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SHORT COMMUNICATIONS

# Highly Regioselective Synthesis of 4-Hydroxy-6-methyl-3-(3-R-sulfanyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-2*H*-pyran-2-ones

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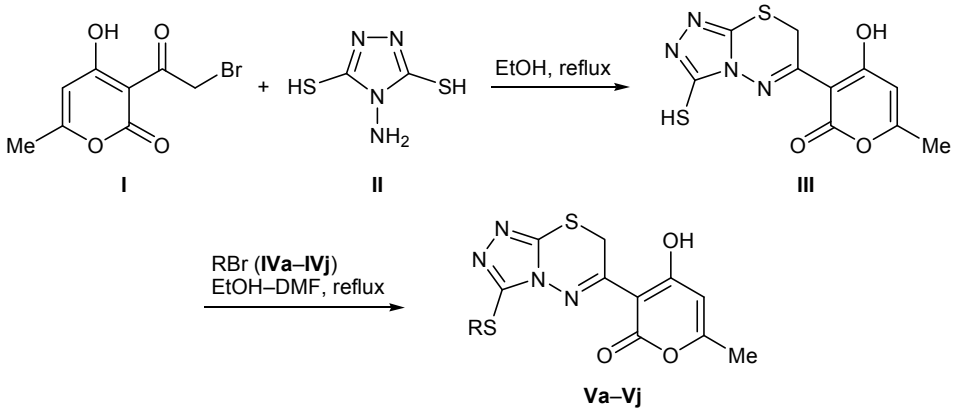
Bicyclic systems based on [1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazine attract interest from the synthetic viewpoint. In particular, [1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazine derivatives exhibit various kinds of pharmacological activity, such as bactericidal [1], CNS stimulating [2], and antimicrobial [3]. Several [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines have also attracted a great deal of interest as a new potent chemotype [4] for selective inhibition of phosphodiesterase 4 (PDE4). In continuation of our search for biologically active nitrogen and sulfur heterocycles [5–8], it was decided to synthesize the title compounds.

The condensation of 4-amino-1,2,4-triazole-3,5-dithiol (**II**) with 3-bromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**I**) resulted in the formation of thiol **III**. The structure of **III** was determined on the basis of its IR, $^1$H NMR, and mass spectra and elemental analysis. The IR spectrum of **III** showed absorption bands at 2749, 1716, and 3448 cm$^{-1}$ due to SH, C=O, and OH groups, respectively. The $^1$H NMR spectrum of **III** displayed a singlet at δ 2.44 ppm, attributed to the free SH group.

Compound **III** was used as key intermediate in the synthesis of novel [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives **Va**–**Vj**. The alkylation of thiol **III** with various alkyl, aralkyl, and phenacyl halides **IVa**–**IVj** in a mixture of anhydrous ethanol and DMF yielded the corresponding sulfides **Va**–**Vj**. Molecule **III** possesses several nucleophilic centers, so that the alkylation of **III** could give rise to different types of products, such as *S*-, *O*-, and *N*-alkyl derivatives and/or their mixtures. However, in our case the only products were *S*-alkyl derivatives **Va**–**Vj** (no other products were detected in the reaction mixtures by TLC), which may be due to high nucleophilicity of the thiol group.

The structure of **Va**–**Vj** was confirmed by spectral data. In the IR spectra of all compounds **Va**–**Vj** we observed absorption bands corresponding to lactone carbonyl and OH groups. The $^1$H NMR spectra of **Va**–**Vj** revealed a singlet in the region δ 4.06–4.52 ppm




R = 4-XC$_6$H$_4$CO (**a**–**g**), PhCH$_2$ (**h**), 4-O$_2$NC$_6$H$_4$CH$_2$ (**i**), BrCH$_2$CH$_2$ (**j**); X = Cl (**a**), Br (**b**), MeO (**c**), Me (**d**), H (**e**), O$_2$N (**f**), Ph (**g**).

due to methylene protons adjacent to the endocyclic sulfur atom. No SH proton signal characteristic of initial compound **III** was present in the $^1$H NMR spectra of **Va**–**Vj**.

In conclusion, we have described an efficient and regioselective method for the synthesis of a series of new [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives. This protocol is characterized by a reaction time of 6 to 10 h, good yield, and simple isolation procedure. Our ongoing efforts for the synthesis of other compounds starting from intermediate product **III** will be reported elsewhere.

