SHORT PAPER

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Synthesis of 1-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetyl-4-alkyl(aryl)thiosemicarbazides and their heterocyclisation to 1,2,4-triazoles and 1,3,4-thiadiazoles†

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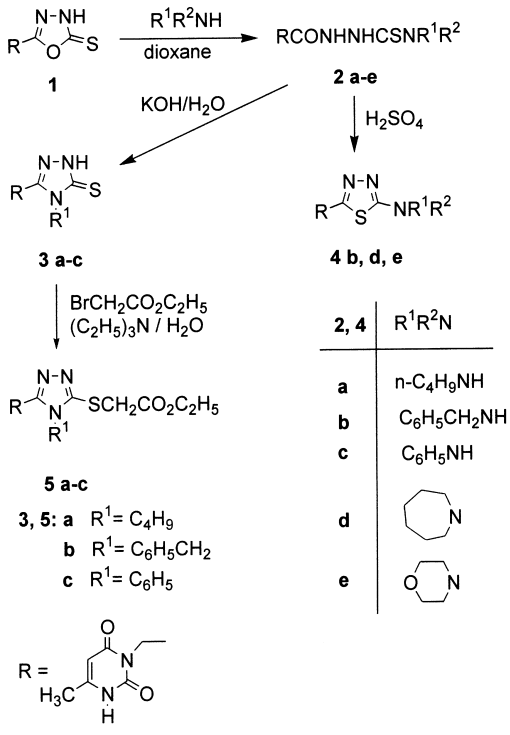
5-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)methyl-1,3,4-oxadiazole-2-thione reacts with amines to give 1-(6-methyl-2,4–dioxo-1,2,3,4-tetrahydro-3–pyrimidinyl)acetyl-4-alkyl(aryl)thiosemicarbazides, which on treatment with base or acid undergo cyclisation to 4-alkyl-1,2,4-triazole-2-thiones or 4-amino-1,3,4-thiadiazoles, respectively.

Keywords: pyrimidines, 1,3,4-oxadiazolethiones, 1,2,4-triazole-2-thiones, 1,3,4-thiadiazoles, thiosemicarbazides

Upon treatment of 5-substituted-1,3,4-oxadiazole-2-thiones with amines different reactions can occur, depending on the substituent at position 5 as well as on the nature of the amine used. Thus, salt formation, nucleophilic substitution of the mercapto group, opening of the 1,3,4-oxadiazole ring with formation of 4-substituted 1-acylthiosemicarbazides, recyclisation reaction of 1,3,4-oxadiazole to 4-substituted 1,2,4-triazole-3-thione are possible.[1-3]

In this paper we report on reactions of 5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinylmethyl)-1,3,4-oxadiazole-2-thione (**1**)[4] with different amines (Scheme 1).



Scheme 1

Refluxing of the 1,3,4-oxadiazole-2-thione **1** with an equimolar amount of primary and secondary aliphatic amines or aniline in dioxane gave the thiosemicarbazides **2a–e** in high yield (72–91%). In the ^{1}H NMR spectra of compounds **2** signals of thiosemicarbazide group protons NHCS (9.27–9.98 ppm) and CONH (10.05–10.54 ppm) are observed. The singlets of the N(3)–CH_2 group [N(3) refers to the pyrimidine ring] (4.46–4.55 ppm) resonate up-field compared to that of the starting compound **1** (5.05 ppm). In the IR spectra, besides the absorption bands of NH (3100 cm^{-1}) and C=O (1725–1708, 1667–1643 cm^{-1}) groups of the uracil moiety, the absorption of the thiosemicarbazide NH (3164–3285 cm^{-1}) and C=O (1694–1665 cm^{-1}) fragments are observed. The C=S absorption appears at 1346–1352 cm^{-1}.

Traditional methods of synthesis 1-acyl-4-substituted thiosemicarbazides are based on the reaction of hydrazides with isothiocyanates. The method described here could be competitive, because of the wider variety of amines commercially available, compared with isothiocyanates.

