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POLYFUNCTIONAL NITRILES IN THE SYNTHESIS OF DERIVATIVES OF 1,3,4-THIADIAZOLO-[3,2-*a*]PYRIMIDINES

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A one-pot method has been developed for the synthesis of 2-R-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-a]pyrimidine by condensation of β-alkylthio(alkoxy)propionitrile, thiosemicarbazide, and ethyl acetoacetate in PPA, and also (7-methyl-5-oxo-5H-1,3,4-thidiazolo[3,2-a]pyrimidin-2-yl)-acetamide from cyanoacetamide, thiosemicarbazide, and ethyl acetoacetate.

Keywords: alkylthio(alkoxy)propionitrile, (7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-acetamide, ethyl acetoacetate, 2-R-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine, PPA, thiosemicarbazide.

In recent times there has been intense investigation associated the chemistry of derivatives of 5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidines (TP) due to their wide range of biological activity. 2R-thio-TPs which have high anticancer activity are of particular interest [1-4].

The most widely used method for the synthesis of derivatives of 1,3,4-thidiazolo[3,2-*a*]pyrimidine is the cyclocondensation of 2-amino-5-R-1,3,4-thiadiazole with ethyl acetoacetate in PPA. It is known that the reaction of nitrile-containing organic compounds with thiosemicarbazide in PPA gave 2-amino-5R-1,3,4-thiadiazoles [5-10] and that the ammonia evolved in the reaction formed ammonium polyphosphate.

In the present work we have found that heating 3-alkylthio(alkoxy)propionitriles with thiosemicarbazide in PPA (95-100°C, 5-6 h) gave 2-aminothiadiazoles **2** in high yield.

This method ensures the more rapid formation of 5-(β-alkylthioethyl)-2-amino-1,3,4-thiadiazole which leads to the decreasing of the reaction time (4-5 h compared with 15-20 h for known methods [11, 12]) and the high yield of the end product (78-84%).

When phenoxypropionitrile was used as the starting material we were unable to obtain the expected 2-amino-5-phenoxyethyl-1,3,4-thiadiazole. This is evidently connected with the instability of phenoxypropionitrile under the reaction conditions.

The interaction of thiosemicarbazide with β-alkylthio(alkoxy)propionitriles **1a-f** in the presence of ethyl acetoacetate in a single stage led to 2-R-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidines **3a-f**.

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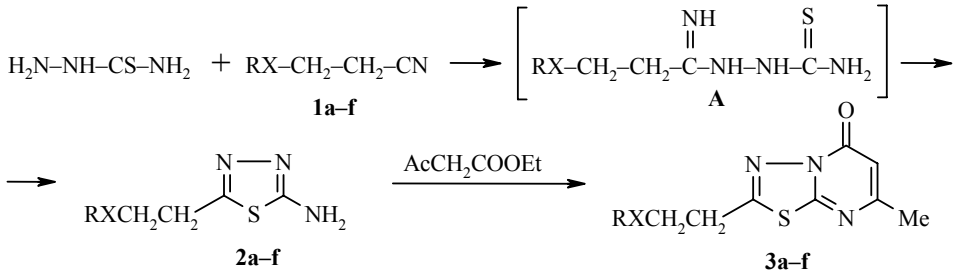
Evidently the nitriles **1** in a medium of PPA are readily converted to iminoesters of PPA [13], which on reaction with thiosemicarbazide are converted into amidrazones **A**, followed by loss of a molecule of ammonia to give compounds **2a-f**.



a X = O, R = Et; **b** X = O, R = C_5H_{11}; **c–f** X = S; **c** R = Me, **d** R = Et, **e** R = Pr, **f** R = Bu

In the IR spectra of compounds **3** there are absorption bands of carbonyl groups in the 1690-1720 cm^{-1} range and C=N and C=C absorptions in the 1590-1640 cm^{-1} range.

In the ^1H NMR spectra there are signals in the 6.17-6.25 ppm range corresponding to protons in position 6 of the rings, and signals in the 2.15-2.20 ppm range (CH_3 in position 7).

We have carried out synthesis of (7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)acetamide by three-step condensation of cyanoacetamide, thiosemicarbazide, and ethyl acetoacetate in PPA (80% yield).

Compound **4** was also obtained by convergent synthesis using the interaction of 2-ethoxy-carbonylmethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine with ammonia in ethanol solution at room temperature (2 h), with subsequent boiling for 1 h (83% yield).

