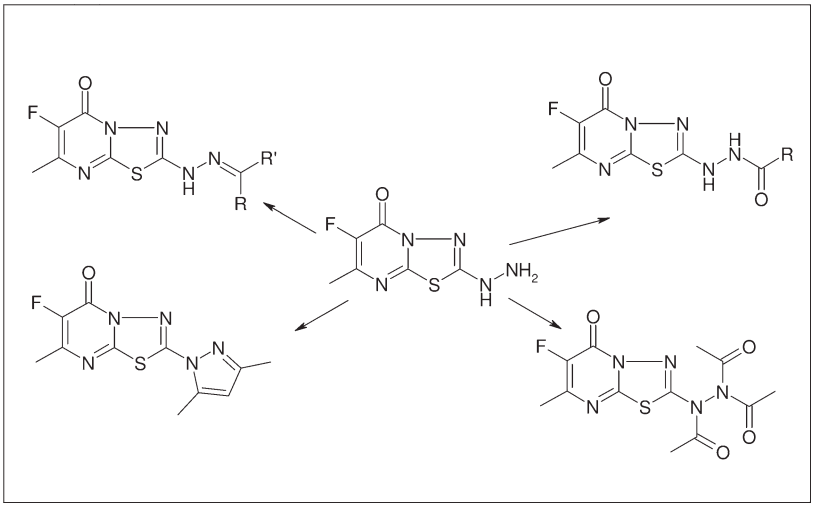
Muhamadsho A. Kukaniev[a] and Cyril Párkányi[b]*

[a]Laboratory of Heterocyclic Compounds, V.I.Nikitin Institute of Chemistry of the Academy of Sciences of the Republic of Tajikistan, 734063 Dushanbe, Tajikistan
[b]Department of Chemistry and Biochemistry, Florida Atlantic University, Boca Raton, Florida 33431-0991
*E-mail: parkanyi@fau.edu

Received July 27, 2010
DOI 10.1002/jhet.773
Published online 4 August 2011 in Wiley Online Library (wileyonlinelibrary.com).



2-Alkyl and 2-arylhydrazine derivatives of 5*H*-2-R-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one were prepared by reaction of 5*H*-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 5*H*-2-R-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one.

J. Heterocyclic Chem., **48**, 1404 (2011).

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

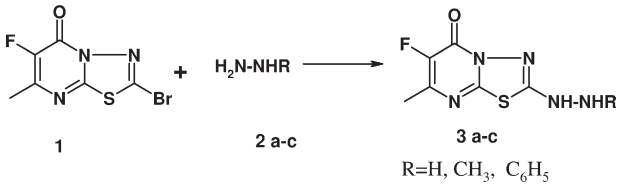
In this work, we studied the possibility of the synthesis of various derivatives of 5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one containing the hydrazine fragment in the position 2 and fluorine in the position 6.

We have initially investigated reactions of different hydrazine derivatives with 5*H*-2-bromo-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one. Reactions of hydrazine derivatives with 5*H*-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** = CH_3, **c** = C_6H_5; 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

Scheme 1



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 ^{1}H-NMR and mass spectroscopy. In the ^{1}H-NMR spectrum of **9,** the signal for the proton in the position 4 of the pyrazole ring is absent. The ^{1}H-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.

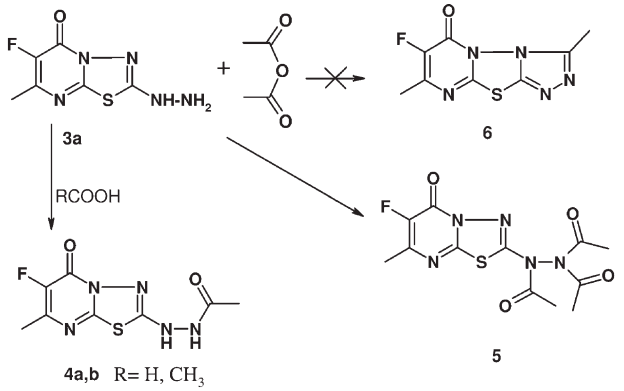
CONCLUSIONS

In the interaction of 5*H*-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.

