Preparation of 5-Methyl-2-sulfanyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-7-ones

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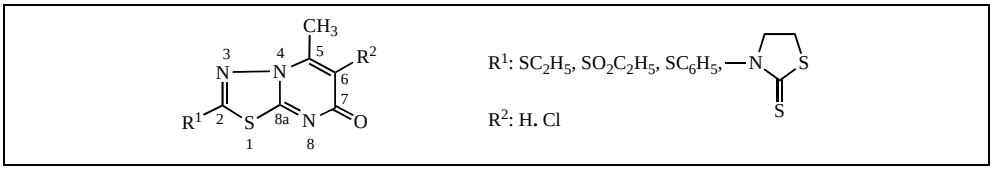

7*H*-1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-7-ones can be prepared by the acylation of 5-amino-1,3,4-thiadiazoles with diketene and subsequent ring closure (dehydration). Whereas arylthio substituents (SC_6H_5) can be introduced in 2-position by the replacement of Br, alkylthio groups (SC_2H_5) have to be already present in the starting 5-amino-1,3,4-thiadiazole. The ambident nucleophile 2-thiazolidinethione reacts in the Br substitution reaction on the N atom.

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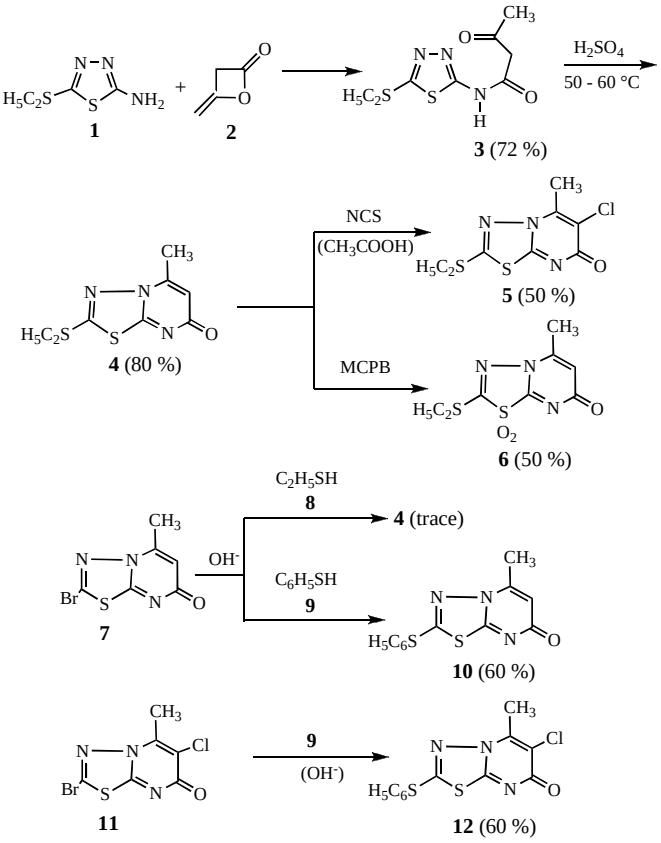
1,3,4-Thiadiazolo[3,2-*a*]pyrimidines exhibit interesting biological and pharmacological properties [1-11]. We elaborated recently the synthesis of 2-amino-7*H*-thiadiazolo[3,2-*a*]pyrimidin-7-ones [12] and report here now on the generation of 2-alkyl– and 2-aryl–thio-7*H*-thiadiazolo[3,2-*a*]pyrimidin-7-ones (Scheme 1). Reaction of 2-amino-1,3,4-thiadiazole **1** and diketene **2** yielded the acylated derivative **3** which could be cyclized to the target compound **4** by the action of sulphuric acid [13]. Chlorination of **4** with *N*-chlorosuccinimide (NCS) led to compound **5** and oxidation with *m*-chloroperoxybenzoic acid (MCPB) to sulfone **6**.

