SYNTHESIS OF 5,7-DIMETHYL-[1,2,4]TRIAZOLO[1,5-*a*]PYRIMIDINE-2-THIOL AND DERIVATIVES VIA (4,6-DIMETHYLPYRIMIDIN-2-YLSULFANYL)ACETOHYDRAZIDE

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Abstract

Treatment of (4,6-dimethylpyrimidin-2-ylsulfanyl)acetohydrazide with carbon disulfide in the solution of potassium hydroxide in ethanol gave 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol not 5-[(4,6-dimethylpyrimidin-2-ylsulfanyl)methyl]-1,3,4-oxadiazole-2-thiol due to the occurrence of a complex mechanism. 5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol was transformed into six *N*-substituted amide derivatives by reaction with different chloroacetamides. The structures of all products were confirmed by IR, NMR, and MS data.

Keywords: [1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol, amide, (4,6-dimethylpyrimidin-2-ylsulfanyl)acetohydrazide.

1. INTRODUCTION

4,6-Disubstituted-pyrimidine-2-thiols and their derivatives with a broad-spectrum of biological activities [1,2] have been considered as potential antitumor agents and attracted the attention of many of chemists and pharmacologists.

To continue our recent study on (4,6-dimethylpyrimidine-2-ylsulfanyl)acetohydrazide [3,4], we presented here the reaction of this hydrazide with carbon disulfide to form 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol as the result of a complex mechanism. This fused heterocyclic system was then converted to its amide derivatives.

2. EXPERIMENTAL

General procedures: All chemicals and solvents were obtained from commercial sources and used without any further purification. Melting points were determined in open capillaries and the values are uncorrected. HR-ESI-MS were taken on a Bruker MicroOTOF-Q II mass spectrometer. IR spectra were measured in KBr discs on a Shimadzu FTIR 8400S spectrophotometer. NMR spectra were recorded on a Bruker Avance spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) using DMSO-d_6 as solvent and tetramethylsilane (0.00 ppm) as an internal standard.

The intermediate compounds **1** and **2** have been synthesized via the procedure reported by Tran Quoc Son and colleagues [1] without further optimization or modification.

5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol (3): To a solution of hydrazide **2** (4.24 g, 20 mmol) and potassium hydroxide (5.60 g, 100 mmol) in anhydrous ethanol (40 mL), carbon disulfide (3.0 mL, 50 mmol) was added. The reaction mixture was refluxed for 8 h. The solvents were evaporated off and the mixture was poured into ice water while stirring. The solution was adjusted to pH 3-4 by dropwise adding 2 N solution of hydrochloric acid. The precipitate obtained was filtered and recrystallized from water to give **3** as white crystals (1.88 g, 52.0 % yield). M.p. 265-266 ^{o}C. IR (ν, cm^{-1}): 3277, 3161 (N-H), 3092, 3051 (C-H aromatic), 2924 (C-H aliphatic), 2758 (S-H), 1639, 1562 (C=N and C=C aromatic). ^{1}H NMR (δ, ppm): 14.00 (1H, *brs,* S<u>H</u>), 7.27 (1H, *s,* Hr-<u>H</u>), 2.62 (3H, *s,* C<u>H</u>$_3$), 2.52 (3H, s, C<u>H</u>$_3$). ^{13}C NMR (δ, ppm): 172.3, 165.0, 147.8, 146.2, 113.0, 24.0, 16.4. HR-ESI-MS (positive mode): *m/z* $[M+H]^+$ calcd. for ($C_7H_8N_4S$+H): 181.0542, found 181.0572.

General procedure for synthesis of 2-(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylthio)-*N*-aryl/hetarylacetamides (4a-f): To a solution of 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol (**3**) (0.36 g, 2 mmol) in acetone (20 mL), anhydrous potassium carbonate (0.28 g, 2

mmol) was added followed by definite aryl/hetaryl 2-chloroacetamide (2 mmol). The reaction mixture was refluxed for 6 h with stirring. The precipitate obtained was filtered and recrystallized from appropriate solvents to give the corresponding amides.

2-[(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)thio]-*N*-(4-ethoxyphenyl) acetamide (**4a**): recrystallized from mixture of EtOH-H_2O as brown needles, 0.41 g, 57.4 % yield. M.p. 241-243 ^oC. IR (ν, cm^{-1}): 3240 (N-H), 3060, 3040 (C-H aromatic), 2920 (C-H aliphatic), 1683 - 1670 (C=O), 1620 (C=N and C=C aromatic). ^1H NMR (δ, ppm): 10.19 (1H, *s*, NH), 7.48 (2H, *d*, ^3J = 9.0 Hz, Ar-H), 6.86 (2H, *d*, ^3J = 9.0 Hz, Ar-H), 7.10 (1H, *s*, Hr-H), 4.19 (2H, *s*, SCH_2), 3.98 (2H, *q*, ^3J = 7.0 Hz, CH_3CH_2), 2.66 (3H, *s*, Hr-CH_3), 2.54 (3H, *s,* Hr-CH_3), 1.30 (3H, *t*, ^3J = 7.0 Hz, CH_3CH_2). ^{13}C NMR (δ, ppm): 165.4, 164.2, 155.0, 154.6, 146.2, 131.9, 120.6, 114.4, 110.4, 63.1, 35.6, 24.4, 16.4, 14.6.

