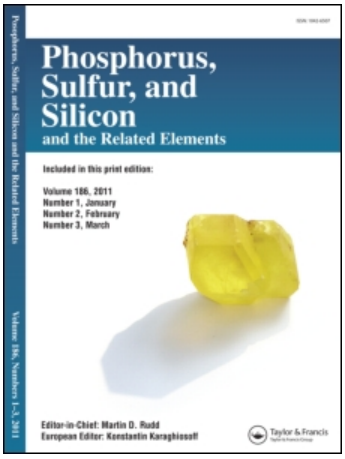

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Synthesis of 3-Aryl-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-7-thiones as Building Blocks for Potentially Biologically Active Compounds

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SYNTHESIS OF 3-ARYL-3,6-DIHYDRO-7*H*-[1,2,3]TRIAZOLO[4,5-*d*]PYRIMIDINE-7-THIONES AS BUILDING BLOCKS FOR POTENTIALLY BIOLOGICALLY ACTIVE COMPOUNDS

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[1,2,3]Triazolo[4,5-d]pyrimidine-7-thiones as building blocks for potentially biologically active compounds were synthesized by the base-catalyzed cyclization of 2-cyanoethanethioamide with arylazides and further reaction of the cyclization products with triethyl orthoformate.

Keywords Azides; heterocyclization; 1,2,3-triazole; [1,2,3]triazolo[4,5-*d*]pyrimidine

INTRODUCTION

1,2,3-Triazolo-pyrimidines are of increasing interest for biological applications.[1–5] For example, triazolo[4,5-*d*]-pyrimidines (8-azaguanines) are inhibitors of the purine nucleoside phosphorylase (PNPase), which is an important enzyme in the purine salvage pathway. It catalyzes the phosphorolysis of guanosine, inosine, and the corresponding 2′-deoxyribose analogs to their purine bases in a reversible reaction.[6] Some compounds possess a high affinity and selectivity for the A_1 and A_{2A} adenosine receptors[7–10] and the ability to inhibit the benzodiazepine receptor.[10] Adenosine is an endogenous nucleoside that mediates a variety of important physiological effects by its specific receptors. All of the adenosine receptor agonists synthesized thus far are structurally related to adenosine itself. Moreover, triazolo[4,5-*d*]-pyrimidine nucleosides were evaluated for antiretroviral activity as active agents in inhibiting reverse transcriptase.[11] In addition, the antiproliferative potential of some 8-azapurine derivatives, reflecting their ability to activate p53 tumor suppressor was described.[12]

With these facts in mind, we studied a synthetic route to triazolo[4,5-*d*]pyrimidines containing a mercapto group. It is known that such a functional group is suitable for modification by alkylation reactions and applicable for creation of substance libraries to be tested for biological activity.

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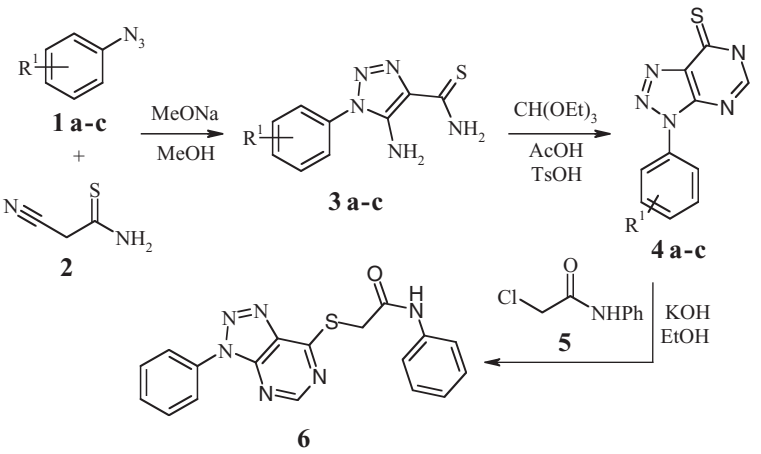
RESULTS AND DISCUSSION