A subsequent introduction of an alkylthio group in 2-position of the 7*H*-thiadiazolo[3,2-*a*]pyrimidin-7-one failed. The 2-bromo compound **7** [12] and ethanethiol (**8**) yielded in an alkaline medium only traces of **4**. The nucleophilicity of thiophenol (**9**) however is strong enough to afford the phenylthio derivative **10**. The 2-bromo-6-chloro compound **11** [12] reacted selectively with **9** in the 2-position (**9**+**11**→**12**).

The structure elucidation of the obtained heterocycles was mainly based on ^{1}H and ^{13}C NMR measurements including two-dimensional shift-correlations HMBC.

Figure 1 shows a comparison of the ^{13}C chemical shifts of **4**, **5** and **6**. The introduction of Cl provokes a low-field shift of C-6 and high-field shifts for the neighboring quaternary carbon atoms C-5 and C-7. The transformation of sulfide **4** to sulfone **6** has a strong influence on the δ values of the ethyl group but does not considerably affect the δ values of the carbon atoms of the heterocyclic scaffold.

Scheme 1



Additionally, we studied the reaction of **7** with an ambident N/S-nucleophile. The 4,5-dihydrothiazole **13** exists almost completely in the thione form **13b**. Deprotonation generates the anion **14**. The ^{13}C NMR measurement of the reaction of **7** and **14** revealed at room

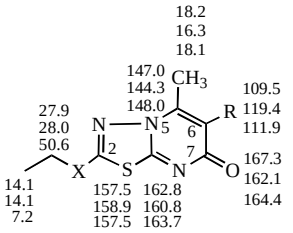
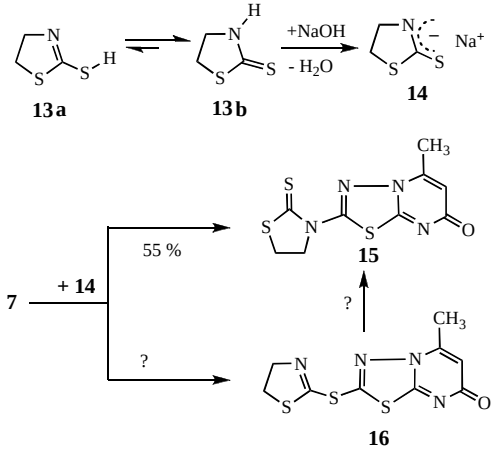


Figure 1. Comparison of the ^{13}C NMR data of the 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones **4** (upper values), **5** (middle) and **6** (lower values), measured in $CDCl_3$ (**4, 5**) and CD_3SOCD_3 (**6**).

temperature a non-uniform process, in the course of which compound **15** was enriched as major product. Whether **15** is a primary or a secondary product formed by a 1,3-rearrangement of **16** remains an open question. There are several related acyl group migrations between S and N mentioned in the literature [14-16] – even one for 1,3-thiazolidine-2-thiones [17]. The pure compound **15**, recrystallized from DMF/H_2O (4:1), did not show an equilibration with **16**.

Scheme 2



EXPERIMENTAL

The melting points, determined on a Stuart Scientific SMP/3 apparatus, are uncorrected. The ^1H and ^{13}C NMR data were obtained on a Bruker AM 400 in $CDCl_3$, CD_2Cl_2, CD_3OD or CD_3SOCD_3 with TMS as internal standard. The EI and FD mass spectra were recorded on a Finnigan M 95 spectrometer. The HRMS measurements were performed on a Micromass QTOF spectrometer by means of the ESI technique.

