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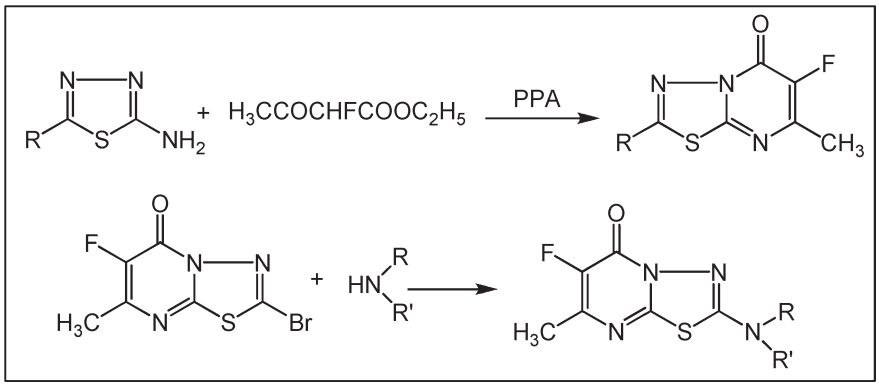


2-Alkyl-, 2-aryl-, and 2-halo-substituted derivatives of 7-methyl-6-fluoro-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-6-one (**3**) were prepared by reaction of 2-substituted 5-amino-1,3,4-thiadiazoles (**1**) and ethyl 2-fluoroacetoacetate (**2**) in polyphosphoric acid. A convenient procedure was developed for the synthesis of new 2-amino derivatives of 2-R-7-methyl-6-fluoro-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-6-one (**5**).

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## INTRODUCTION

Although research on 1,3,4-thiadiazolo[3,2-*a*]pyrimidines is not a new one—the first article devoted to this problem was published 50 years ago [1], new articles devoted to the chemistry and biological activity of these compounds have been recently published [2–13]. In 2004, a monograph on chemistry and biological activity of 1,3,4-thiadiazolo[3,2-*a*]pyrimidines was published in Russian, but the book could not cover all the aspects of the aforementioned field [14]. Although different syntheses of these compounds are presented in the above publications, not much information can be found about the synthesis of fluorine derivatives of this group of compounds. Patents on 2-trifluoromethyl derivatives [15] and 7-fluorosubstituted 1,3,4-thiadiazolo[3,2-*a*]pyrimidines [16] are available. Also a few articles on the synthesis of 6-chloro-, 6-bromo-, and 6-nitro-1,3,4-thiadiazolo[3,2-*a*]pyrimidines [16–22] have been published. However, there is no information available on the synthesis of the derivatives of this class with a fluoro group in the position 6.

## RESULTS AND DISCUSSION

In this work, we studied the possibilities of the synthesis of various derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine containing the fluorine group in the position 6.

The reaction of 2-substituted 5-amino-1,3,4-thiadiazoles (**1a–e**) with ethyl 2-fluoroacetoacetic ester in polyphosphoric acid (PPA) leads to the formation of

**Scheme 1**

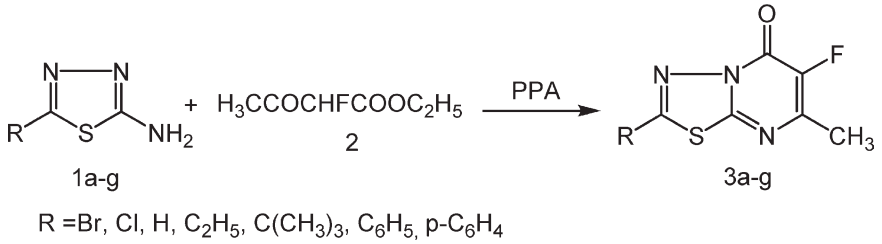


**Table 1**

The new derivatives **3**.

| 3 | R | Yield (%) | Mp (°C) |
|---|---|---|---|
| a | Br | 80 | 219 |
| b | Cl | 69 | 174 |
| c | H | 30 | 164 |
| d | $C_2H_5$ | 46 | 148 |
| e | $C(CH_3)_3$ | 36 | 117 |
| f | $C_6H_5$ | 70 | 200 |
| g | *p*-$CH_3C_6H_4$ | 73 | 255 |

2-substituted 6-fluoro-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines, which can be isolated in a 30–80% yield (Scheme 1). The results are summarized in Table 1.

The structures of **3a–g** were confirmed by elemental analysis and $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR, and mass spectra. The $^1$H NMR spectra of compounds **3a–g** display a doublet for the protons of the methyl group at 2.2–2.4 ppm with spin–spin coupling constant of 3.73 Hz, which relates to the interactions of the fluorine atom with the methyl group (Fig. 1).

