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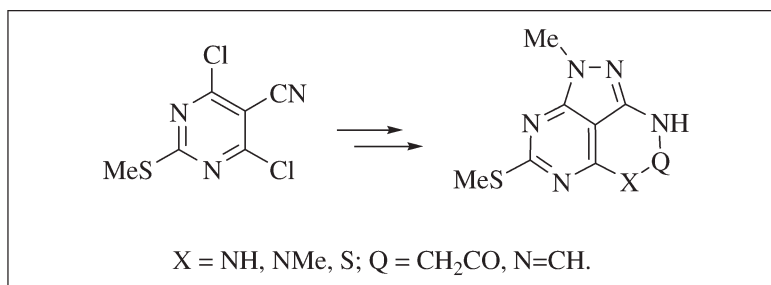
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A simple and efficient synthesis of novel *ortho*- and *peri*-annulated heterocyclic systems—2,6,7,9-tetrahydro-8*H*-pyrazolo[5,4,3-*de*]pyrimido[4,5-*e*][1,4]diazepine, 2,6,7,9-tetrahydro-8*H*-pyrazolo[5,4,3-*de*]pyrimido[5,4-*f*][1,4]thiazepine, and 6,9-dihydro-2*H*-pyrazolo[3,4,5-*ef*]pyrimido[5,4-*f*][1,2,4]triazepine is described.

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INTRODUCTION

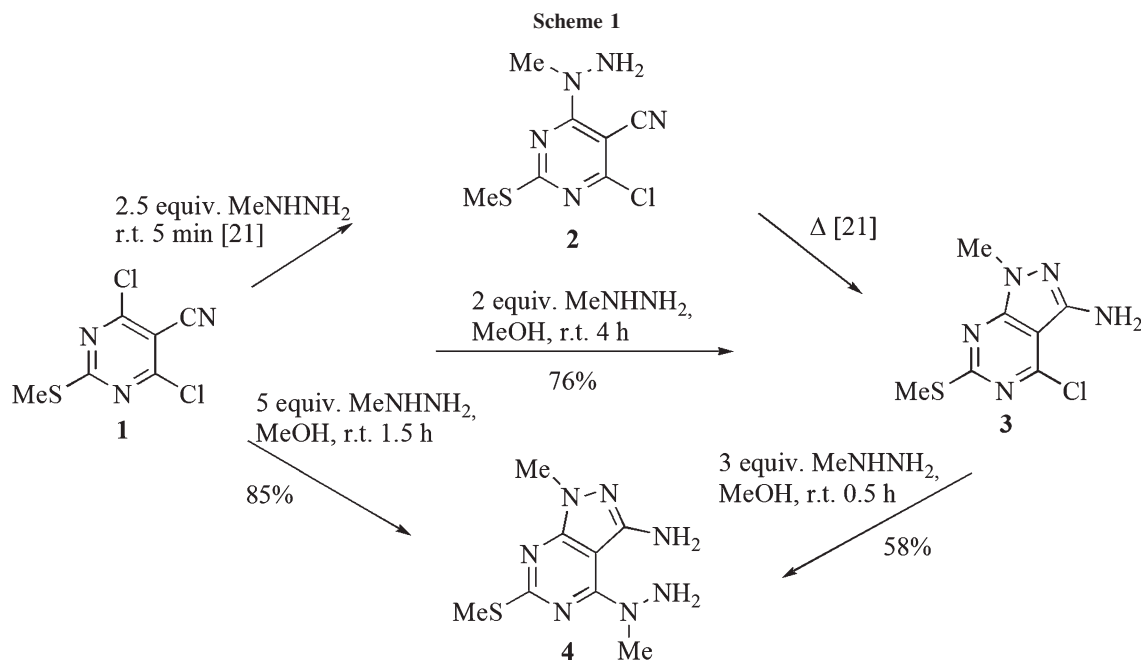
The importance of fused pyrimidines, which are common sources for the development of new potential therapeutic agents, is well known. Among them, the pyrazolo[3,4-*d*]pyrimidine and their tricyclic relatives are of considerable interest. They are reported to possess tyrosine kinase inhibitory [1–3], antimicrobial [4,5], antifungal [6], adenosine deaminase inhibitory [7,8], antibacterial [9], DNA polymerase III inhibitory [10], antihypertensive [11], and anticancer [12] activities. Some derivatives are useful in DNA sequencing [13] or as antiproliferative and proapoptotic agents toward some cancer cells [14,15]. Pyrazolo[3,4-*d*]pyrimidine nucleosides fused with azepinone moiety were expected to form base pairs with deoxythymidine or 2,6-diaminopurine [16]. In this context and continuing our studies on the synthesis of fused pyrimidine heterocycles [17–19] with anticipated biological and pharmaceutical activities, we report herein a synthesis of hitherto unreported heterocyclic systems containing pyrazolo[3,4-*d*]pyrimidine framework.