***N*-[5-(Ethylthio)-1,3,4-thiadiazol-2-yl]-3-oxobutanamide (3).** A mixture of 1.61 g (10.0 mmol) 2-amino-5-ethylthio-1,3,4-thiadiazole (**1**) [18] and 1.68 g (20.0 mmol) diketene (**2**) [18] were refluxed in 200 mL of benzene for 20 h. The solution was concentrated till the product started to precipitate. After standing overnight at 8 °C, a colorless solid was collected by filtration and recrystallized from methanol; 1.77 g (72 %) of compound **3** was obtained which melted at 172 °C. ^1H NMR ($CDCl_3$): δ 1.43 (t, ^3J = 7.1 Hz, 3H, CH_3), 2.20 (q, ^3J = 7.1 Hz, 2H, SCH_2), 2.32 (s, 3 H, CH_3), 3.88 (s, 2H, CH_2), 12.75 (s, 1H, NH). The enol form, which exhibits in $CDCl_3$ an olefinic proton at δ = 5.67 (s, 1H) and a methyl singlet at δ = 2.03 (s, 3H), amounts to 28 % (obtained by integration of these two signals). ^{13}C NMR (CD_3SOCD_3): δ 14.8 (CH_3), 28.2 (SCH_2), 30.4 ($COCH_3$), 50.7 (CH_2), 158.4, 158.9 (C_q), 165.7 (NHCO), 202.0 (CO). FD MS: *m/z* (%) 245 (100) [M^+].

Anal. Calcd. for $C_8H_{11}N_3O_2S_2$ (245.3): C, 39.17; H, 4.52; N, 17.13; S, 26.14. Found: C, 38.95; H, 4.43; N, 16.97; S, 26.39.

2-Ethylthio-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (4). Amide **3** (2.45 g, 10.0 mmol) was added under stirring to 15 mL of conc. H_2SO_4 and kept for 14 h at 50-60 °C. The mixture was cooled to -5 °C and slowly poured on 200 g of crushed ice. The aqueous phase was neutralized with 10 % $NaHCO_3$ and 3 times extracted with 200 mL of $CHCl_3$, each. The solvent was removed and the residue recrystallized from methanol. Compound **4** (1.82 g, 80 %) melted at 95 °C. ^1H NMR ($CDCl_3$): δ 1.43 (t, ^3J = 7.1 Hz, 3H, CH_3), 2.23 (q, ^3J = 7.1 Hz, 2H, CH_2), 2.44 (s, 3H, 5-CH_3), 6.04 (s, 1H, 6-H). FD MS: *m/z* (%) 227 (100) [M^+]. HRMS (ESI): calculated for [$C_8H_9N_3OS_2$ + Na^+] 250.0085, found 250.0081.

6-Chloro-2-ethylthio-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-7-one (5). *N*-Chlorosuccinimide (267.1 mg, 2.0 mmol) and 227.3 mg (1.0 mmol) **4** were added at ambient temperature to 3 mL of acetic acid. After heating for 2 h at 95 °C, the volatile parts were removed in vacuum. The residue was treated with 5 mL of water and extracted with $CHCl_3$ (5 x 30 mL). Column chromatography (30 x 2.5 cm SiO_2, $CHCl_3/CH_3OH$ 94:6) yielded 131 mg (50 %) of a powder which melted after recrystallization from ethanol at 182 °C. ^1H NMR ($CDCl_3$): δ 1.46 (t, ^3J = 7.1 Hz, 3H, CH_3), 2.25 (q, ^3J = 7.1 Hz, 2H, CH_2), 2.69 (s, 3H, 5-CH_3). FD MS: *m/z* (%) 263/261 (100) [M^+], Cl isotope pattern. HRMS (ESI): calculated for [$C_8H_8{}^{35}ClN_3OS_2$ + Na^+] 283.9695, found 283.9700.

2-Ethylsulfonyl-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (6). A solution of 518 mg (3.0 mmol) 3-chloroperoxybenzoic acid (MCPB) in 20 mL of CH_2Cl_2 was added dropwise to 227 mg (1.0 mmol) **4** dissolved in 15 mL of CH_2Cl_2. After 40 h stirring at room temperature, the solution was concentrated till a solid started to precipitate. Filtration after 12 h at 8 °C and repetition of the procedure with the mother liquor led to 130 mg (50 %) of **6** which melted after recrystallization from ethanol at 164 °C. ^1H NMR (CD_2Cl_2): δ 1.47 (t, ^3J = 7.1 Hz, 3H, CH_3), 2.53 (s, 3H, 5-CH_3), 3.52 (q, ^3J = 7.1 Hz, 2H, CH_2), 6.22 (s, 1H, 6-H). FD MS: *m/z* (%) 259 (100) [M^+]. HRMS (ESI): calculated for [$C_8H_9N_3O_3S_2$ + Na^+] 281.9983, found 281.9996.