1-Acyl-4-substituted thiosemicarbazides are useful for synthesis of biologically active 1,2,4-triazoles[5] and 1,3,4-thiadiazoles.[6] The acylthiosemicarbazides **2a–c** on treatment with potassium hydroxide underwent cyclisation to 4-alkyl-1,2,4-triazole-2-thiones **3a–c**. In the ^{1}H NMR spectra of **3** the N(3)-CH_2 group signals are located down field in comparison with those of the thiosemicarbazides **2a–c**. Also the NH group chemical shifts characteristic of 1,2,4-triazole-2-thiones are observed in the down field region at 13.64–13.92 ppm. The IR spectra exhibit absorption bands at 1340–1353 cm^{-1}, characteristic for a C=S group.

Treatment of thiosemicarbazides **2b**,**d**,**e** with conc. sulfuric acid resulted in a different mode of cyclisation, to form 2-amino-1,3,4-thiadiazoles **4b**,**d**,**e**. In the ^{1}H NMR spectra the N(3)–CH_2 group peaks are shifted downfield (5.07–5.14 ppm) than those of corresponding thiosemicarbazides **2b**,**d**,**e** (4.46–4.47 ppm). On the other hand, there is a significant difference in the shift of the methylene group protons in the benzyl substituent of 2-benzylamino-1,3,4-thiadiazole **4b** and 4-benzyl-1,2,4-triazole-3-thione **3b** due to the magnetic anisotropy of the aromatic triazole ring: the signal of the N–CH_2 protons in **3b** is located downfield (5.36 ppm) compared with that of **4b** (3.83 ppm).

Alkylation of 4-alkyl-1,2,4-triazole-3-thiones **3a–c** with ethyl bromoacetate in the presence of triethylamine in water gave 4-alkyl-3-ethoxycarbonylmethylsulfanyl-1,2,4-triazoles **5a–c**. The ^{1}H NMR of **5a–c** show shifts of the SCH_2 group in the region of 4.03–4.05 ppm. In the IR spectra of **5a–c** absorp-

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 1 Experimental, physico-chemical and spectral data for compounds **2–5**

