

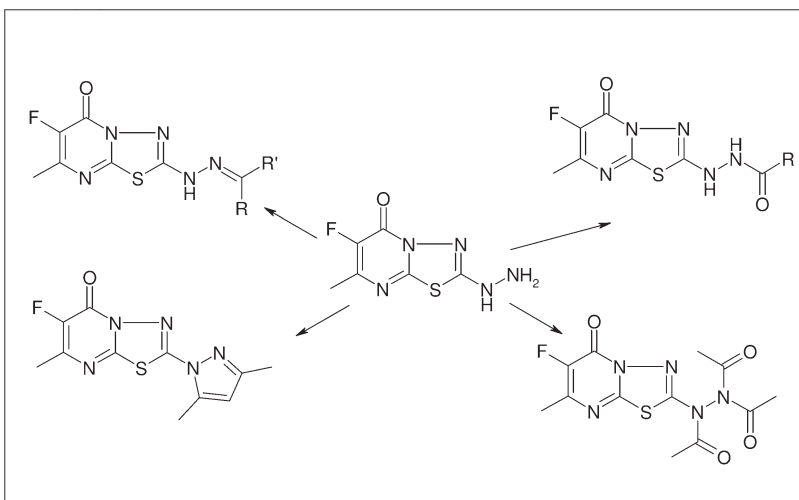
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2-Alkyl and 2-arylhydrazine derivatives of 5H-2-R-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one were prepared by reaction of 5H-2-bromo-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one with hydrazine derivatives. A convenient procedure was developed for the preparation of new hydrazine derivatives of 5H-2-R-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one.

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INTRODUCTION

Hydrazine derivatives are widely used in the synthesis of different heterocyclic systems [1–3]. There are only four published papers devoted to the synthesis and chemical conversion of hydrazine derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine [4–7]. It is well known that bromine in the 2-position of 1,3,4-thiazolo[3,2-*a*]pyrimidine can easily undergo substitution by different nucleophiles [8–11].

RESULTS AND DISCUSSION

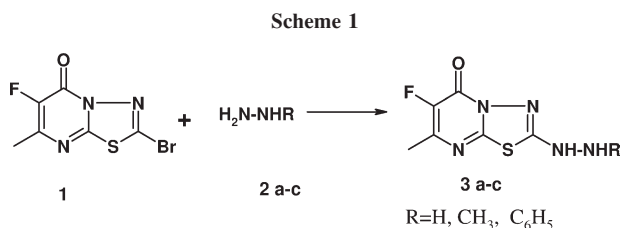
In this work, we studied the possibility of the synthesis of various derivatives of 5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one containing the hydrazine fragment in the position 2 and fluorine in the position 6.

We have initially investigated reactions of different hydrazine derivatives with 5H-2-bromo-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one. Reactions of hydrazine derivatives with 5H-2-bromo-6-fluoro-7-methyl-

1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one were carried out in methanol at room temperature. Upon addition of the hydrazino derivatives, the reaction mixture became warm and, because of this, the addition was carried out dropwise. The yield of the reaction products was from 70 to 90%. The reaction yielded selectively **3a–c** (**a** = H, **b** = CH₃, **c** = C₆H₅; Scheme 1).

According to the refs. 12–14, the reaction of hydrazine derivatives of nitrogen-containing heterocyclic compounds, in which the hydrazine group is in the *ortho* position with respect to the ring nitrogen, with carboxylic acids under various conditions affords triazolo derivatives. However, the reaction of hydrazines **2** with formic acid and acetic acid produced only hydrazine derivatives but not the cyclization products (Scheme 2). The reaction of hydrazines **2** with acetic anhydride resulted in acylation products of the hydrazines but did not give any condensation products.

Condensation of hydrazine **3a** with acetone yielded **7a**. Heating of **3a** in acetone afforded hydrazino derivatives of **3a** in a high yield (Scheme 3). **3a** reacted with



benzaldehyde in anhydrous dimethyl formamide to give **7b**. Also, a 3-h reaction of **3a** with acetylacetone in PPA at 100°C afforded the pyrazole **8** (Scheme 3). The bromination of **8** with bromine in acetic acid gives **9**.