5-Methyl-2-phenylthio-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (10). A solution of sodium thiophenolate [18] (142 mg, 1.0 mmol) in 7 mL of ethanol/water (1:1) was added dropwise under stirring to 246 mg (1.0 mmol) **7** [12] dissolved in 5 mL of ethanol. After 1 h at room temperature, the volatile parts were removed in vacuum, the solid residue washed with water and recrystallized from 1,4-dioxane. ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 6.04 (s, 1H, 6-H), 7.53 (m, 3H, *m*-H, *p*-H, Phenyl), 7.71 (m, 2H, *o*-H, Phenyl). ^{13}C NMR (CD_3OD): δ 18.1 (CH_3), 110.0 (HC-6), 128.3, 131.7, 132.9, 136.7 (C, Phenyl), 150.9, 163.5, 165.4, 170.7 (C_q). FD MS: *m/z* (%) 275 (100) [M^+].

Anal. Calcd. for $C_{12}H_9N_3OS_2$ (275.3): C, 52.35; H, 3.29; N, 15.26. Found: C, 52.03; H, 3.49; N, 15.50.

The same procedure applied to **7** and ethanethiol (**8**) yielded only traces of **4** which could be observed in the ^{1}H NMR spectrum.

6-Chloro-5-methyl-2-phenylthio-7*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-7-one (12). A solution of sodium thiophenolate [18] (142 mg, 1.00 mmol) in 7 mL of ethanol/water (1:1) was added dropwise under stirring to a suspension of 281 mg (1.0 mmol) **11** [12] in 5 mL of ethanol. After 2 h at ambient temperature, the volatile parts were removed in vacuum the residue was washed with water and recrystallized from ethanol. Yield 186 mg (60 %), m. p. 148 °C . ^{1}H NMR ($CDCl_3$): δ 2.65 (s, 3H, CH_3), 7.46 (m, 2H, *m*-H, Phenyl), 7.56 (m, 1H, *p*-H, Phenyl), 7.65 (m, 2H, *o*-H, Phenyl). ^{13}C NMR (CD_2Cl_2): δ 16.4 (CH_3), 119.6 (C-6), 127.1, 130.9, 132.1, 135.8 (C, Phenyl), 144.8, 161.6, 161.9, 162.1 (C_q). FD MS: *m/z* (%) 311/309 (100) [M^+], Cl pattern. HRMS (ESI): calculated for [$C_{12}H_8{}^{35}ClN_3OS_2 + Na^+$] 331.9695, found 331.9685.

5-Methyl-2-(2-thioxo-1,3-thiazolidin-3-yl)-7*H*-[1,3,4]thia-diazolo[3,2-*a*]pyrimidin-7-one (15). A solution of 141 mg (1.0 mmol) of sodium 4,5-dihydrothiazole-2-thiolate (**14**) [18,19] in 15 mL of ethanol/water (1:1) was slowly added to 246 mg (1.0 mmol) of **7** dissolved in 10 mL of ethanol. After 1 h of stirring the solvent was removed in vacuum, the residue was washed with water and recrystallized from DMF/water 4:1. The obtained powder (157 mg, 55 %) melted at 224 °C. ^{1}H NMR (CD_3SOCD_3): δ 2.41 (s, 3H, CH_3), 3.70 (t, 2H, SCH_2), 4.81 (t, 2H, NCH_2), 6.14 (s, 1H, 6-H). ^{13}C NMR (CH_3SOCD_3): δ 17.0 (CH_3), 29.1 (SCH_2), 57.3 (NCH_2), 110.0 (HC-6), 146.9, 149.2, 159.4, 167.3 (C_q), 199.0 (CS). FD MS: *m/z* (%) 284 (100) [M^+].

Anal. Calcd. for $C_9H_8N_4OS_3$ (284.4): C, 38.01; H, 2.84; N, 19.70. Found: C, 37.80; H, 3.01; N, 19.50.

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