Our next aim was to study the possibility of the synthesis of 2-amino-6-fluoro-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines **5a–g**, based on the reaction of 2-bromo-6-fluoro-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo-[3,2-*a*]pyrimidine **3a** with ammonia (**4a**), primary amines (**4b–c**), and secondary amines (**4d–f**). 2-Bromo-6-fluoro-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine **3a** reacted selectively with **4a–f** in the 2-position giving the new derivatives **5a–f** (Scheme 2 and Table 2).

Refluxing of amines **5a** and **5b** with acetic anhydride did not give the acyl derivatives **6a** and **6b** (Scheme 3).

## CONCLUSIONS

The interaction of 2-bromo-6-fluoro-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine with nucleophiles such as amines led only to substitution of the bromine atom located in the position 2 of the ring, but the fluorine atom located in the position 6 of the ring is not replaced. Fluorine atom located in the position 6 of the ring exhibits

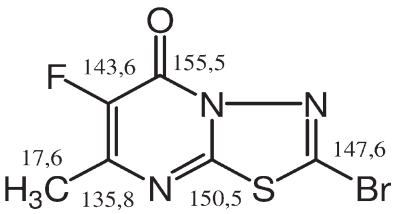



**Figure 1.** The $^{13}$C NMR data of **3a** measured in $CDCl_3$.

spin–spin interaction with protons of the methyl group in the position 7. The exocyclic amino group in 2-amino-6-fluoro-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*] pyrimidines has acidic properties and does not undergo acylation.

## EXPERIMENTAL

Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide pellets on a UR-20. $^1$H, $^{13}$C, and $^{19}$F NMR spectra were measured on a Varian Mercury 400 instrument. The $^{19}$F NMR spectra are not discussed here. Mass spectra were obtained on a Thermo Electron LCQ Deca (San Jose, CA) ion trap mass spectrometer fitted with an electrospray ionization (ESI) source, with the *m*/*z* range of 100–1000 Da. Elemental analyses were performed by Desert Analytics (Tucson, AZ). 2-Amino-1,3,4-thiadiazole [23], 2-amino-5-phenyl-1,3,4-thiadiazole [24], and 2-amino-5-bromo-1,3,4-thiadiazole [25] were obtained as described in the literature.

**General procedure for the preparation of 2R-6-fluoro-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines.** A mixture of PPA (10 g) and 2-amino-5-R-1,3,4-thiadiazole (0.001 mol) was placed in a flask and ethyl 2-fluoroacetoacetic ester (0.001 mol) was added. The reaction mixture was stirred for 8 h at 100°C, cooled, and poured into 100 mL of ice-cold water. The precipitate was filtered, washed on the filter with 30 mL of ice-cold water, and poured into 100 mL of ice-cold water. The precipitate was filtered, washed on the filter with 30 mL of ice-cold water, and dried in air for 12 h.

***2-Bromo-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (3a).*** Yield 2.11 g (80%), mp 219°C., ir (potassium bromide) $\upsilon_{max}$ cm$^{-1}$: 1700 (C=O), 1590 (C=N); $^1$H NMR ($CDCl_3$): 2.24 ppm (d, 3H from $CH_3$), $^{13}$C NMR ($CDCl_3$): 17.6 ($CH_3$), 135.8 (C-7), 143.6 (C-6), 147.4 (C-2), 150.5 (C-8), 155.5 (C-5). ESI MS: *m*/*z* (%) 264.07(75), 266.07 (100). Anal. Calcd. for $C_6H_3BrFN_3OS$: C, 27.29; H, 1.15; N, 15.91. Found: C, 27.62; H, 1.14; N,15.81.

***2-Chloro-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (3b).*** Yield 1.53 g (69%), mp 174°C. $^1$H NMR ($CDCl_3$):

**Scheme 2**

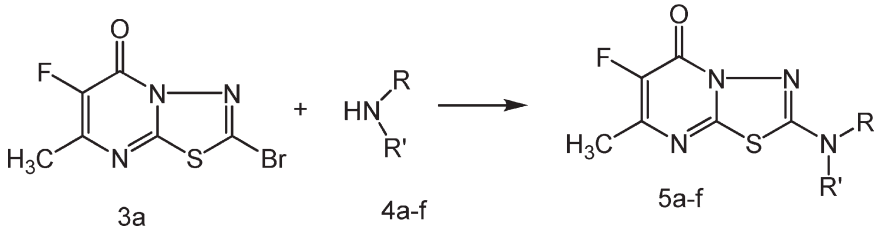


**Table 2**

The new derivatives **5**.

| 5 | R | R′ | Yield (%) | Mp (°C) |
|---|---|---|---|---|
| a | H | H | 93 | 276 |
| b | H | $CH_3$ | 84 | 288 |
| c | H | $C_2H_5$ | 84 | 275 |
| d | $C_2H_5$ | $C_2H_5$ | 84 | 126 |
| e | —$(CH_2)_2$—O—$(CH_2)_2$— | | 67 | 237 |
| f | —$(CH_2)_5$— | | 74 | 182 |
| g | —$(CH_2)_2$—NH—$(CH_2)_2$— | | 73 | 194 |

2.26 ppm (d, 3H from $CH_3$), ESI MS: *m/z* (%) 220.13 (100). Anal. Calcd. for $C_6H_3ClFN_3OS$: C, 32.81; H, 1.38; N, 19.13. Found: C, 32.89; H, 1.33; N,19.09.