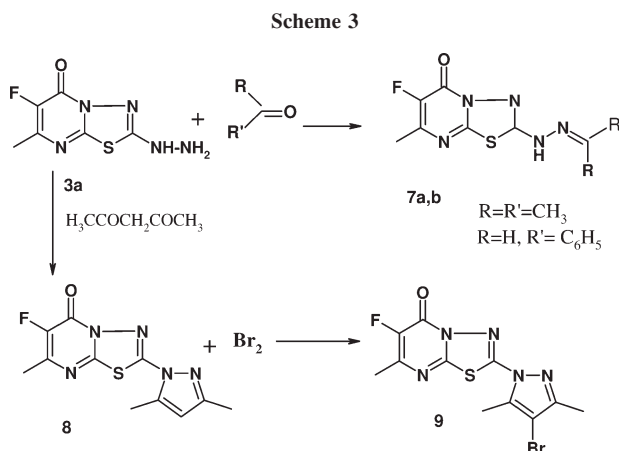
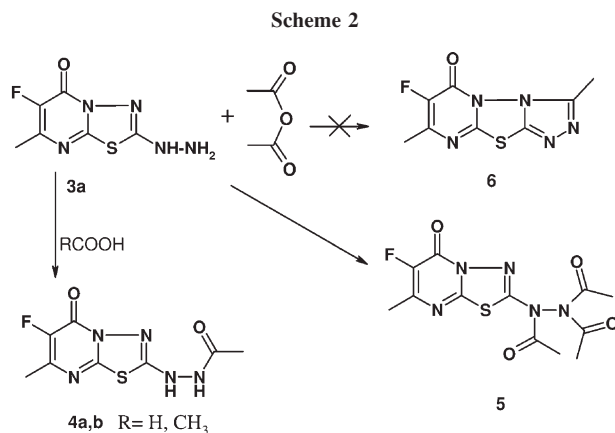
The structures of resulting compounds were confirmed by elemental analysis and ¹H-NMR and mass spectroscopy. In the ¹H-NMR spectrum of **9**, the signal for the proton in the position 4 of the pyrazole ring is absent. The ¹H-NMR spectra of the compounds **3–9** display a doublet for the methyl protons at 2.20–2.30 ppm with a spin-spin coupling constant of 3.73 Hz, which reflects the interaction between the fluorine atom and the methyl group.

CONCLUSIONS

In the interaction of 5H-2-bromo-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one with the derivatives of hydrazine, the substituted bromine atom is located in the position 2 of the ring and the fluorine atom in the position 6 is not replaced. 5H-2-hydrazino-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one in the reaction with organic acids and anhydrides formed acylation products but no ring closure took place.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ¹H spectra were measured on a Varian Mercury 400 instrument. Mass spectra were obtained on a Thermo Electron LCQ Deca (San Jose, CA) ion



trap mass spectrometer fitted with an electrospray ionization (ESI) source. The *m/z* range was 100–1000 Da. Elemental analyses were performed by Desert Analytics, Tucson, AZ. 5H-2-Bromo-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one was obtained according to the ref. 15.

General procedure for the preparation of 2H-2R-hydrazino-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones (3a–c). Compound **1a** (2.64 g, 10.0 mmol) was dissolved in methanol (25 mL) and then the appropriate hydrazine (10.0 mmol) dissolved in methanol (5 mL) was added at room temperature with stirring. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice/water (100 mL), and the precipitated products (**3a–c**) were filtered off and washed with water.

5H-2-Hydrazino-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3a). Yield 2.05 g (95%), m.p. 288°C; ¹H-NMR (dimethylformamide-*d*₇): 2.24 ppm (d, 3H from CH₃), 5.65 ppm (s, 2H from NH₂), 9.65 ppm (s, H from NH); ESI ms: *m/z* (%), 216.07(100). Anal. Calcd. for C₆H₆FN₅OS: C, 33.49; H, 2.81; N, 32.54; S, 14.90. Found: C, 33.69; H, 2.80; N, 32.48; S, 14.89.