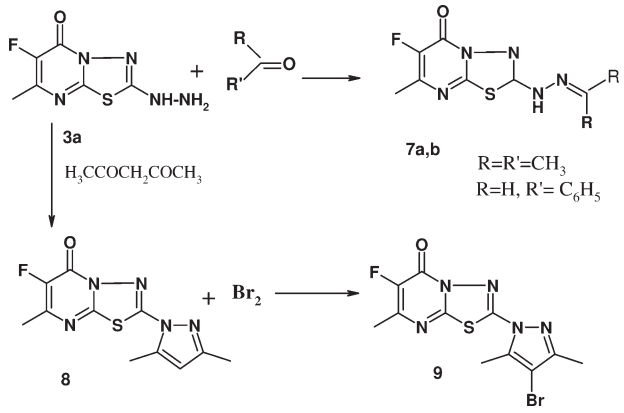
EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H 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. 5*H*-2-Bromo-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one was obtained according to the ref. 15.

Scheme 2



Scheme 3



General procedure for the preparation of 2*H*-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]-pyrimidine-5-one (3a). Yield 2.05 g (95%), m.p. 288°C; ^{1}H-NMR (dimethylformamide-d_7): 2.24 ppm (d, 3H from CH_3), 5.65 ppm (s, 2H from NH_2), 9.65 ppm (s, H from NH); ESI ms: *m/z* (%), 216.07(100). Anal. Calcd.for $C_6H_6FN_5OS$: 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; ^{1}H-NMR (dimethyl sulfoxide-d_6): 2.22 ppm (d, 3H from CH_3), 3.22 ppm (s, 3H from CH_3), 5.56 ppm (s, 2H from 2 NH), ESI ms: *m/z* (%) 230.07 (100). Anal. Calcd. for $C_7H_8FN_5OS$: 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; ^{1}H-NMR (dimethyl sulfoxide-d_6): 2.24 ppm (d, 3H from CH_3), 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 $C_{12}H_{10}FN_3OS$: 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. ^{1}H-NMR (dimethyl sulfoxide-d_6): 2.25 ppm (d, 3H from CH_3), 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 $C_7H_6FN_5O_2S$: C, 34.57; H, 2.49; N, 28.79. Found: C, 34.48; H, 2.45; N, 28.66.

5H-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. ^{1}H-NMR (dimethyl sulfoxide-d_6): 1.94 ppm (s, 3H from CH_3), 2.27 ppm (d, 3H from CH_3), 10.30 ppm (s, H from NH), 10.49 ppm (s, H from NH); ESI ms: *m*/*z* (%) 258.07 (100). Anal. Calcd. for $C_8H_8FN_5O_2S$: C, 37.35; H, 3.13; N, 27.22. Found: C, 37.43; H, 3.15; N, 27.20.

5H-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. ^{1}H-NMR (dimethyl sulfoxide-d_6): 2.29 ppm (d, 3H from CH_3), 2.33 ppm (s, 3H from CH_3), 2.47 ppm (s, 3H from CH_3), 2.49 ppm (s, 3H from CH_3); ESI ms: *m*/*z* (%) 342.07 (100). Anal. Calcd. for $C_{12}H_{12}FN_5O_4S$: C, 42.23; H, 3.54; N, 20.52. Found; C, 42.33 H, 3.48; N, 20.38.

5H-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 5h 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; ^{1}H-NMR (dimethyl sulfoxide-d_6): 1.92 ppm (s, 3H from CH_3), 1.95 ppm (s, 3H from CH_3), 2.26 ppm (d, 3H from CH_3), 11.88 ppm (s, H from NH); ESI ms: *m*/*z* (%) 256.07 (100). Anal. Calcd. for $C_9H_{10}FN_5OS$: C, 42.35; H, 3.95; N, 27.43. Found: C, 42.43; H, 3.58; N, 27.24.