***6-Fluoro-7-methyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (3c).*** Yield 0.55 g (30%), mp 164°C. $^1$H NMR ($CDCl_3$): 2.37 ppm (d, 3H from $CH_3$), 8.78 ppm (s, 1H from CH), ESI MS: *m/z* (%) 186.13 (100). Anal. Calcd. for $C_6H_6FN_3OS$: C, 38.92; H, 2.18; N, 22.69. Found: C, 38.54; H, 2.16; N, 22.54.

***2-Ethyl-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (3d).*** Yield 1.00g (46%), mp 148°C. $^1$H NMR ($CDCl_3$): 1.45 ppm (t, 3H from $CH_3$), 2.39 ppm (d, 3H from $CH_3$), 3.15 ppm (q, 2H from $CH_2$), ESI MS: *m/z* (%) 214.13 (100). Anal. Calcd. for $C_8H_8FN_3OS$: C, 45.05; H, 3.78; N, 19.71. Found: C, 45.17; H, 3.66; N, 19.56.

***2-Tert-butyl-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (3e).*** Yield 1.40 g, mp 117°C. $^1$H NMR ($CDCl_3$): 1.49 ppm (c, 9H from 3 $CH_3$), 2.39 ppm (d, 3H from $CH_3$), ESI MS: *m/z* (%): 242.20 (100). Anal. Calcd. for $C_{10}H_{12}FN_3OS$: C, 49.78; H, 5.01; N, 17.41; S, 13.29. Found: C, 49.84; H, 5.55; N, 17.14; S, 13.16.

***6-Fluoro-7-methyl-2-phenyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (3f).*** Yield 2.43 g (70%), mp 200°C. $^1$H NMR (DMSO-$d_6$): 2.37 ppm (d, 3H from $CH_3$), 7.64 ppm (m, 2H from Ph-H), 7.71 ppm (m, 1H from Ph-H), 8.00 ppm (m, 2H from Ph-H), ESI MS: *m/z* (%) 262.07 (100). Anal. Calcd. for $C_{12}H_8FN_3OS$: C, 55.16; H, 3.09; N, 16.08. Found: C, 55.21; H, 3.02; N, 15.98.

***6-Fluoro-7-methyl-2-p-tolyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (3g).*** Yield 2.63 g (73%), mp 255°C. $^1$H NMR (DMSO-$d_6$): 2.25 ppm (d, 3H from $CH_3$), 2.38 ppm (c, 3H from $CH_3$), 7.41 ppm (d, 2H from Ph-H), 7.69 ppm (d, 2H from Ph-H), ESI MS: *m/z* (%), 276.07 (100). Anal. Calcd. for $C_{13}H_{10}FN_3OS$: C, 56.72; H, 3.66; N, 15.26. Found: C, 56.41; H, 3.59; N, 15.12.

**General procedure for the preparation of 2-amino-6-fluoro-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines (5a–e).** Compound **1a** (2.64 g, 0.01 mol) was dissolved in methanol and then an amine (0.02 mol) was added with stirring. The reaction mixture was stirred at room temperature for 5 h and then refluxed for 10 min. After cooling the reaction mixture was poured into ice-water (100 mL). The precipitated compounds **5a**–**e** were filtered off and washed with water.

***2-Amino-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (5a).*** Yield 1.85 g (93%), mp 276°C. $^1$H NMR (DMSO-$d_6$): 2.14 ppm (c, 3H from $CH_3$), 7.20 ppm (s, 2H from $NH_2$), ESI MS: *m/z* (%) 201.07 (100). Anal. Calcd. for $C_6H_5FN_4OS$: C, 36.00; H, 2.52; N, 27.99. Found; C, 36.10; H, 2.49; N, 27.91.

***6-Fluoro-7-methyl-2-methylamino-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (5b).*** Yield 1.80 g (84%), mp 288°C. $^1$H NMR (DMSO-$d_6$): 2.21 ppm (d, 3H from $CH_3$), 2.88 ppm (d, 3H from $CH_3$), 8.19 ppm (q, 1H from NH), ESI MS: *m/z* (%) 215.13 (100). Anal. Calcd. for $C_7H_7FN_4OS$: C, 39.25; H, 3.29; N, 26.15. Found; C, 39.33 H, 3.24; N, 26.13.