**4-Hydroxy-3-(3-sulfanyl-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazin-6-yl)-6-methyl-2*H*-pyran-2-one (III).** A mixture of 1 mmol of 3-bromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**I**) and 1 mmol of 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**II**) was dissolved in 10 mL of anhydrous ethanol, and the mixture was refluxed for 6 h. A solid separated and was collected by filtration, dried, and recrystallized from ethanol**.** Yield 0.251 g (85%), yellow solid, mp 231–233°C. IR spectrum, ν, cm$^{-1}$: 3448 (OH), 2749 (SH), 1716 (C=O). $^1$H NMR spectrum, δ, ppm: 2.28 s (3H, $CH_3$), 2.44 s (1H, SH), 4.49 s (2H, $CH_2$), 6.34 s (1H, CH), 14.07 s (1H, OH). Mass spectrum, *m*/*z* ($I_{rel}$, %): 297 (100) $[M + 1]^+$, 241 (18). Found, %: C 48.53; H 2.72; N 18.91; S 21.64. $C_{10}H_8N_4O_3S_2$. Calculated, %: C 48.57; H 2.74; N 18.90; S 21.68. *M* 296.32.

**4-Hydroxy-6-methyl-3-(3-R-sulfanyl-7*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-2*H*-pyran-2-ones Va–Vj (***general procedure***).** Thiol **III**, 1 mmol, was dissolved in a mixture of 5 mL of dimethylformamide and 5 mL of anhydrous ethanol, 1 mmol of alkylating agent **IVa**–**IVj** was added, and the mixture was heated for 8 h under reflux (80–90°C), cooled, and poured into water. The precipitate was filtered off, dried, and recrystallized from methanol.

**3-{3-[2-(4-Chlorophenyl)-2-oxoethylsulfanyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl}-4-hydroxy-6-methyl-2*H*-pyran-2-one (Va).** Yield 0.358 g (80%), yellow solid, mp 157–159°C. IR spectrum, ν, cm$^{-1}$: 3433 (OH), 1732 (C=O), 1686 (C=O). $^1$H NMR spectrum, δ, ppm: 2.25 s (3H, $CH_3$), 4.06 s (2H, $CH_2$), 4.95 s (2H, $CH_2$), 6.18 s (1H, CH), 7.62 d (2H, $H_{arom}$, $J$ = 8.4 Hz), 8.03 d (2H, $H_{arom}$, $J$ = 8.4 Hz). $^{13}$C NMR spectrum, $\delta_C$, ppm: 22.1, 24.4, 38.0, 97.0, 100.6, 129.1, 130.2, 133.9, 138.6, 142.5, 148.5, 154.2, 161.6, 164.8, 170.2, 192.2. Mass spectrum, *m*/*z* ($I_{rel}$, %): 449 (93) $[M + 1]^+$, 435 (35), 284 (10), 225 (26). Found, %: C 48.11; H 2.89; N 12.4; S 14.25. $C_{18}H_{13}ClN_4O_4S_2$. Calculated, %: C 48.16; H 2.92; N 12.48; S 14.29. *M* 448.90.

**3-{3-[2-(4-Bromophenyl)-2-oxoethylsulfanyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl}-4-hydroxy-6-methyl-2*H*-pyran-2-one (Vb).** Yield 0.419 g (85%), yellow solid, mp 108–110°C. IR spectrum, ν, cm$^{-1}$: 3265 (OH), 1740 (C=O), 1681 (C=O). $^1$H NMR spectrum, δ, ppm: 2.26 s (3H, $CH_3$), 4.43 s (2H, $CH_2$), 4.97 s (2H, $CH_2$), 6.17 s (1H, CH), 7.79 d (2H, $H_{arom}$, $J$ = 6.0 Hz), 7.90 d (2H, $H_{arom}$, $J$ = 8.8 Hz), 14.00 s (1H, OH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 22.1, 24.2, 38.0, 100.4, 101.1, 127.8, 129.3, 131.8, 132.3, 141.9, 149.3, 155.7, 163.9, 165.0, 172.8, 192.3. Mass spectrum, *m*/*z* ($I_{rel}$, %): 495 (23) $[M + 2]^+$, 493 (23) $[M]^+$, 417 (16), 395 (18), 46 (46). Found, %: C 43.78; H 2.69; N 11.3; S 13.10. $C_{18}H_{13}BrN_4O_4S_2$. Calculated, %: C 43.82; H 2.66; N 11.36; S 13.00. *M* 493.35.