In pursuing our studies, we needed to synthesize 1,2,3-triazolo[4,5-*d*]pyrimidine derivatives bearing a substituent suitable for modification. A well known synthetic route to 1,2,3-triazolo[4,5-*d*]pyrimidine is the reaction of azides with 2-cyanoacetamide. The next step was the formation of the pyrimidine cycle by reaction with a bi-electrophilic reagent. However, further modification of 1,2,3-triazolo[4,5-*d*]pyrimidines hardly occurs because of the low nucleophilicity of oxygen. In some cases, oxygen was replaced by chlorine to input new substituents.[8]

In the current work, we used 2-cyanoethanethioamide **2** for the base-catalyzed cyclization reaction with arylazides **1**. By the reaction of the appropriate azides with **2** in the presence of sodium methoxide in methanol at room temperature, 5-amino-1-aryl-1*H*-1,2,3-triazole-4-carbothioamides **3a–c** were formed in good yields. Furthermore, the appropriate pure compounds **3** precipitated from the reaction medium. They may be used for other reactions or analyzed without further purification. It is of note that the thiocarbamoyl group is less electron-withdrawing in spite of the carbamoyl group, and may give poor yields of aminotriazoles. However, in our case, the yields of compounds **3** are 74–87%, similar to the results of 1,2,3-triazole-4-carboamide yields. Previously, 1,2,3-triazole-4-carbothioamide **3a** was synthesized by a two-step reaction by L'abbe et al.[13]

Compounds **3a–c** were heated with triethyl orthoformate to form the corresponding 1,2,3-triazolo[4,5-*d*]pyrimidines **4a–c**.

The compound **4a** easily reacted with 2-chloro-*N*-phenylacetamide **5** to yield **6.** This reaction showed one of the possible variations of **4a–c** type structures (Scheme 1).



R^1 = H (**a**), 4-Me (**b**), 4-NO_2 (**c**).

Scheme 1

The structure of the compounds was substantiated from microanalytical and spectral data. Analytical, ^{1}H NMR, and mass spectral data were in agreement with the proposed structures.

As a result, we have an optimized method for the synthesis of 1,2,3-triazolo[4,5-*d*]pyrimidines suitable for modification on the base of cyclization reaction of 2-cyanoethanethioamide with azides. This convenient synthesis provides access to polynuclear heterocycles, which contain the basic ring structure found in molecules that exhibit biological activity.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Mercury 400 MHz instrument using TMS as an internal reference and DMSO-d_6 as a solvent. The mass spectra were recorded on an Agilent 1100 chromatomass spectrometer at 70 eV. The starting materials were commercially available and/or prepared in accordance to procedures in the literature for **1a–c**.[14] Yields of products were not optimized.

Synthesis of 5-Amino-1-aryl-1*H*-1,2,3-triazole-4-carbothioamides (3a–c)

To the solution of sodium methoxide (540 mg, 10.0 mmol) in dry methanol (20 mL), 2-cyanoethanethioamide **2** (10.0 mmol) was added. To this solution, arylazide **1** (10.0 mmol) in dry methanol (2 mL) was added dropwise, and a solid started to precipitate. The mixture was stirred for 24 h. The resulting suspension was filtered, and the solid product was washed with water and methanol to yield the corresponding 1,2,3-triazole-4-carbothioamides **3a–c**.

5-Amino-1-phenyl-1*H*-1,2,3-triazole-4-carbothioamide (3a). This compound was isolated as a white powder, mp 198–199°C (ethanol) (Lit.[13] 193–195°C) in 74% yield.

5-Amino-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carbothioamide (3b). This compound was isolated as a white powdered solid, mp 184–185°C (ethanol) in 87% yield. ^{1}H NMR ppm: δ 2.46 (s, 3H, CH_3), 7.23 (s, 2H, NH_2), 7.40 (d, 2H, ^3J 8.4, C_6H_4), 7.45 (d, 2H, ^3J 8.4, C_6H_4), 8.99 (s, 2H, $CSNH_2$). MS m/z: 233 (M^+). Anal. requires for $C_{10}H_{11}N_5S$ (233.29) calcd./found: C, 51.48/51.63; H, 4.75/4.82; N, 30.02/29.97.