RESULTS AND DISCUSSION

For the synthesis, an easily available 4,6-dichloro-2-methylthiopyrimidine-5-carbonitrile (**1**) [20] has been used as starting material. Earlier, we reported that compound **1** under the treatment with a slight excess of methylhydrazine in several minutes forms 4-(1-methylhydrazino)pyrimidine-5-carbonitrile **2**, which under the

crystallization conditions or heating in 1,4-dioxane easily underwent cyclization to pyrazolo[3,4-*d*]pyrimidine **3** [21] (Scheme 1). To obtain compounds **3** and **4** useful for further cyclization reactions, we reinvestigated the interaction of **1** with methylhydrazine. It was found that formation of **3** takes place already at room temperature, when the reaction of **1** with 2 equivalents of methylhydrazine is carried out for several hours. After 4 h, pyrazolo[3,4-*d*]pyrimidine **3** was obtained in 76% yield. Performing the reaction of **1** with five equivalents of methylhydrazine at room temperature gave 3-amino-1-methyl-4-(1-methylhydrazino)-6-methylthiopyrazolo[3,4-*d*]pyrimidine (**4**) in 85% yield already after 1.5 h. Compound **4** was also obtained by treatment of **3** with an excess of methylhydrazine at room temperature (Scheme 1). In the ¹H NMR spectrum of compound **4**, additional signals of methyl and amino groups at 3.34 ppm and 6.32 ppm, respectively, are observed when compared with the spectrum of compound **3**. The ¹³C NMR spectrum of **4** is characterized by an additional N–Me signal at 41.1 ppm.

In our preliminary communication [22], we reported on an unexpected course of the reaction of methyl *N*-(6-chloro-2-methylthiopyrimidin-4-yl)-*N*-methylaminoethanoate (**5**) [17] with methylhydrazine to give tricyclic heterocycle—pyrazolo[5,4,3-*de*]pyrimido[4,5-*e*][1,4]diazepine (**6**) (Scheme 2). The same derivative **6** was also obtained by the reaction of 4-chloro-6-methylthiopyrazolo[3,4-*d*]pyrimidin-3-amine (**3**) with methyl *N*-methylaminoethanoate in the presence of potassium carbonate at reflux temperature of tetrahydrofuran (THF). To



expand this methodology for the synthesis of similar *ortho*- and *peri*-fused heterocycles, compound **3** was treated with methyl aminoethanoate. However, under conditions described for the synthesis of **6**, only starting materials were recovered. Heating the reaction mixture at 100°C in dimethylformamide (DMF) in the presence of potassium carbonate led to the substitution reaction product **7**. Formation of *ortho*- and *peri*-annulated heterocycle was not observed. Conversely, the reaction of **3** with methyl mercaptoethanoate under the analogous conditions (K₂CO₃/DMF/90°C) proceeded with the formation of 2-methyl-4-methylthio-2,6,7,9-tetrahydro-8*H*-pyrazolo [5,4,3-*de*]pyrimido[5,4-*f*][1,4]thiazepin-8-one (**8**). The same reaction under milder reaction conditions (K₂CO₃/THF/Δ) gave the substitution product **9**.

