of compound VII. m.p. 80–82 °C (from a mixture of 2-propanol-water). IR (cm⁻¹): 3492 (NH₂), 3260 (NH), 1676 (C = O). ¹H NMR (CDCl₃, δ ppm): 1.40 (t, 3H, J = 7.2 Hz, CH₂), 1.49 (t, 3H, J = 7.2 Hz, CH₂), 2.59 (s, 3H, SCH₂), 4.38 (q, 2H, J = 7.2 Hz, OCH₂), 5.25 (s, 2H, NH). ¹³C NMR (CDCl₃, δ ppm): 14.8, 52.5; N, 19.02; formula: C₁₇H₂₄N₂O₅S (396.462). calculated, %: C, 48.43; H, 5.25; N, 19.02; formula: C₁₇H₂₄N₂O₅S (396.35). calculated, %: C, 48.64; H, 5.44; N, 18.91.
that base-promoted cyclisation reactions of the obtained compounds into the pyrrolo[2,3-d]pyrimidine-4-ylglycinates... are accompanied by deprotection reactions.

CONCLUSIONS

Synthesis of ethyl N-alkoxy carbonyl- and N-methanesulphonyl-N-(5-cyano-2-methylthiopyrimidin-4-yl)glycinates has been accomplished. It has been found that base-promoted cyclisation reactions of the obtained compounds into the pyrrolo[2,3-d]pyrimidine-4-ylglycinates... are accompanied by deprotection reactions.

References