5-Amino-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carbothioamide (3c). This compound was isolated as a white powdered solid, mp 232–233°C (ethanol) in 82% yield. ^{1}H NMR ppm: δ 7.64 (s, 2H, NH_2), 7.93 (d, 2H, ^3J 8.4, C_6H_4), 8.43 (d, 2H, ^3J 8.4, C_6H_4 H-2,6), 9.07 (s, 2H, $CSNH_2$). MS m/z: 264 (M^+). Anal. requires for $C_9H_8N_6O_2S$ (264.26) calcd./found: C, 40.90/40.80; H, 3.05/3.17; N, 31.80/31.94.

Synthesis of Compounds (4a–c)

The suspension of the appropriate compound **3** (50 mmol) in triethyl orthoformate (25 mL), acetic acid (40 mL), and 0.2 g of TsOH were refluxed for 4 h at 95–100°C. The reaction medium was cooled to room temperature. The solid was filtered and recrystallized from the mixture of EtOH–DMF. Physical and spectral properties of the compounds (**4a–c**) are given below.

3-Phenyl-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-7-thione (4a). This compound was isolated as a white powder, mp 188–189°C (ethanol–DMF) (Lit.[15] 191°C) in 84% yield.

3-(4-Methylphenyl)-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-7-thione (4b). This compound was isolated as a white powdered solid, mp 152–153°C (ethanol–DMF) in 81% yield. ^{1}H NMR ppm: δ 2.44 (s, 3H, CH_3), 7.17 (d, 2H, ^3J 8.0, Ph

H-3,5), 7.80 (d, 2H, ^3J 8.0, Ph H-2,6), 8.60 (s, 1H, pyrimidine), 11.22 (s, 1H, NH). MS m/z: 243 (M^+). Anal. requires for $C_{11}H_9N_5S$ (243.29) calcd./found: C, 54.30/54.14; H, 3.73/3.80; N, 28.79/28.62; S, 13.18/13.07.

3-(4-Nitrophenyl)-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-7-thione (4c). This compound was isolated as a white powdered solid, mp 277–278°C (ethanol–DMF) in 89% yield. ^{1}H NMR ppm: δ 7.55 (d, 2H, ^3J 8.4, C_6H_4 H-3,5), 8.61 (d, 2H, ^3J 8.4, C_6H_4 H-2,6), 8.64 (s, 1H, pyrimidine), 11.30 (s, 1H, NH). MS m/z: 274 (M^+). Anal. requires for $C_{10}H_6N_6O_2S$ (274.26) calcd./found: C, 43.79/43.64; H, 2.21/2.18; N, 30.64/30.49; S, 11.69/11.52.

N-Phenyl-2-[(3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)sulfanyl] acetamide (6)

To a solution of potassium hydroxide (560 mg, 10.0 mmol) and compound **4a** (2.3 g, 10.0 mmol)) in ethanol (30 mL), 2-chloro-*N*-phenylacetamide **2** (1.7 g, 10.0 mmol) was added. The reaction medium was cooled to room temperature. The solid was filtered and recrystallized from the mixture of EtOH–DMF. This compound was isolated as a white powdered solid, mp 195–196°C (ethanol–DMF) in 95% yield. ^{1}H NMR ppm: δ 7.03 (t, 1H, ^3J 7.8, Ph H-4), 7.27 (t, 2H, ^3J 7.8, Ph H-3,5), 7.54 (t, 1H, ^3J 7.8, Ph H-4), 7.58 (d, 2H, ^3J 7.8, Ph H-2,6), 7.66 (t, 2H, ^3J 7.8, Ph H-3,5), 8.18 (d, 2H, ^3J 7.8, Ph H-2,6) 8.95 (s, 1H, pyrimidine), 10.34 (s, 1H, NH). MS m/z: 362 (M^+). Anal. requires for $C_{18}H_{14}N_6OS$ (362.41) calcd./found: C, 59.65/59.48; H, 3.89/4.04; N, 23.19/23.14; S, 8.85/8.71.

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