Table 1. Characteristics of the Compounds Synthesized

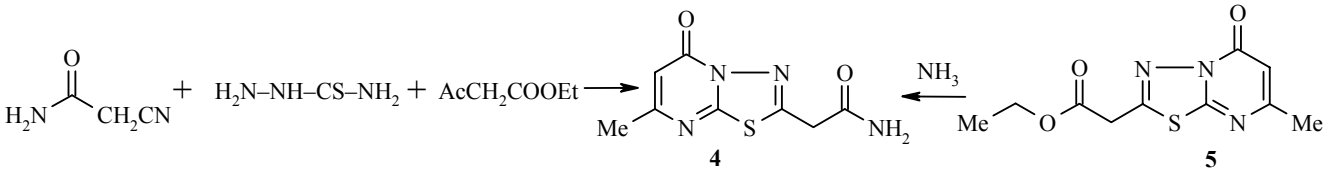
Com-pound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		C	H		
2a	$C_6H_{11}N_3OS$	41.74 / 41.60	6.77 / 6.40	128-130	82
2b	$C_9H_{16}N_3OS$	50.17 / 50.20	7.30 / 7.53	134-136	85
2c	$C_5H_9N_3S_2$	34.20 / 34.26	5.11 / 5.18	160-162	76
2d	$C_6H_{11}N_3S_2$	38.00 / 38.07	5.85 / 5.86	158-160	77
2e	$C_7H_{13}N_3S_2$	41.31 / 41.35	6.42 / 6.44	165-167	87
2f	$C_8H_{15}N_3S_2$	44.13 / 44.21	6.85 / 6.96	168-170	91
3a	$C_{10}H_{13}N_3O_2S$	50.67 / 50.19	5.60 / 5.48	130-132	78
3b	$C_{13}H_{18}N_3O_2S$	55.88 / 55.69	6.71 / 6.47	50-54	77
3c	$C_9H_{11}N_3OS_2$	44.51 / 44.79	4.18 / 4.59	173-175	47
3d	$C_{10}H_{13}N_3OS_2$	47.07 / 47.04	5.10 / 5.13	86-88	68
3e	$C_{11}H_{15}N_3OS_2$	48.99 / 49.04	5.59 / 5.61	59-61	69
3f	$C_{12}H_{17}N_3OS_2$	50.88 / 50.86	6.01 / 6.05	38-0	65
4	$C_8H_8N_4O_2S$	42.39 / 42.85	3.28 / 3.60	>250	83