5H-2-(N'-Methylhydrazino)-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3b). Yield 2.08 g (90.8%), m.p. 269°C; ¹H-NMR (dimethyl sulfoxide-*d*₆): 2.22 ppm (d, 3H from CH₃), 3.22 ppm (s, 3H from CH₃), 5.56 ppm (s, 2H from 2 NH), ESI ms: *m/z* (%) 230.07 (100). Anal. Calcd. for C₇H₈FN₅OS: C, 36.68; H, 3.52; N, 30.55; F 8.29. Found: C, 36.28; H, 3.41; N, 30.02; F, 8.02.

5H-2-(N'-Phenylhydrazino)-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3c). Yield 2.14 g (73%), m.p. 274°C; ¹H-NMR (dimethyl sulfoxide-*d*₆): 2.24 ppm (d, 3H from CH₃), 6.95 ppm (m, 3H from Ph-H), 7.25 ppm (m, 2H from Ph-H), 8.78 ppm (s, H from NH), 10.48 ppm (s, H from NH); ESI ms: *m/z* (%) 292.13 (100). Anal. Calcd. for C₁₂H₁₀FN₅OS: C, 49.48; H, 3.46; N, 24.04. Found: C, 49.40; H, 3.39; N, 23.98.

General procedure for the preparation of 5H-2R-N'-(6-fluoro-7-methyl-5-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-hydrazines (4a,b). The solution of **3a** (2.15 g, 10.0 mmol) in a carboxylic acid (25 mL) was refluxed for 5 h and then poured into ice/water. The precipitate was collected by filtration, dried, and crystallized from methanol.

5H-N'-Formyl-(6-fluoro-7-methyl-5-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-hydrazine (4a). Yield 1.50 g (61.70%),

m.p. 275°C. ¹H-NMR (dimethyl sulfoxide-*d*₆): 2.25 ppm (d, 3H from CH₃), 8.19 ppm (s, 3H from CH), 10.40 ppm (s, H from NH), 10.64 ppm (s, H from NH); ESI ms: *m/z* (%) 244.07 (100). Anal. Calcd. for C₇H₆FN₅O₂S: C, 34.57; H, 2.49; N, 28.79. Found: C, 34.48; H, 2.45; N, 28.66.

5*H*-N'-Acetyl-(6-fluoro-7-methyl-5-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)hydrazine (4b). Yield 2.20 g (85.60%), mp 318°C. ¹H-NMR (dimethyl sulfoxide-*d*₆): 1.94 ppm (s, 3H from CH₃), 2.27 ppm (d, 3H from CH₃), 10.30 ppm (s, H from NH), 10.49 ppm (s, H from NH); ESI ms: *m/z* (%) 258.07 (100). Anal. Calcd. for C₈H₈FN₅O₂S: C, 37.35; H, 3.13; N, 27.22. Found: C, 37.43; H, 3.15; N, 27.20.

5*H*-N',N'',N'''-Triacetyl-(6-fluoro-7-methyl-5-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)hydrazine (5). A solution of **3a** (2.15 g, 10.0 mmol) in acetic anhydride (25 mL) was refluxed for 6 h and then poured into ice/water. The precipitate was collected by filtration, dried, and crystallized from methanol. Yield 2.04 g (59.82%), m.p. 197°C. ¹H-NMR (dimethyl sulfoxide-*d*₆): 2.29 ppm (d, 3H from CH₃), 2.33 ppm (s, 3H from CH₃), 2.47 ppm (s, 3H from CH₃), 2.49 ppm (s, 3H from CH₃); ESI ms: *m/z* (%) 342.07 (100). Anal. Calcd. for C₁₂H₁₂FN₅O₄S: C, 42.23; H, 3.54; N, 20.52. Found: C, 42.33; H, 3.48; N, 20.38.