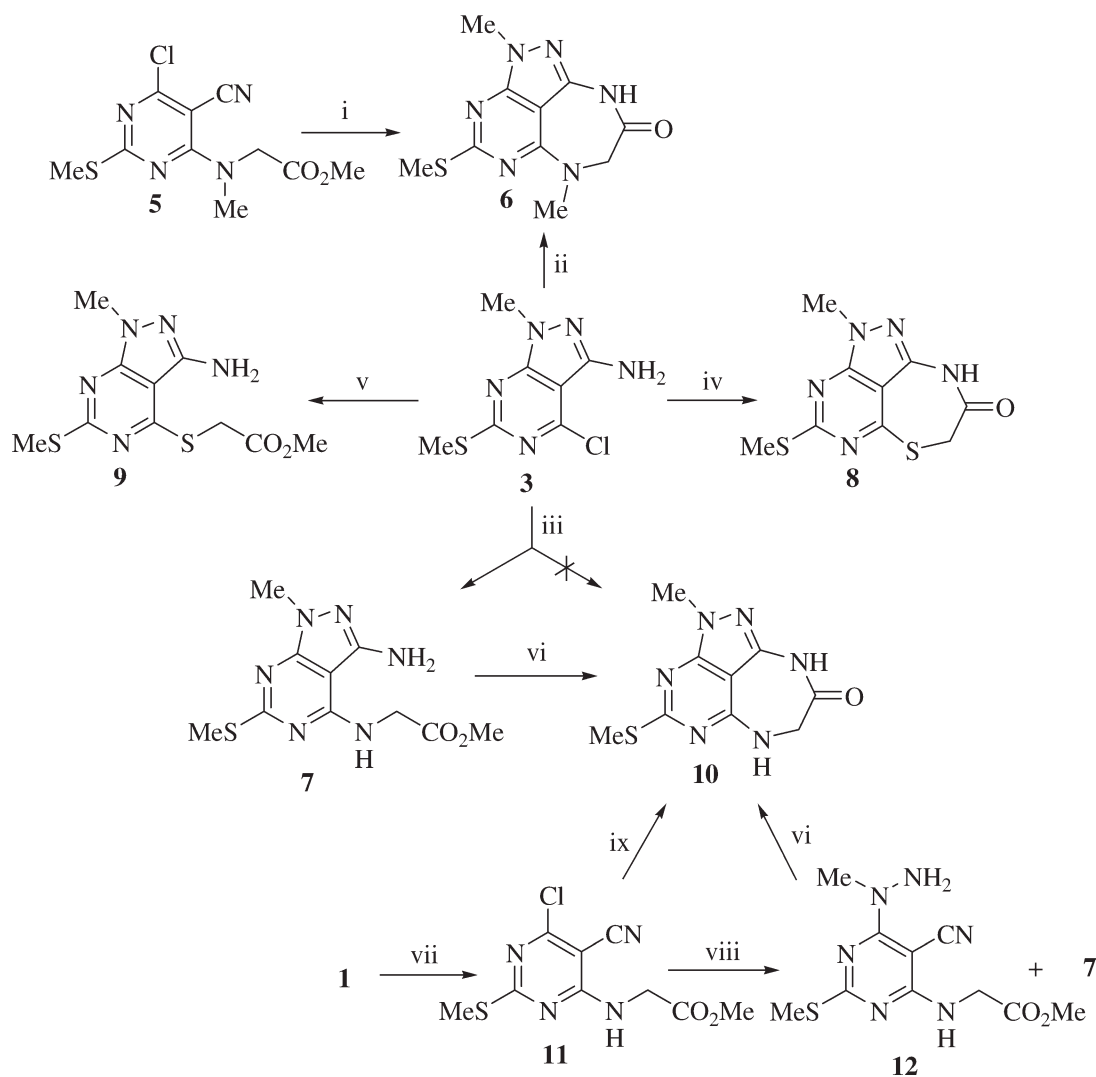
Intramolecular cyclocondensation reaction of methyl *N*-(3-amino-6-methylthiopyrazolo[3,4-*d*]pyrimidin-4-yl) aminoethanoate (**7**) to form tricyclic heterocycle **10** under basic conditions was not successful. The reason for such behavior, probably, is the formation of an unreactive anion in the reaction of **7** with bases due to rather acidic NH group in the aminoethanoate side chain. We have found that conversion of **7** into **10** can be achieved under acidic conditions. Thus, heating of compound **7** in acetic acid gave the desired diazepine **10** in 62% yield. This prompted us to elaborate a more efficient method for the preparation of the desired tricyclic system **10**. For this purpose, compound **11** was synthesized by the reaction of **1** with methyl aminoethanoate in the presence of sodium carbonate. Reaction of **11** with methylhydrazine proceeded with the formation of a mixture of substitution product **12** and pyrazolopyrimi-

dine **7**. Attempts to stop the reaction at the formation of hydrazinopyrimidine **12** failed. Compound **12** appeared to undergo smooth cyclization to pyrazolopyrimidine **7** even under the isolation procedures or under purification by column chromatography and as a result mixtures of **12** and **7** were always obtained. Nevertheless, this mixture can be used for the synthesis of **10**. Thus, heating of the mixture of **7** and **12** in glacial acetic acid afforded compound **10** in 52% yield. Taking into account these results we decided to perform the synthesis of **10** by one-pot procedure using tandem substitution/annulation reactions of compound **11** with methylhydrazine. Compound **11** reacted with an excess of methylhydrazine at room temperature, then glacial acetic acid was added, and the reaction mixture was refluxed for 13 h to give compound **10**.