**4-Hydroxy-3-{3-[2-(4-methoxyphenyl)-2-oxoethylsulfanyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl}-6-methyl-2*H*-pyran-2-one (Vc).** Yield 0.386 g (87%), yellow solid, mp 109–111°C. IR spectrum, ν, cm$^{-1}$: 3464 (OH), 1740 (C=O), 1670 (C=O). $^1$H NMR spectrum, δ, ppm: 2.28 s (3H, $CH_3$), 4.40 s (2H, $CH_2$), 4.93 s (2H, $CH_2$), 6.19 s (1H, CH), 7.09 d (2H, $H_{arom}$, $J$ = 6.8 Hz), 7.95 d (2H, $H_{arom}$, $J$ = 8.4 Hz). $^{13}$C NMR spectrum, $\delta_C$, ppm: 22.0, 24.4, 38.1, 55.5, 100.4, 101.1, 114.4, 128.1, 129.2, 130.7, 141.9, 149.2, 154.6, 162.3, 163.5, 174.4, 191.4. Found, %: C 51.38; H 3.69; N 12.64; S 14.52. $C_{19}H_{16}N_4O_5S_2$. Calculated, %: C 51.34; H 3.63; N 12.60; S 14.43.

**4-Hydroxy-6-methyl-3-{3-[2-(4-methylphenyl)-2-oxoethylsulfanyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazin-6-yl}-2*H*-pyran-2-one (Vd).** Yield 0.363 g (85%), yellow solid, mp 86–88°C. IR spectrum, ν, cm$^{-1}$: 3449 (OH), 1730 (C=O), 1684 (C=O). $^1$H NMR spectrum, δ, ppm: 2.19 s (3H, $CH_3$), 2.40 s (3H, $CH_3$), 4.42 s (2H, $CH_2$), 4.97 s (2H, $CH_2$), 6.24 s (1H, CH), 7.38 d (2H, $H_{arom}$, $J$ = 7.6 Hz), 7.88 d (2H, $H_{arom}$, $J$ = 8.4 Hz). $^{13}$C NMR spectrum, δ, ppm: 22.4, 23.1, 24.8, 38.1, 100.3, 105.5, 129.5, 130.3, 132.7, 142.2, 144.2, 149.3, 155.0, 162.8, 163.5, 174.5, 192.5. Found, %: C 53.39; H 3.79; N 13.12; S 14.92. $C_{19}H_{16}N_4O_4S_2$. Calculated, %: C 53.26; H 3.76; N 13.08; S 14.97.

**4-Hydroxy-6-methyl-3-[3-(2-oxo-2-phenylethylsulfanyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl]-2*H*-pyran-2-one (Ve).** Yield 0.310 g (75%), yellow solid, mp 88–90°C. IR spectrum, ν, cm$^{-1}$: 3451 (OH), 1738 (C=O), 1679 (C=O). $^1$H NMR spectrum, δ, ppm: 2.26 s (3H, $CH_3$), 4.45 s (2H, $CH_2$), 5.02 s (2H, $CH_2$), 6.15 s (1H, CH), 7.59–7.69 m (3H, $H_{arom}$), 7.97–

8.04 m (2H, $H_{arom}$). Mass spectrum, *m*/*z* ($I_{rel}$, %): 415 (13) $[M + 1]^+$, 405 (10), 389 (50), 367 (100), 217 (8), 105 (25), 46 (12). Found, %: C 52.19; H 3.46; N 13.56; S 15.44. $C_{18}H_{14}N_4O_4S_2$. Calculated, %: C 52.16; H 3.40; N 13.52; S 15.47. *M* 414.45.

**4-Hydroxy-6-methyl-3-{3-[2-(4-nitrophenyl)-2-oxoethylsulfanyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazin-6-yl}-2*H*-pyran-2-one (Vf).** Yield 0.321 g (70%), yellow solid, mp 223–225°C. IR spectrum, ν, $cm^{-1}$: 3464 (OH), 1740 (C=O), 1682 (C=O). $^1H$ NMR spectrum, δ, ppm: 2.25 s (3H, $CH_3$), 4.52 s (2H, $CH_2$), 5.07 s (2H, $CH_2$), 6.15 s (1H, CH), 8.20 d (2H, $H_{arom}$, *J* = 8.8 Hz), 8.27 d (2H, $H_{arom}$, *J* = 8.8 Hz): Found, %: C 47.12; H 2.89; N 15.28; S 13.99. $C_{18}H_{13}N_5O_6S_2$. Calculated, %: C 47.05; H 2.85; N 15.24; S 13.96. *M* 493.35.