2-[(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)thio]-*N*-(3-hydroxyphenyl) acetamide (**4b**): recrystallized from DMF as yellow prisms, 0.35 g, 53.2 % yield. M.p. 248-249 ^oC. IR (ν, cm^{-1}): 3555, 3314, 3105 (O-H and N-H), 1678 (C=O), 1633, 1606 (C=N and C=C aromatic). ^1H NMR (δ, ppm): 10.10 (1H, *s*, NH), 9.40 (1H, *brs*, OH), 7.05 (2H, *m*, Ar-H), 6.84 (2H, *m*, Hr-H and Ar-H), 6.45 (1H, *dd*, ^3J = 8.0 Hz, ^4J = 1.5 Hz, Ar-H), 4.05 (1H, *s*, SCH_2), 2.93 (3H, *s*, Hr-CH_3), 2.49 (3H, *s,* Hr-CH_3). ^{13}C NMR (δ, ppm): 165.7, 164.9, 157.6, 157.5, 155.3, 139.6, 139.5, 129.4, 111.6, 110.7, 109.9, 106.3, 39.0, 24.3, 18.9. HR-ESI-MS (positive mode): *m/z* $[M+H]^+$ calcd. for ($C_{15}H_{15}N_5O_2S$+H): 330.1019, found 330.1025.

2-[(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)thio]-*N*-(4-methylphenyl) acetamide (**4c**): recrystallized from DMF as white prisms, 0.42 g, 64.2 % yield. M.p. 154-155 ^oC. IR (ν, cm^{-1}): 3233, 3178 (N-H), 2993, 2924 (C-H aliphatic), 1668 (C=O), 1633, 1606 (C=N and C=C aromatic). ^1H NMR (δ, ppm): 10.19 (1H, *s*, NH), 7.36 (2H, *d*, ^3J = 8.5 Hz, Ar-H), 7.07 (2H, *d*, ^3J = 8.5 Hz, Ar-H), 6.83 (1H, *s*, Hr-H), 4.06 (2H, *s*, SCH_2), 2.91 (3H, *s*, Hr-CH_3), 2.48 (3H, *s,* Hr-CH_3).

2-[(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)thio]-*N*-phenylacetamide (**4d**): recrystallized from mixture of DMF-EtOH as white prisms, 0.38 g, 60.7 % yield. M.p. 236-238 ^oC. IR (ν, cm^{-1}): 3204, 3190 (N-H), 3017 (C-H aromatic), 2918 (C-H aliphatic), 1682 (C=O), 1631, 1601 (C=N and C=C aromatic). ^1H NMR (δ, ppm): 10.20 (1H, *s*, NH), 7.48 (2H, *d*, ^3J = 7.5 Hz, Ar-H), 7.28 (2H, *dd*, $^3J_1$ = $^3J_2$ = 7.5 Hz, Ar-H), 7.04 (1H, *t*, ^3J = 7.5 Hz, Ar-H), 6.83 (1H, *d,* ^4J = 1.0 Hz, Hr-H), 4.07 (2H, *s*, SCH_2), 2.93 (3H, *s,* Hr-CH_3), 2.49 (3H, *s,* Hr-CH_3). ^{13}C NMR (δ, ppm): 165.8, 164.8, 155.3, 145.1, 139.6, 138.6, 128.7, 123.5, 119.1, 111.5, 39.0, 24.3, 18.9.