Amino and hydrazino groups in compound **4** are properly positioned for construction of a triazepine moiety with one carbon electrophile. Indeed, when **4** reacted with an excess of triethyl orthoformate in the presence of ammonium chloride as an acidic catalyst, pyrazolo-[3,4,5-*ef*]pyrimido[5,4-*f*][1,2,4]triazepine was formed (Scheme 3).

Cyclocondensation of compound **4** with triethyl orthoformate can give either heterocycle **13** or isomeric triazepine **13a**. We expected that simple ¹H NMR NOE experiment showing interaction between protons of N—CH₃ and NH groups could be an effective method to elucidate the structure of an isomer formed in the reaction. However, a signal of protons of N—CH₃ group partially overlapped with a signal of residual water in DMSO-*d*₆ (because of low solubility of compound **13**, NOE experiment was not

Scheme 2

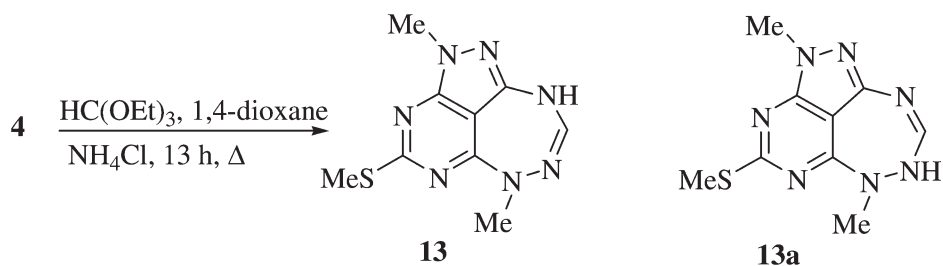


Reagents and conditions: (i) MeNHNH₂, MeOH, 4 days, room temperature; (ii) MeNHCH₂CO₂Me·HCl, K₂CO₃, THF, 8 h, Δ; (iii) NH₂CH₂CO₂Me·HCl, K₂CO₃, DMF, 2 h, 100°C; (iv) HSCH₂CO₂Me, K₂CO₃, DMF, 5.5 h, 90°C; (v) HSCH₂CO₂Me, K₂CO₃, THF, 6 h, Δ; (vi) AcOH, 1.5 h, 60°C; (vii) NH₂CH₂CO₂Me·HCl, Na₂CO₃, MeOH, 0.5 h, room temperature; (viii) MeNHNH₂, MeOH 1 h, , room temperature; (ix) 1. MeNHNH₂, MeOH, 75 min, room temperature; 2. AcOH, 12 h, Δ.

possible to carry out in other solvents), and the experiment could not give trustworthy results. Nevertheless, performed long range ¹H-¹H COSY NMR experiment did not show any interaction between protons of N-CH₃ and

NH groups. This together with the earlier obtained results on an analogous reaction in the thieno[2,3-*d*]pyrimidine series [23] allowed to conclude that formation of derivative **13** took place.

Scheme 3



CONCLUSIONS

In summary, we have developed a simple and efficient methods for the preparation novel *ortho*- and *peri*-fused heterocyclic systems consisting of structural units of pyrimidine, pyrazole, and 1,4-diazepine, 1,4-thiazepine, or 1,2,4-triazepine. Tandem substitution/annulation reactions of 3-amino-4-chloro-6-methylthiopyrazolo[3,4-*d*]pyrimidine with methyl *N*-methylaminoethanoate or mercaptoethanoate to give 2,6,7,9-tetrahydro-8*H*-pyrazolo[5,4,3-*de*]pyrimido[4,5-*e*][1,4]diazepin-8-one and -[5,4-*f*][1,4]thiazepin-8-one, respectively, were found to proceed under basic conditions, whereas the lactam formation of methyl *N*-(3-aminopyrazolo[3,4-*d*]pyrimidin-4-yl)aminoethanoate can be achieved under acidic conditions. The chemical potential of these novel heterocycles described herein are currently under investigation.

EXPERIMENTAL

General. Melting points were determined in open capillaries using digital melting point IA9100 series apparatus (Fischer Scientific) and are uncorrected. Infrared (IR) spectra were run on a Perkin-Elmer FT-IR spectrophotometer Spectrum BX II in KBr. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer (300 and 75 MHz, respectively) using residual solvents signals as internal standard. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F₂₅₄ aluminium plates (Merck). Visualization was accomplished by UV light.