***6-Fluoro-7-methyl-2-ethylamino-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (5c).*** Yield 1.93 g (84%), mp 275°C. $^1$H NMR (DMSO-$d_6$): 1.18 ppm (t, 3H from $CH_3$), 2.23 ppm (d, 3H from $CH_3$), 3.32 ppm (q, 2H from $CH_2$), 8.24 ppm (t, 1H from NH), ESI MS: *m/z* (%) 229.13 (100). Anal. Calcd. for $C_8H_9FN_4OS$: C, 42.10; H, 3.97; N, 24.55. Found; C, 42.16; H, 3.75; N, 24.43.

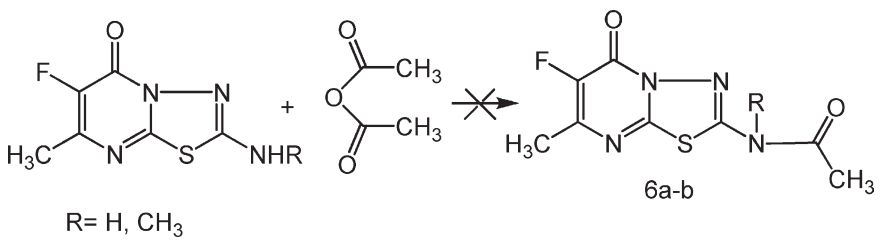
***2-Diethylamino-6-fluoro-7-methyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (5d).*** Yield 1.93 g, (84%), mp 126°C. $^1$H NMR ($CDCl_3$): 1.22 ppm (t, 6H from 2 $CH_3$), 2.27 ppm (d, 3H from $CH_3$), 3.45 ppm (q, 4H from 2 $CH_2$), $^{13}$C NMR ($CDCl_3$): 12.8 ($CH_3$), 17.6 ($CH_3$), 45.9 ($CH_2$), 135.8 (C-7), 143.6, (C-6), 147.6 (C-2), 155.4, (C-8), 159.1 (C-5), ESI MS: *m/z* (%) 257.13 (100). Anal. Calcd. for $C_{10}H_{13}FN_4OS$: C, 46.86; H, 5.11; N, 21.86; S, 12.51. Found: C, 46.97; H, 5.75; N, 21.69; S, 12.61.

***6-Fluoro-7-methyl-2-morpholin-4-yl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (5e).*** Yield 1.82 g, (67%), mp 237°C. $^1$H NMR ($CDCl_3$): 2.29 ppm (d, 3H from $CH_3$), 3.50 ppm (d, 4H from 2 $CH_2$), 3.76 ppm (d, 4H from 2 $CH_2$), $^{13}$C NMR ($CDCl_3$): 17.4 ($CH_3$), 48.5 ($CH_2$), 66.0 ($CH_2$), 144.0 (C-7), 145.9, (C-6), 151.0 (C-2), 152.8, (C-8), 160.5 (C-5), ESI MS: *m/z* (%) 271,20 (100). Anal. Calcd. for $C_{10}H_{11}FN_4O_2S$: C, 44.44; H, 4.10; F, 7.03; N, 20.88. Found; C, 44.54; H, 4.03; F, 7.10; N, 20.48.

***6-Fluoro-7-methyl-2-piperidin-1-yl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (5f).*** Yield 2.00 g (74%), mp 182°C. $^1$H NMR ($CDCl_3$): 1.64 ppm (m, 6H from 3 $CH_2$), 2.23 ppm (d, 3H from $CH_3$), 3.46 ppm (m, 4H from 2 $CH_2$), $^{13}$C NMR ($CDCl_3$): 17.3 ($CH_3$ ), 23.8 ($CH_2$), 25.2 ($CH_2$), 49.9 ($CH_2$), 144.0 (C-7), 145.4 (C-6), 151.0 (C-2), 154.5, (C-8), 160.1 (C-5), ESI MS: *m/z* (%) 269.20 (100). Anal. Calcd. for $C_{11}H_{13}FN_4OS$: C, 49.24; H, 4.88; N, 20.88. Found: C, 49.29; H, 4.83 N, 20.81.

***6-Fluoro-7-methyl-2-piperazin-1-yl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (5g).*** Yield 1.96 g (73%), mp 194°C. $^1$H NMR ($CDCl_3$): 2.55 ppm (d, 3H from $CH_3$), 2.79 ppm (m, 4H from

**Scheme 3**



2 $CH_2$), 3.26 ppm (s, 1H from NH), 3.38 ppm (m, 4H from 2 $CH_2$), ESI MS: *m/z* (%) 270.07 (100). Anal. Calcd. for $C_{10}H_{12}FN_5OS$: C, 44.60; H. 4.49; N, 26.01. Found: C, 44.69; H, 4.43; N, 25.98.

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