Table 2. Spectroscopic Characteristics of Compounds **2a-f, 3a-f,** and **4**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm*
2a	3110 – 3275 (NH_2), 2850 – 2960 (alkyl), 1635 (NH_2, def), 1525 (C=N)	3.60 (2H, t, CH_2CH_2); 3.05 (2H, t, CH_2CH_2); 3.51 (2H, q, CH_2); 1.24 (3H, t, CH_3)
2b	3115 – 3325 (NH_2), 2850 – 2960 (alkyl), 1635 (NH_2, def), 1525 (C=N)	3.62 (2H, t, CH_2CH_2); 3.05 (2H, t, CH_2CH_2); 2.52 (2H, t, CH_2); 1.44 (6H, m, $(CH_2)_3$); 0.88 (3H, t, CH_3)
2c	3270 – 3120 (NH_2), 2960 – 2920 (alkyl), 1640 (NH_2, def), 1525 (C=N)	5.50 (2H, br. s, NH_2); 3.06 (2H, t, CH_2CH_2); 2.80 (2H, t, CH_2CH_2); 2.04 (3H, s, CH_3)
2d	3100 – 3250 (NH), 2870 – 2970 (alkyl), 1630 (NH_2, def), 1535 (C=N)	5.35 (2H, br. s, NH_2); 3.00 (2H, t, CH_2CH_2); 2.75 (2H, t, CH_2CH_2), 2.50 (2H, q, CH_2); 1.15 (3H, t, CH_3)
2e	3120 – 3280 (NH_2), 2875 – 2965 (alkyl), 1635 (NH_2, def), 1525 (C=N)	4.50 (2H, br. s, NH_2); 3.03 (2H, t, CH_2CH_2); 2.80 (2H, t, CH_2CH_2); 2.45 (2H, t, CH_2); 1.53 (2H, sext., CH_2); 0.80 (3H, t, CH_3)
2f	3100 – 3270 (NH_2), 2873 – 2960 (alkyl), 1625 (NH_2, def), 1520 (C=N)	5.45 (2H, br. s, NH_2); 3.00 (2H, t, CH_2CH_2); 2.83 (2H, t, CH_2CH_2); 2.50 (2H, t, $CH_3(CH_2)_2CH_2$); 1.44 (4H, m, $(CH_2)_2$); 0.88 (3H, t, CH_3)
3a	2865 – 2965 (alkyl), 1965 (C=O), 1577 (C=N)	6.25 (1H, s, CH); 3.66 (2H, t, CH_2CH_2); 3.03 (2H, t, CH_2CH_2); 3.50 (2H, q, CH_2); 2.20 (3H, s, CH_3); 1.27 (3H, t, CH_2CH_3)
3b	2867 – 2967 (alkyl), 1695 (C=O), 1576 (C=N)	6.25 (1H, s, CH); 3.69 (2H, t, CH_2CH_2); 3.00 (2H, t, CH_2CH_2); 2.50 (2H, t, CH_2); 2.25 (3H, s, CH_3); 1.45 (6H, m, $(CH_2)_3$); 0.85 (3H, t, CH_3)
3c	2865 – 2965 (alkyl), 1690 (C=O), 1570 (C=N), 1400 (C–S–C)	6.25 (1H, s, CH); 3.20 (2H, t, CH_2CH_2); 2.91 (2H, t, CH_2CH_2); 2.27 (3H, s, CH_3); 2.21 (3H, s, CH_3)
3d	2865 – 2965 (alkyl), 1690 (C=O), 1570 (C=N), 1400 (C–S–C)	6.23 (1H, s, CH); 3.21 (2H, t, CH_2CH_2); 2.93 (2H, t, CH_2CH_2); 2.50 (2H, q, CH_2); 2.30 (3H, s, CH_3); 1.23 (3H, t, CH_2CH_3)
3e	2865 – 2965 (alkyl), 1690 (C=O), 1570 (C=N), 1400 (C–S–C)	6.20 (1H, s, CH); 3.23 (2H, t, CH_2CH_2); 2.90 (2H, t, CH_2CH_2); 2.50 (2H, t, CH_2); 2.33 (3H, s, CH_3); 1.28 (2H, m, CH_2); 0.83 (3H, t, CH_3)
3f	2865 – 2965 (alkyl), 1690 (C=O), 1570 (C=N), 1400 (C–S–C)	6.20 (1H, s, CH); 3.19 (2H, t, CH_2CH_2); 2.88 (2H, t, CH_2CH_2); 2.50 (2H, t, CH_2); 2.30 (3H, s, CH_3); 1.45 (4H, m, $(CH_2)_2$); 0.83 (3H, t, CH_3)
4	3400 (NH_2), 1710 (C=O), 1690 (C=O), 1570 (C=N)	7.28 (1H, c, NH_2); 6.22 (H, c, CH); 3.97 (2H, s, CH_2); 2.20 (3H, s, CH_3)

* In the ^1H NMR spectra coupling through three bonds with standard values with free rotation around the C-C bond with J = 6-7 Hz were observed, so these are not noted further in Table 2.

The IR spectrum of amide **4** contains stretching bands corresponding to two carbonyl groups at 1710 and 1690 cm^{-1} and an absorption band of an NH_2 in the 3400 cm^{-1} region. The ^1H NMR spectrum of compound **4**



contains signals in the form of four singlets at 7.28, 6.22, 3.97, and 2.20 ppm corresponding to protons of the amide group, a proton at position 6 of the heterocycle, two protons of a methylene group and three protons of the methyl group.

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions (internal standard HMDS (δ 0.005 ppm) were recorded on a Tesla BS-58773 C (100 MHz) spectrometer. IR spectra of KBr tablets were recorded on a UR-20 spectrometer. Melting temperatures were determined with a Boetius microthermal block.

Compound 5 was made by a known method [14].

5-(β-Alkylthioethyl)-2-amino-1,3,4-thiadiazoles 2a,b, 5-(β-Alkoxyethyl)-2-Amino-1,3,4-thiadiazoles 2c-f, and 2-R-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidines 3a-f (General Method). A mixture of the corresponding nitrile **1** (10 mmol), thiosemicarbazide (0.91 g, 10 mmol) and PPA (10 g) was heated for 5-6 h on a boiling water bath, and, in the case of compounds **3a-f**, ethyl acetoacetate (1.05 mmol) was added and the mixture heated for an additional 3 h. Water (50 ml) was then added and the solution was neutralized to pH 7-8 with 20% NaOH solution. Crystals were transferred to a filter, washed with water, dried in the air, and recrystallized from aqueous dioxane.

(7-Methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)acetamide (4). Concentrated ammonia (2 ml) was added with stirring to a solution of 2-ethoxycarbonylmethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (2.21 g, 11 mmol) in ethanol (15 ml), stirred at room temperature for 2 h, then heated for 1 h. The reaction mixture was poured into water (50 ml). The precipitate was filtered and washed with water and dried. The product was crystallized from aqueous dioxane (1:1). Yield 1.59 g (83%).

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