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SYNTHESIS AND PROPERTIES OF (6-METHYL-2-OXO-4-THIOXO-1,2,3,4-TETRAHYDRO-3-PYRIMIDINYL)ACETIC ACID METHYL ESTER

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2-amino-5-bromo-1,3,4-thiadiazole, 2-bromo-6-phenyl-imidazo[2,1-b]-1,3,4-thiadiazole, 2,5-dibromo-6-phenylimidazo[2,1-b]-1,3,4-thiadiazole, 2-morpholino-5-morpholinomethyl-6-phenylimidazo[2,1-b]-1,3,4-thiadiazole.

Keywords: 2-amino-5-bromo-1,3,4-thiadiazole, 2-bromo-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole, 2,5-dibromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole, 2-morpholino-5-morpholinomethyl-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole.

Interest in derivatives of imidazo[2,1-*b*]-1,3,4-thiadiazole is linked first of all with the search for new biologically active substances and the design of medicinal preparations based on them [1-4]. The most common method of synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles is the reaction of 5-R-2-amino-1,3,4-thiadiazoles with α-halo ketones [5-7], which however does not provide the possibility of synthesizing a wide range of derivatives of imidazo[2,1-*b*]-1,3,4-thiadiazole.

With the aim of broadening the range of derivatives and the search for new biologically active substances, we have developed a method of synthesizing 2-bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole from 2-amino-5-bromo-1,3,4-thiadiazole and 2-bromoacetophenone.

On interacting 2-amino-5-bromo-1,3,4-thiadiazole with 2-bromoacetophenone in boiling alcohol the hydrobromide of 5-bromo-2-imino-3-phenacyl-2,3-dihydro-1,3,4-thiadiazole (**1**) was formed, and is precipitated. As a result of further (10-15 h) boiling salt **1** in alcohol, 2-bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (**2**) was obtained in 78% yield after cooling and neutralization with an equimolar quantity of sodium acetate.

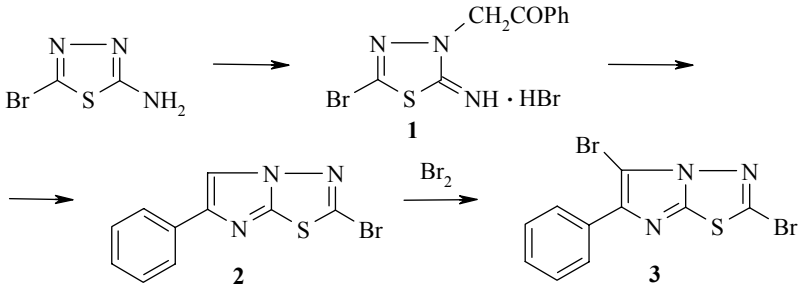

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TABLE 1. Characteristics of the Compounds Synthesized

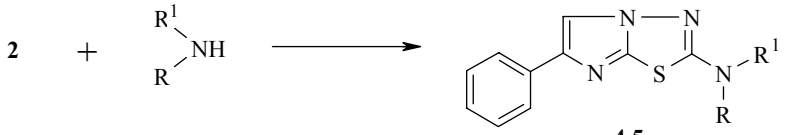
Compound	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm. (*J*, Hz)	Yield, %
		C	H				
1	$C_{10}H_9Br_2N_3S$	31.32 / 31.68	2.22 / 2.39	245-247	3130 (NH), 2980 (C=C), 1715 (C=O)		95
2	$C_{10}H_6BrN_3S$	42.48 / 42.87	2.11 / 2.15	196-198	1640 (C=N), 1610 (C=C)	8.7 (1H, s, H-5); 7.80-7.32 (5H, m, C_6H_5)	78
3	$C_{10}H_5Br_2N_3S$	33.19 / 33.45	1.17 / 1.31	130-132	1610 (C=N), 1570 (C=C)	7.70-7.22 (5H, m, C_6H_5)	83
4	$C_{14}H_{11}N_3S$	61.47 / 61.73	4.18 / 4.24	111-113	1620 (C=N), 1565 (C=C), 3110 (C–H)	8.49 (1H, s, C_5H); 7.80-7.37 (5H, m, C_6H_5), 3.64 (2H, q, CH_2); 1.20 (3H, t, $J \approx 7$, CH_3)	69
5	$C_{14}H_{14}N_4OS$	58.39 / 58.72	4.78 / 4.92	208-210	1621 (C=N), 1583 (C=C), 3100 (C–H)	8.23 (1H, s, H-5); 7.94-7.20 (5H, m, C_6H_5); 3.65 (4H, d, $J = 4.5$, CH_2); 3.53 (4H, d, CH_2)	94
6	$C_{19}H_{23}N_5O_2S$	59.08 / 59.19	5.98 / 6.01	218-220	1621 (C=N), 1578 (C=C)	7.60-7.36 (5H, m, C_6H_5); 3.64 (4H, d, CH_2); 3.56 (4H, d, $J = 4.5$, CH_2); 3.46 (2H, s, CH_2); 3.40 (4H, d, $J = 4.5$, CH_2); 3.30 (4H, d, CH_2)	61