4-Chloro-1-methyl-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-amine (3). To a solution of compound **1** (2.00 g, 9.09 mmol) in methanol (70 mL), a solution of methylhydrazine (0.99 mL, 0.86 g, 18.6 mmol) in methanol (10 mL) was added dropwise. The mixture was stirred at room temperature for 4 h, the precipitate was filtered off, dried, and recrystallized to give 1.58 g (76%) of compound **2**, mp 188–189°C (from 2-propanol). Lit. [21]: mp 190–192°C. ^{13}C NMR (CDCl₃): δ 14.7, 33.4, 100.8, 146.7, 153.1, 153.9, 170.8. IR, cm⁻¹: 3467, 3287 (NH₂). Anal. Calcd. for C₇H₈ClN₅S: C, 36.60; H, 3.51. Found: C, 36.85; H, 3.78.

1-Methyl-4-(1-methylhydrazino)-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-amine (4).

- A. To a solution of compound **1** (0.50 g, 2.27 mmol) in THF (25 mL), methylhydrazine (0.6 mL, 0.52 g, 11.3 mmol) was added. The mixture was stirred at room temperature for 1.5 h and then water (25 mL) was added. THF was evaporated under reduced pressure, the resulting solid was filtered off, washed with diethyl ether, and dried in drying pistol to give 0.46 g (85%) of compound **4**, mp 250–251°C. ^1H NMR (DMSO-*d*₆): δ 2.47 (s, 3H, SCH₃), 3.34 (s, 3H, NCH₃), 3.57 (s, 3H, NCH₃), 5.48 (s, 2H, NH₂), 6.32 (s, 2H, NH₂). ^{13}C NMR (DMSO-*d*₆): δ 14.1, 33.1, 41.1, 87.8, 148.4, 155.0, 159.1, 167.0. IR, cm⁻¹: 3407, 3250, 3147 (2×NH₂). Anal. Calcd. for C₈H₁₃ClN₇S: C, 40.15; H, 5.48. Found: C, 40.29; H, 5.58.
- B. To a solution of compound **3** (0.30 g, 1.31 mmol) in THF (15 mL), methylhydrazine (0.208 mL, 0.18 g, 3.92 mmol)

was added. The mixture was stirred at room temperature for 0.5 h and then water was added. The resulting solid was filtered off, washed with diethyl ether, and dried in drying pistol to give 0.18 g (58%) of compound **4**, mp 250–251°C.

2,6-Dimethyl-4-methylthio-2,6,7,9-tetrahydro-8*H*-pyrazolo[5,4,3-*de*]pyrimido[4,5-*e*][1,4]diazepin-8-one (6). To solution of compound **3** (0.10 g, 0.44 mmol) in THF (10 mL), methyl *N*-methylaminoethanoate hydrochloride (0.09 g, 0.65 mmol) and potassium carbonate (0.18 g, 1.30 mmol) were added. The mixture was refluxed for 8 h and cooled to room temperature. Then, water was added to the reaction mixture and the resulting precipitate was filtered off, dried, and recrystallized to give 0.08 g (70%) of compound **6**, mp 264–268°C (dec.) (from benzene). ^1H NMR (DMSO-*d*₆): δ 2.54 (s, 3H, SCH₃), 3.19 (s, 3H, NCH₃), 3.75 (s, 3H, NCH₃), 4.20 (s, 2H, CH₂), 11.23 (s, 1H, NH). ^{13}C NMR (DMSO-*d*₆): δ 14.3, 33.7, 37.0, 60.0, 91.9, 141.0, 154.1, 159.1, 167.2, 170.4. IR, cm⁻¹: 3344 (NH), 1670 (CO). Anal. Calcd. for C₁₀H₁₂N₆OS: C, 45.44; H, 4.58; N, 31.80. Found: C, 45.77; H, 4.97; N, 32.18.

Methyl *N*-[3-amino-1-methyl-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]aminoethanoate (7). To a solution of compound **3** (0.10 g, 0.43 mmol) in DMF (5 mL), methyl aminoethanoate hydrochloride (0.08 g, 0.65 mmol) and potassium carbonate (0.16 g, 1.18 mmol) was added. The mixture was stirred at 100°C for 2 h and cooled to room temperature. Then, water was added and the product was extracted with dichloromethane. Solvent was evaporated under reduced pressure and the residue was recrystallized to give 0.03 g (24%) of compound **7**, mp >200°C (dec.) (from benzene). ^1H NMR (DMSO-*d*₆): δ 2.42 (s, 3H, SCH₃), 3.57 (s, 3H, NCH₃), 3.66 (s, 3H, OCH₃), 4.17 (d, *J* = 5.7, 2H, CH₂), 5.78 (br s, 2H, NH₂), 7.93 (t, *J* = 5.7, 1H, NH). ^{13}C NMR (CDCl₃): δ 14.0, 33.1, 42.8, 52.4, 88.4, 147.6, 154.3, 156.0, 168.4, 171.4. IR, cm⁻¹: 3379, 3355, 3270 (NH, NH₂), 1730 (CO). Anal. Calcd. for C₁₀H₁₄N₆O₂S: C, 42.54; H, 5.00; N, 29.77. Found: C, 42.85; H, 5.26; N, 30.07.