Compound yield/%	M.p./°C (solvent)	Found (required)/% C	H	N	ν_{max}/ cm^{-1}	δ_H
2a (72)	192–194 (H_2O)	46.25 (45.99)	5.84 (6.11)	22.30 (22.35)	3285, 3100 NH) 1708, 1665, 1643 (CO) 1348 (CS)	0.92 (3H, t, *J* 7 Hz, CH_3), 1.4 (4H, m, CH_2CH_2), 2.11 (3H, s, CH_3), 3.40 (2H, m, NCH_2), 4.46 (2H, s, NCH_2), 5.55 (1H, s, CH), 7.58 (1H, s, CS<u>NH</u>CH_2), 9.33 (1H, s, CONH<u>NH</u>CS), 10.54 (1H, s, CO<u>NH</u>NHCS), 11.27 (1H, s, NH)
2b (87)	226–227 (MeOH+dioxane)	52.12 (51.86)	4.99 (4.93)	20.13 (20.16)	3285, 3096 (NH) 1709, 1690, 1651 (CO) 1345 (CS)	2.07 (3H, s, CH_3), 4.47 (2H, s, NCH_2), 4.74 (2H, s, NCH_2), 5.51 (1H, s, CH), 7.27 (5H, m, C_6H_5), 8.34 (1H, s, CS<u>NH</u>CH_2), 9.51 (1H, s, CONH<u>NH</u>CS), 10.17 (1H, s, CO<u>NH</u>NHCS), 11.22 (1H, s, NH)
2c (85)	198–199 (H_2O)	50.63 (50.44)	4.37 (4.53)	20.84 (21.01)	3227 (NH) 1708, 1693, 1656 (CO) 1352 (CS)	2,11 (3H, s, CH_3), 4.55 (2H, s, NCH_2,), 5.54 (1H, s, CH), 7,52 (5H, m, C_6H_5), 9,38-9,80 (1H, m, <u>NH</u>CS), 10,16-10,46 (1H, m, CO<u>NH</u>), 11.24 (1H, s, NH)
2d (81)	233.5–234.5 ($PrOH+H_2O$)	49.77 (49.54)	6.13 (6.24)	20.41 (20.63)	3207, 3164, 3105 (NH) 1725, 1693, 1648 (CO) 1346 (CS)	1.49 (4H, m, $(CH_2)_2$), 1.71 (4H, m, $(CH_2)_2$), 2.09 (3H, s, CH_3), 3.78 (4H, m, $N(CH_2)_2$), 4.47 (2H, s, NCH_2), 5.57 (1H, s, CH), 9.27 (1H, s, CONH<u>NH</u>CS), 10.05 (1H, s, CO<u>NH</u>NHCS), 11.20 (1H, s, NH)
2e (91)	233.5–234.5 (H_2O)	44.28 (44.03)	5.22 (5.23)	21.23 (21.39)	3196 (NH) 1716, 1683, 1667 (CO) 1347 (CS)	2.07 (3H, s, CH_3), 3.66 (4H, t, *J* 7 Hz, $O(CH_2)_2$), 3.77 (4H, t, *J* 7 Hz, $N(CH_2)_2$), 4.46 (2H, s, NCH_2), 5.50 (1H, s, CH), 9.68 (1H, s, CONH<u>NH</u>CS), 10.10 (1H, s, CO<u>NH</u>NHCS), 11.21 (1H, s, NH)
3a (68)	247–248 (H_2O)	49.01 (48.80)	5.80 (5.80)	23.70 (23.71)	3109 (NH) 1715, 1643 (CO) 1353 (CS)	0.98 (3H, t, *J* 7 Hz, CH_3), 1.50 (4H, m, CH_2CH_2), 2.12 (3H, s, CH_3), 4.04 (2H, t, *J* 7 Hz, NCH_2), 5.05 (2H, s, NCH_2), 5.59 (1H, s, CH), 11.38 (1H, s, NH), 13.64 (1H, s, NH)
3b (93)	>300 (EtOH+DMF)	54.93 (54.70)	4.53 (4.59)	21.13 (21.26)	3086 (NH) 1715, 1643 (CO) 1348 (CS)	2.03 (3H, s, CH_3), 4.95 (2H, s, NCH_2), 5.36 (2H, s, NCH_2), 5.48 (1H, s, CH), 7.33 (5H, m, C_6H_5), 11.26 (1H, s, NH), 13.83 (1H, s, NH)
3c (63)	266 (H_2O)	53.38 (53.32)	4.36 (4.15)	22.38 (22.21)	3095 (NH) 1721, 1652 (CO) 1340 (CS)	2.06 (3H, s, CH_3), 4.75 (2H, s, NCH_2), 5.48 (1H, s, CH), 7.53 (5H, m, C_6H_5), 11.27 (1H, s, NH), 13.92 (1H, s, H)
4b (46)	>300 (H_2O+DMF)	54.96 (54.70)	4.50 (4.59)	21.40 (21.26)	3290, 3169, 3100 (NH) 1709, 1633 (CO)	2.08 (3H, s, CH_3), 3.83 (2H, s, NCH_2), 5.10 (2H, s, NCH_2), 5.55 (1H, s, CH), 7.25 (5H, m, C_6H_5), 7.30 (1H, s, NH), 11.26 (1H, s, NH)
4d (58)	178–200 (H_2O)	52.60 (52.32)	5.85 (5.96)	22.07 (21.79)	3163, 3050 (NH) 1716, 1660 (CO)	1.51 (4H, m, $(CH_2)_2$), 1.74 (4H, m, $(CH_2)_2$), 2.06 (3H, s, CH_3), 3.45 (4H, m, $N(CH_2)_2$), 5.07 (2H, s, NCH_2), 5.54 (1H, s, CH), 11.20 (1H, s, NH)
4e (50)	266–267 (H_2O)	46.67 (46.59)	5.08 (4.89)	22.85 (22.64)	3165, 3080 (NH) 1706, 1637 (CO)	2.07 (3H, s, CH_3), 3.42 (4H, t, *J* 7 Hz, $O(CH_2)_2$), 3.69 (4H, t, *J* 7 Hz, $N(CH_2)_2$), 5.14 (2H, s, NCH_2), 5.56 (1H, s, CH), 11.33 (1H, s, NH)
5a (76)	89–90 ($CH_3CO_2C_4H_9$)	50.44 (50.38)	5.26 (6.08)	18.43 (18.36)	3104 (NH) 1718, 1637 (CO) 1175 (C-O-C)	0.93 (3H, t, *J* 7 Hz, CH_3), 1.18 (3H, t, *J* 7 Hz, CH_3), 1.45 (4H, m, CH_2CH_2), 2.10 (3H, s, CH_3), 4.05 (2H, s, SCH_2), 4.08 (2H, t, *J* 7 Hz, NCH_2) 4.19 (2H, q, *J* 7 Hz, OCH_2), 5.05 (2H, s, NCH_2), 5.55 (1H, s, CH), 11.28 (1H, s, NH)
5b (78)	103–105 (EtOH)	54.63 (54.92)	5.16 (5.09)	17.08 (16.85)	3086 (NH) 1726, 1630 (CO) 1179 (C-O-C)	1.18 (3H, t, *J* 7 Hz, CH_3), 2.06 (3H, s, CH_3), 4.03 (2H, s, SCH_2), 4.21 (2H, q, *J* 7 Hz, OCH_2), 5.05 (2H, s, NCH_2), 5.34 (2H, s, NCH_2), 5.50 (1H, s, CH), 11.27 (1H, s, NH)
5c (73)	119–121 ($CH_3CO_2C_4H_9$)	54.01 (53.86)	4.92 (4.77)	17.64 (17.45)	3091 (NH) 1740, 1648 (CO) 1171 (C-O-C)	1.20 (3H, t, *J* 7 Hz, CH_3), 2.07 (3H, s, CH_3), 4.04 (2H, s, SCH_2), 4.12 (2H, q, *J* 7 Hz, OCH_2), 4.88 (2H, s, NCH_2), 5.50 (1H, s, CH), 7.63 (5H, m, aromatic), 11.22 (1H, s, NH)