5H-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 $C_{13}H_{10}FN_5OS$: C, 51.48; H, 3.32; N, 23.09. Found: C, 51.55; H, 3.39; N, 23.02.

5H-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 *5H*-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; ^{1}H-NMR (dimethyl sulfoxide-d_6): 2.15 ppm (s, 3H from CH_3), 2.31 ppm (d, 3H from CH_3), 262 ppm (d, 3H from CH_3), 6.38 ppm (s, broad, H from CH); ESI ms: *m*/*z* (%) 280.27 (100). Anal. Calcd. for $C_{11}H_{10}FN_5OS$: C, 47.31; H, 3.61; N, 25.07. Found: C, 47.32; H, 3.35; N, 24.80.

5H-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. ^{1}H-NMR (dimethyl sulfoxide-d_6): 2.24 ppm (s, 3H from CH_3), 2.31 ppm (d, 3H from CH_3), 2.64 ppm (s, 3H from CH_3); ESI ms: *m*/*z* (%) 358.13 (75), 360.13 (100). Anal. Calcd. for $C_{11}H_9$ $BrFN_5OS$: C, 36.89; H, 2.53; N, 19.55. Found: C, 36.93; H, 2.47; N, 19.39.

Acknowledgment. The authors are grateful to the Fulbright Foundation for a grant provided to M. A. Kukaniev.

REFERENCES AND NOTES

[1] Hipparagi, S. M.; Majunder, U. K.; Nargund, L. V. G.; Vinaykumar, R. Indian J Heterocycl Chem 2007, 16, 401.

[2] Katz, L. (Schenley Industries, Inc.). U.S. Pat. 2659730 19531117, 1953; Chem Abstr 1955, 49, 12325.

[3] Bijev, A. T.; Prodanova, P. Chem Heterocycl Compd 2007, 43, 306.

[4] Shukurov, S.; Artykova, D. A.; Nasyrov, I. M.; Zakharov, K. S.; Karakhanov, R. A. Izv Akad Nauk Ser Khim 1993, 219.

[5] Shukurov, S. Sh.; Artykova, D. A.; Zakharov, K. S.; Kukaniev, M. A.; Osimov, D. M. Khim Geterotsikl Soedin 1994, 560.

[6] Shukurov, S. Sh.; Artykova, D. A.; Dzhalolov, S. S.; Nasyrov, I. M.; Zakharov, K. S. Izv Vyssh Ucheb Zaved Khim Khim Tekhnol 1993, 36, 29.

[7] Okabe, T.; Taniguchi, E.; Maekawa, K. Bull Chem Soc Jpn 1974, 47, 2813.

[8] Kukaniev, M. A.; Salimov, T. M.; Murvatulloeva, M. S.; Imatshoev, I. Kh. Pharm Chem J 2006, 40, 421.

[9] Shukurov, S. S.; Kukaniev, M. A.; Nasyrov, I. M.; Zakharov, K. S.; Karakhanov, R. A. Izv Akad Nauk Ser Khim 1993, 1957.

[10] Kukaniev, M. A.; Shukurov, S. Sh.; Nasyrov, I. M.; Zakharov, K. S. Dokl Akad Nauk Tadzhik SSR 1990, 33, 821.

[11] Kukaniev, M. A.; Nurov, U.; Shukurov, S. Sh.; Khodzhibaev, Yu. Russ Chem Bull (Translation of Izv Akad Nauk Ser Khim) 1999, 48, 1143.

[12] Beyer, H.; Stehwen, D. Arch Pharm 1953, 286, 13.

[13] Efros, I. S.; Davidenkov, L. R. Zh Obshch Khim 1951, 21, 2046.

[14] Druer, J.; Ringier, B. H. Helv Chem Acta 1951, 34, 195.

[15] Kukaniev, M. A., Párkányi, C. J Heterocycl Chem, to appear.