2-Methyl-4-methylthio-2,6,7,9-tetrahydro-8*H*-pyrazolo[5,4,3-*de*]pyrimido[5,4-*f*][1,4]thiazepin-8-one (8). To a solution of compound **3** (0.20 g, 0.87 mmol) in DMF (10 mL), methyl mercaptoethanoate (0.082 mL, 0.10 g, 0.91 mmol) and anhydrous potassium carbonate (0.13 g, 0.96 mmol) were added. The mixture was stirred at 90°C for 5.5 h. Then, water was added, and the precipitate formed was filtered off, dried, and recrystallized to give 0.14 g (60%) of compound **8**, mp >265°C (dec.) (from acetonitrile). ^1H NMR (DMSO-*d*₆): δ 2.58 (s, 3H, SCH₃), 3.84 (s, 3H, NCH₃), 4.00 (s, 2H, CH₂), 11.26 (s, 1H, NH). ^{13}C NMR (DMSO-*d*₆): δ 14.4, 33.8, 35.2, 103.6, 140.8, 152.5, 167.9, 168.2, 169.4. IR, cm⁻¹: 3092 (NH), 1670 (CO). Anal. Calcd. for C₉H₉N₅OS₂: C, 40.44; H, 3.39; N, 26.20. Found: C, 40.26; H, 3.60; N, 26.22.

Methyl (3-amino-1-methyl-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thioethanoate (9). To a solution of compound **3** (0.10 g, 0.44 mmol) in THF (5 mL), methyl mercaptoethanoate (0.046 mL, 0.055 g, 0.52 mmol) and anhydrous potassium carbonate (0.072 g, 0.52 mmol) were added. The mixture was refluxed for 6 h and cooled to room temperature. Then, water was added, and the resulting precipitate was filtered off, dried, and recrystallized to give 0.108 g (83%) of compound **9**, mp 168–169°C (from 2-propanol). ^1H NMR (DMSO-*d*₆): δ 3.65 (s, 3H, NCH₃), 3.68 (s, 3H, OCH₃), 4.21

(s, 2H, CH₂), 5.55 (s, 2H, NH₂), SCH₃ signal overlaps with residual DMSO signals; ¹³C NMR (DMSO-*d*₆): δ 14.4, 31.2, 33.1, 35.2, 100.9, 146.8, 152.5, 161.5, 169.3, 169.5. IR, cm⁻¹: 3287, 3165 (NH₂), 1740 (CO). Anal. Calcd. for C₁₀H₁₃N₅O₂S₂: C, 40.12; H, 4.38, N, 23.39. Found: C, 40.09; H, 4.36; N, 22.85.

2-Methyl-4-methylthio-2,6,7,9-tetrahydro-8H-pyrazolo [5,4,3-*de*]pyrimido[4,5-*e*][1,4]diazepin-8-one (10).

- A. A solution of compound **7** (0.04 g, 0.14 mmol) in glacial acetic acid (10 mL) was heated at 60°C for 1.5 h and then cooled to room temperature. The resulting precipitate was filtered off, dried, and recrystallized to give 0.022 g (63%) of compound **10**, mp >280°C (dec.) (from DMF). ¹H NMR (DMSO-*d*₆): δ 2.51 (s, 3H, SCH₃), 3.75 (s, 3H, NCH₃), 4.00 (d, *J* = 3.3 Hz, 2H, CH₂), 8.20 (br s, 1H, NH), 11.19 (br s, 1H, NHCO). ¹³C NMR (DMSO-*d*₆): δ 14.2, 33.6, 51.6, 91.5, 141.3, 154.3, 160.3, 167.9, 170.7. IR, cm⁻¹: 3102, 3107 (NH), 1682 (CO). Anal. Calcd. for C₉H₁₀N₆OS: C, 43.19; H, 4.03. Found: C, 43.20; H, 4.18.
- B. A solution of a mixture of compounds **7** and **12** (0.2 g) in glacial acetic acid (10 mL) was heated at 60°C for 75 min and then cooled to room temperature. The resulting precipitate was filtered off, dried, and recrystallized to give 0.092 g (52%) of compound **10**, mp >280°C (dec.) (from DMF).
- C. To a suspension of compound **11** (0.05 g, 0.183 mmol) in methanol (5 mL), methylhydrazine (0.039 mL, 0.034 g, 0.734 mmol) was added. The mixture was stirred at room temperature for 75 min, then glacial acetic acid (0.5 mL) was added and the reaction mixture was refluxed for 12 h. After cooling to room temperature the precipitate was filtered off and recrystallized to give 0.014 g (30%) of compound **10**, mp >280°C (dec.) (from DMF).