tion bands of C–O–C of the ester group are observed in the range 1171–1179 cm^{-1}; the ester C=O band is overlapped by the C=O vibrations of the uracil moiety. Furthermore the characteristic absorption band of C=S group for 1,2,4-triazole-2-thiones **3a–c** in the region 1350 cm^{-1} was not found in the IR spectra of compounds **5a–c**.

Experimental

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded in Nujol mulls on a Perkin-Elmer FT spectrophotometer Spectrum BX II ^{1}H-NMR spectra were recorded on a Tesla 587A instrument using tetramethylsilane as internal standard in DMSO-d_6 as solvent. The reactions and purity of com-

pounds was controlled by TLC on Silufol UV 254 plates (KAVALIER, Czech Rep.) Microanalyses were performed at the Microanalyses Laboratory of the Department of Organic Chemistry of Vilnius University. Experimental, physico-chemical and spectral data for compounds **2–5** are given in Table 1.

1-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetyl-4-alkyl(aryl)-thiosemicarbazides (**2a–e**). To a suspension of **1** (0.75 g, 3 mmol) in dry dioxane (12 ml) the corresponding amine (3 mmol) was added. The reaction mixture was stirred at reflux (in the cases of hexamethyleneimine and morpholine for 2 h, for butylamine and benzylamine 5 h, and for aniline 22 h) and then cooled. The precipitate was filtered off, washed with a small amount of dioxane, and recrystallised to give **2a–e**.

4-Alkyl(aryl)-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)methyl-1,2,4-triazole-3-thiones (**3a–c**): A solution of the corresponding compound **2a–c** (1 mmol) in 10 ml of 10% KOH (for **2c** 20% KOH) was stirred at room temperature for 4 h and acidified with conc. HCl to pH ~ 4. The solid was filtered off, washed with water, dried and recrystallised to give **3a–c**.

2-Alkyl(aryl)amino-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)methyl-1,3,4-thiadiazoles (**4b**,**d**,**e**): Compound **2b**,**d** or **e** (1.5 mmol) was dissolved in conc. H_2SO_4 (2 ml) and stirred on a boiling water bath (or, in the case of **2b**, at room temperature) for 10 min, then cooled to –5°C and poured into ice-water (10 ml). The solution was neutralised with 20% KOH to pH ~ 5 under ice-cooling at < 5°C. The solid was filtered off, washed with water and recrystallised to give **4b**,**d**,**e**.

4-Alkyl(aryl)-3-ethoxycarbonylmethylsulfanyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)methyl-1,2,4-triazoles (**5a–c**): To a suspension of **3a**,**b** or **c** (1 mmol) in water (10 ml) triethylamine (1 mmol, 0.1 g, 0.14 ml) and ethyl bromoacetate (1 mmol, 0.17 g, 0.11 ml) was added dropwise. The reaction mixture was stirred at 40°C for 2 h, then cooled. The precipitate was filtered off, washed with water, dried and recrystallized to give **5a–c**.

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