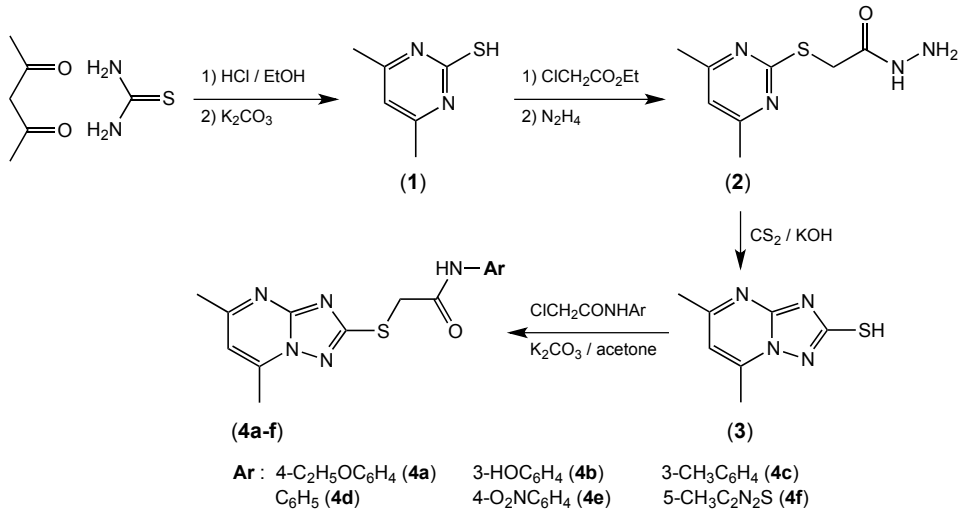
2-[(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)thio]-*N*-(4-nitrophenyl) acetamide (**4e**): recrystallized from DMF as dark red prisms, 0.57 g, 79.6 % yield. M.p. 168-169 ^oC. IR (ν, cm^{-1}): 3447 (O-H, N-H), 3049, 3013 (C-H aromatic), 2930 (C-H aliphatic), 1682 (C=O), 1633 (C=N and C=C aromatic). ^1H NMR (δ, ppm): 10.77 (1H, *s*, NH), 8.20 (2H, *d*, ^3J = 9.0 Hz, Ar-H), 7.75 (2H, *d*, ^3J = 9.0 Hz, Ar-H), 6.84 (1H, *d,* ^4J = 1.0 Hz, Hr-H), 4.16 (2H, *s*, SCH_2), 2.92 (3H, *d,* ^4J = 1.0 Hz, Hr-CH_3), 2.49 (3H, *s,* Hr-CH_3). ^{13}C NMR (δ, ppm): 166.9, 165.1, 155.3, 145.1, 144.8, 142.5, 139.5, 125.0, 118.9, 111.6, 39.0, 24.4, 18.9. HR-ESI-MS (positive mode): *m/z* $[M+H]^+$ calcd. for ($C_{15}H_{14}N_6O_3S$+H): 359.0921, found 359.0937.

2-[(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)thio]-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)acetamide (**4f**): recrystallized from DMF-H_2O as brown prisms, 0.25 g, 37.3 % yield. M.p. 253-256 ^oC. IR (ν, cm^{-1}): 3483 (N-H), 3155, 3005 (C-H aromatic), 2929 (C-H aliphatic), 1695 (C=O), 1626 (C=N and C=C aromatic). ^1H NMR (δ, ppm): 12.59 (1H, *s*, NH), 6.86 (1H, *d,* ^4J = 1.0 Hz, Hr-H), 4.19 (2H, *s*, SCH_2), 2.90 (3H, *d,* ^4J = 1.0 Hz, Hr-CH_3), 2.59 (3H, *s,* Hr-CH_3), 2.50 (3H, *s,* Hr-CH_3). HR-ESI-MS (positive mode): *m/z* $[M+H]^+$ calcd. for ($C_{12}H_{13}N_7OS_2$+H): 336.0696, found 336.0686.

3. DISCUSSION

From the commercially available and inexpensive starting materials, acetylacetone and thiourea, all products and intermediate compounds were synthesized as shown in scheme 1. The intermediate compounds **1** and **2** have been reported in our previous publications [3, 4].

Arylacetohydrazides, generally in reaction with CS_2 in the solution of potassium hydroxide in ethanol, should cyclize to give 5-substituted-1,3,4-oxadiazol-2-thiol as in recent reports by groups of Tashfeen Akhtar (2008) or Mohammad Amir (2011) [10,11]. However, when (4,6-dimethylpyrimidin-2-ylsulfanyl)acetohydrazide was used for the same procedure, we did not obtain the expected compounds, but 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol.



Scheme 1: Synthetic pathway for preparation of [1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol derivatives