**3-[3-(2-Biphenyl-4-yl-2-oxoethylsulfanyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl}-4-hydroxy-6-methyl-2*H*-pyran-2-one (Vg).** Yield 0.367 g (75%), yellow solid, mp 127–129°C. IR spectrum, ν, $cm^{-1}$: 3435 (OH), 1737 (C=O), 1674 (C=O). $^1H$ NMR spectrum, δ, ppm: 2.24 s (3H, $CH_3$), 4.49 s (2H, $CH_2$), 5.03 s (2H, $CH_2$), 6.15 s (1H, CH), 7.71–7.85 m (6H, $H_{arom}$), 7.95–8.12 m (3H, $H_{arom}$), 14.00 s (1H, OH). Found, %: C 58.79; H 3.75; N 11.47; S 13.12. $C_{24}H_{18}N_4O_4S_2$. Calculated, %: C 58.76; H 3.70; N 11.42; S 13.07.

**3-[3-(Benzylsulfanyl)-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin-6-yl]-4-hydroxy-6-methyl-2*H*-pyran-2-one (Vh).** Yield 0.289 g (75%), yellow solid, mp 103–105°C. IR spectrum, ν, $cm^{-1}$: 3320 (OH), 1727 (C=O). $^1H$ NMR spectrum, δ, ppm: 2.26 s (3H, $CH_3$), 4.05 s (2H, $CH_2$), 4.35 s (2H, $CH_2$), 6.05 s (1H, CH), 7.28–7.40 m (5H, $H_{arom}$), 13.70 s (1H, OH). Found, %: C 52.88; H 3.69; N 14.54; S 16.52. $C_{17}H_{14}N_4O_3S_2$. Calculated, %: C 52.84; H 3.65; N 14.50; S 16.59.

**3-[3-(4-Nitrobenzylsulfanyl)-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazin-6-yl]-4-hydroxy-6-methyl-2*H*-pyran-2-one (Vi).** Yield 0.344 g (80%), yellow solid, mp 89–91°C. IR spectrum, ν, $cm^{-1}$: 3448 (OH), 1745 (C=O). $^1H$ NMR spectrum, δ, ppm: 2.25 s (3H, $CH_3$), 4.47 s (2H, $CH_2$), 4.97 s (2H, $CH_2$), 6.20 s (1H, CH), 7.66 d (2H, $H_{arom}$, *J* = 8.8 Hz), 8.16 d (2H, $H_{arom}$, *J* = 8.8 Hz), 13.71 s (1H, OH). Found, %: C 47.38; H 3.14; N 16.28; S 14.82. $C_{17}H_{13}N_5O_5S_2$. Calculated, %: C 47.33; H 3.04; N 16.23; S 14.86.

**3-[3-(2-Bromoethylsulfanyl)-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazin-6-yl]-4-hydroxy-6-methyl-2*H*-pyran-2-one (Vj).** Yield 0.282 g (70%), yellow solid, mp 213–215°C. IR spectrum, ν, $cm^{-1}$: 3448 (OH), 1745 (C=O). $^1H$ NMR spectrum, δ, ppm: 2.28 s (3H, $CH_3$), 3.24 t (2H, $CH_2$), 3.87 t (2H, $CH_2$), 4.49 s (2H, $CH_2$), 6.14 s (1H, CH), 14.08 s (1H, OH). Found, %: C 35.79; H 2.79; N 13.84; S 15.94. $C_{12}H_{11}BrN_4O_3S_2$. Calculated, %: C 35.74; H 2.75; N 13.89; S 15.90.

The melting points (uncorrected) were determined using an Electrothermal digital melting point apparatus. The purity of the isolated compounds was checked by TLC using ethyl acetate–hexane (3 : 7) as eluent. The IR spectra were measured on a Galaxy series FT-IR 5000 spectrophotometer using KBr disks. The $^1H$ NMR spectra were recorded on a Bruker WM-400 spectrometer (400 MHz) in DMSO-$d_6$ using TMS as internal reference.

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