5*H*-6-Fluoro-2-(*N'*-isopropylidene-hydrazino)-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (7a). A solution of **3a** (2.15 g, 10 mmol) in acetone (25 mL) was refluxed for 5 h and then poured into ice/water. The precipitate was collected by filtration, dried, and crystallized from methanol. Yield 2.21 g (81.75%), mp 288°C; ¹H-NMR (dimethyl sulfoxide-*d*₆): 1.92 ppm (s, 3H from CH₃), 1.95 ppm (s, 3H from CH₃), 2.26 ppm (d, 3H from CH₃), 11.88 ppm (s, H from NH); ESI ms: *m/z* (%) 256.07 (100). Anal. Calcd. for C₉H₁₀FN₅OS: C, 42.35; H, 3.95; N, 27.43. Found: C, 42.43; H, 3.58; N, 27.24.

5*H*-2-(*N'*-Benzylidene-hydrazino)-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (7b). A hydrazine **3a** (2.15 g, 10.0 mmol) was dissolved in dimethylformamide (15 mL) at room temperature and to this solution benzaldehyde (1.06 g, 10.0 mmol) was added. The mixture was stirred for 5 h at room temperature and then poured into ice-water. The precipitate was collected by filtration, dried, and crystallized from dimethylformamide-dioxane (4:1). Yield 2.14 g (73%), mp 274°C; ESI ms: *m/z* (%) 304.07 (100). Anal. Calcd. for C₁₃H₁₀FN₅OS: C, 51.48; H, 3.32; N, 23.09. Found: C, 51.55; H, 3.39; N, 23.02.

5*H*-2-(3,5-Dimethylpyrazol-1-yl)-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (8). A mixture of PPA (10 g) and 5*H*-2-hydrazino-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (2.15 g, 10.0 mmol) was placed in a flask and acetylacetone (1.0 g, 10.0 mmol) was added. The reaction mixture was stirred for 3 h at 100°C, cooled, and poured into 100 mL of ice/cold water. The precipitate was separated by filtration, washed on the filter with 50 mL of ice/cold water, and dried on air for 12 h. Recrystallization from methanol gave 2.5 g (89.6%) of **8**, m.p. 215°C; ¹H-NMR (dimethyl sulfoxide-*d*₆): 2.15 ppm (s, 3H from CH₃), 2.31 ppm (d, 3H from CH₃), 262

ppm (d, 3H from CH₃), 6.38 ppm (s, broad, H from CH); ESI ms: *m/z* (%) 280.27 (100). Anal. Calcd. for C₁₁H₁₀FN₅OS: C, 47.31; H, 3.61; N, 25.07. Found: C, 47.32; H, 3.35; N, 24.80.

5*H*-2-(4-Bromo-3,5-dimethyl-pyrazol-1-yl)-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (9). To 2.79 g (10.0 mmol) of 5*H*-2-(3,5-dimethylpyrazol-1-yl)-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one dissolved in acetic acid (10 mL), 1.59 g (10.0 mmol) bromine, dissolved in acetic acid (5 mL), was added dropwise at ambient temperature within 10 min. The reaction mixture was stirred for 2 h. A saturated aqueous solution of sodium acetate (0.82 g, 10.0 mmol) was slowly added under cooling. The formed precipitate was collected by filtration and washed with water (4 × 15 mL). Recrystallization from dioxane yielded **9** (3.43 g, 95.8%), m.p. 217°C. ¹H-NMR (dimethyl sulfoxide-*d*₆): 2.24 ppm (s, 3H from CH₃), 2.31 ppm (d, 3H from CH₃), 2.64 ppm (s, 3H from CH₃); ESI ms: *m/z* (%) 358.13 (75), 360.13 (100). Anal. Calcd. for C₁₁H₉ BrFN₅OS: C, 36.89; H, 2.53; N, 19.55. Found: C, 36.93; H, 2.47; N, 19.39.

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