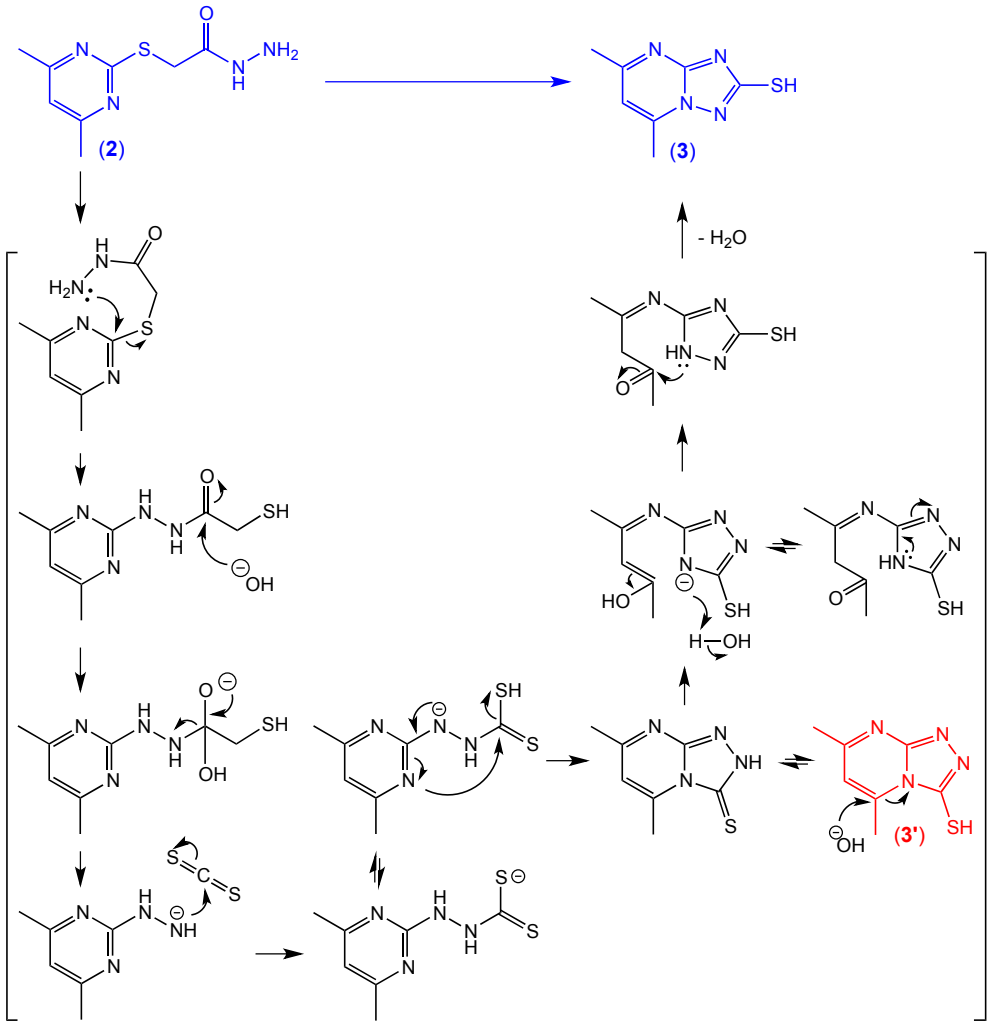


Figure 1: Plausible mechanism of the formation of 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol (**3**)

The IR spectrum of compound **3** obtained from hydrazide **2** showed not only a lack of the absorbance band at 1690 cm^{-1} represented for C=O bond of the hydrazide but also an appearance of the absorption at 2758 cm^{-1} which was attributable to S-H bond. Characteristic absorption for N-H bonds in the hydrazino $–NHNH_2$ group at 3277 cm^{-1} and 3161 cm^{-1} also did not appear in the spectrum. It means that a cyclization has been clearly occurred.

Besides, ^1H NMR spectrum of compound **3**

showed only four signals with the integral intensity of 1:1:3:3, respectively, in which the signals of two methyl groups are not equivalent. The -SCH_2- group therefore has been obviously cleaved from the molecule of hydrazide **2** or 5-(4,6-dimethypyrimidine)-2-ylsulfanyl-1,3,4-oxadiazol-2-thiol was not formed in our reaction condition.

The HRMS of **3** as shown in the experimental section was clearly inappropriate to the molecular weight of 5-(4,6-dimethypyrimidine)-2-ylsulfanyl-1,3,4-oxadiazol-2-thiol.

In the same manner as the reaction of benzothiazol-2-ylacetohydrazide, the rearrangement of (4,6-dimethylpyrimidin-2-ylsulfanyl)aceto-hydrazide when it was treated with CS_2 might happen to form 5,7-dimethyl-[1,2,4]triazolo[3,4-*a*]pyrimidine-3-thiol (**3'**) [5, 6]. However, in our case, the NMR data of compound **3** is agreeable with the spectral data of 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol [8], not **3'** [7]. Thus, we assume after the formation of the intermediate **3'**, the reaction is continued, converting **3'** to 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol (**3**) [9]. A total plausible mechanism of the formation of compound **3** from hydrazide **2** was described in detail in Figure 1.

5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol (**3**) was then treated with different *N*-aryl/hetaryl 2-chloroacetamides to easily give 2-(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylthio)-*N*-aryl/hetarylacetamides (**4a-f**). The IR, NMR, and MS data of these products were presented in the experimental section.

4. CONCLUSION

In the framework of synthesis of potential bioactive heterocyclic compounds, we have prepared six amide derivatives containing 2-(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-thiol via (4,6-dimethylpyrimidin-2-ylsulfanyl)acetohydrazide compound. We herein also discussed and suggested the mechanism of the formation of this heterocyclic compound.

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