Methyl *N*-(6-chloro-5-cyano-2-methylthiopyrimidin-4-yl)aminoethanoate (11). To a solution of compound **1** (0.40 g, 1.82 mmol) in methanol (15 mL), methyl aminoethanoate hydrochloride (0.46 g, 3.64 mmol) and sodium carbonate (0.60 g, 5.64 mmol) were added. The mixture was stirred at room temperature for 0.5 h, then water was added and the resulting precipitate was filtered off, dried, and recrystallized to give 0.4 g (81%) of compound **11**, mp 173–174°C (from 2-propanol). ¹H NMR (CDCl₃): δ 2.53 (s, 3H, SCH₃), 3.84 (s, 3H, OCH₃), 4.32 (d, *J* = 5.4 Hz, 2H, CH₂), 6.23 (br s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 14.4, 43.6, 52.7, 85.6, 114.3, 161.2, 161.6, 170.2, 175.4. IR, cm⁻¹: 3277 (NH); 2218 (CN); 1739 (CO). Anal. Calcd. for C₉H₉N₄ClO₂S: C, 39.64; H, 3.33; N, 20.54. Found: C, 40.16; H, 3.34; N, 20.44.

Methyl *N*-(3-amino-1-methyl-6-methylthio-1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)aminoethanoate (7) and methyl *N*-[5-cyano-6-(1-methylhydrazino)-2-methylthiopyrimidin-4-yl]aminoethanoate (12). To a solution of compound **11** (0.2 g, 0.73 mmol) in methanol (10 mL), a solution of methylhydrazine (0.13 mL, 0.108 g, 2.35 mmol) in methanol (10 mL) was added dropwise. The mixture was stirred at room temperature for 1 h, then filtered through 1 cm silica gel (Merck Silica gel 60, 40–63 μm) layer. Solvent was evaporated under reduced pressure to give 0.16 g (76%) of a mixture of compounds **7** and **12** in a ratio 1:1.

Compound **12**: ¹H NMR (DMSO-*d*₆): δ 2.35 (s, 3H, SCH₃); 3.26 (s, 3H, NCH₃); 3.64 (s, 3H, OCH₃); 4.08 (d, *J*

= 5.7 Hz, 2H, CH₂); 5.06 (s, 2H, NH₂); 7.31 (t, *J* = 5.7 Hz, 1H, NH).

2,6-Dimethyl-4-methylthio-6,9-dihydro-2H-pyrazolo[3,4,5-*ef*]pyrimido[5,4-*f*][1,2,4]triazepine (13). To a suspension of **9** (0.10 g, 0.42 mmol) in dioxane (5 mL), triethyl orthoformate (0.35 mL, 0.31 g, 2.1 mmol) and ammonium chloride (0.11 g, 2.1 mmol) were added. The mixture was refluxed for 13 h and then cooled to room temperature. Water was added; the resulting precipitate was filtered off and dried to give 0.07 g (67%) of compound **13**, mp 264–266°C (dec.) (from benzene). ¹H NMR (DMSO-*d*₆): δ 2.50 (s, 3H, SCH₃), 3.40 (s, 3H, NCH₃), 3.72 (s, 3H, NCH₃), 6.49 (d, *J* = 4.2 Hz, 1H, CH), 9.91 (d, *J* = 4.2 Hz, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 14.4, 33.6, 39.1, 84.8, 131.2, 142.1, 152.7, 153.7, 169.6. IR (KBr), cm⁻¹: 3260, 3198 (NH). Anal. Calcd. for C₉H₁₁N₇S: C, 43.36; H, 4.45. Found: C, 43.44; H, 4.33.

REFERENCES AND NOTES

- [1] Hanke, J. H.; Gardner, J. P.; Dow, R. L.; Changelian, P. S.; Brissette, W. H.; Weringer, E. J.; Pollok, B. A.; Connelly, P. A. *J Biol Chem* 1996, 271, 695.
- [2] Bishop, A. C.; Kung, C.; Shah, K.; Witucki, L.; Shokat, K. M.; Liu, Y. *J Am Chem Soc* 1999, 121, 627.
- [3] Bain, J.; Plater, L.; Elliott, M.; Shpiro, N.; Hastie, C. J.; McLauchlan, H.; Klevernic, I.; Arthur, J. S. C.; Alessi, D. R.; Cohen, P. *Biochem J* 2007, 408, 297.
- [4] Abunada, N. M.; Hassaneen, H. M.; Kandile, N. G.; Miqdad, O. A. *Molecules* 2008, 13, 1501.
- [5] Abdel-Gawad, S. M.; Ghorab, M. M.; El-Sharief, A. M. Sh.; El-Telbany, F. A.; Abdel-Alla, M. *Heteroatom Chem* 2003, 14, 530.
- [6] Vicentini, C. B.; Romagnoli, C.; Andreotti, E.; Mares, D. *J Agric Food Chem* 2007, 55, 10331.
- [7] La Motta, C.; Sartini, S.; Mugnaini, L.; Salerno, S.; Simorini, F.; Taliani, S.; Marini, A. M.; Da Settimo, F.; Lavecchia, A.; Novellino, E.; Antonioli, L.; Fornai, M.; Blandizzi, C.; Del Tacca, M. *J Med Chem* 2009, 52, 1681.
- [8] Da Settimo, F.; Primofiore, G.; La Motta, C.; Taliani, S.; Simorini, F.; Marini, A. M.; Mugnaini, L.; Lavecchia, A.; Novellino, E.; Tusciano, D.; Martini, C. *J Med Chem* 2005, 48, 5162.
- [9] Bakavoli, M.; Bagherzadeh, G.; Vaseghifar, M.; Shiri, A.; Pordel, M.; Mashreghi, M.; Pordeli, P.; Araghi, M. *Eur J Med Chem* 2010, 45, 647.
- [10] Ali, A.; Taylor, G. E.; Ellsworth, K.; Harris, G.; Painter, R.; Silver, L. L.; Young, K. *J Med Chem* 2003, 46, 1824.
- [11] Tseng, S. S.; Epstein, J. W.; Levin, J. I. U.S. Patent 5,013,737, 1991. Available at: <http://www.freepatentsonline.com/5013737.pdf>, accessed July 2009.
- [12] Kawasaki, A. M.; Wotring, L. L.; Townsend, L. B. *J Med Chem* 1990, 33, 3170.
- [13] Brown, D.; Loakes, D.; Williams, D.; Hill, F.; Kumar, S.; Nampalli, S.; McDougall, M.; Hamilton, A.; Smith, C.; Simmonds, A. C.; Cummins, W. J.; Finn, P. U.S. Patent 6,600,028, 2003. Available at: <http://www.freepatentsonline.com/6600028.pdf>, accessed July 2009.
- [14] Schenone, S.; Bruno, O.; Bondavalli, A. F.; Ranise, A.; Mosti, L.; Menozzi, G.; Fossa, P.; Donnini, S.; Santoro, A.; Ziche, M.; Manetti, F.; Botta, M. *Eur J Med Chem* 2004, 39, 939.
- [15] Carraro, F.; Naldini, A.; Pucci, A.; Locatelli, G. A.; Maga, G.; Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Brullo, C.; Fossa, P.; Menozzi, G.; Mosti, L.; Modugno, M.; Tintori, C.; Manetti, F.; Botta, M. *J Med Chem* 2006, 49, 1549.
- [16] Seela, F.; Zulauf, M. *J Chem Soc Perkin 1*, 1998, 19, 3233.

- [17] Tumkevicius, S.; Sarakauskaite, Z.; Masevicius, V. *Synthesis* 2003, 9, 1377.
- [18] Tumkevicius, S.; Masevicius, V. *Synlett* 2004, 13, 2327.
- [19] Tumkevicius, S.; Masevicius, V. *Synthesis* 2007, 24, 3815.
- [20] Santilli, A. A.; Kim, D. H.; Wanser, S. V. *J Heterocycl Chem* 1971, 8, 445.
- [21] Tumkevicius, S. *Chem Heterocycl Comp* 1996, 32, 716.
- [22] Masevicius, V.; Juskenas, R.; Tumkevicius, S. *Chem Heterocycl Comp* 2007, 43, 1593.
- [23] Tumkevicius, S.; Agrofoglio, L.A.; Kaminskas, A.; Urbelis, G.; Zevaco, T. A.; Walter, O. *Tetrahedron Lett* 2002, 43, 695.