In the IR spectrum of compound **1** there were absorption bands in the region of 1712 cm^{-1} indicating the presence of a carbonyl group in the molecule. These bands were absent from the IR spectrum of 2-bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (**2**). In the ^1H NMR spectrum of compound **2** a signal appeared at 8.71 ppm corresponding to the proton in position 5 of the ring.

We carried out the bromination of compound **2** with molecular bromine in a medium of acetic acid. It is known from the literature that the proton in position 5 of imidazo[2,1-*b*]-1,3,4-thiadiazole is reactive and reacts readily by electrophilic substitution [8].

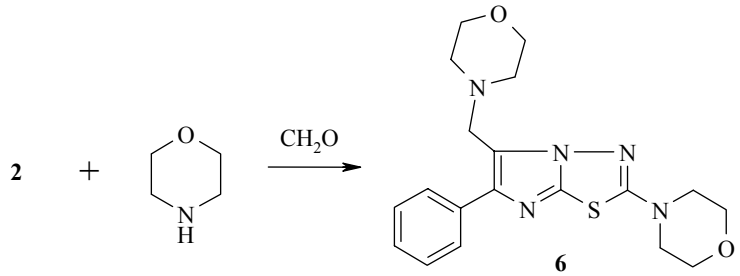
On interacting 2-bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (**2**) with molecular bromine in glacial acetic acid, 2,5-dibromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (**3**) was obtained in 83% yield. The proton signal in the region of 8.71 ppm was absent from the ^1H NMR spectrum of compound **3**, which indicates the substitution of the proton in position 5 of the ring by bromine.

The synthesis of 2-amino-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole from 2,5-diamino-1,3,4-thiadiazole and 2-bromoacetophenone [6-8] has limited possibilities. Consequently, with the aim of developing new methods of obtaining amino derivatives of imidazo[2,1-*b*]-1,3,4-thiadiazole, we investigated the reaction of 2-bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (**2**) with various amines. It was found that on interacting bromide **2** with diethylamine and morpholine in alcohol the corresponding amines **4** and **5** were obtained in high yield.



R = R^1 = Et, (– CH_2CH_2–)$_2$O **4,5**

On investigating the reaction of 2-bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole with an excess of morpholine in the presence of formalin it was established that under these conditions nucleophilic substitution of the bromine atom in position 2 occurs and also aminomethylation at position 5 of the imidazo[2,1-*b*]-1,3,4-thiadiazole system. As a result 2-morpholino-5-morpholinomethyl-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (**6**) was obtained.



6

In the ^1H NMR spectrum of compound **6** there was no signal for the proton at position 5 and signals were displayed at 3.46 ppm as a singlet and four doublets in the region of 3.30-3.64 ppm, assigned to the morpholine fragment and indicating that this compound had been obtained.

EXPERIMENTAL

The IR spectra were recorded on a UR 20 spectrometer in KBr disks, and the ^1H NMR spectra on a Tesla 5873C (100 MHz) instrument in DMSO-d_6, internal standard was HMDS. Melting points were determined on a Boetius micro hot stage. The characteristics of the compounds obtained are given in Table 1.

2-(5-Bromo-2-imino-2,3-dihydro-1,3,4-thiadiazol-3-yl)acetophenone Hydrobromide (1). A solution of 5-amino-2-bromo-1,3,4-thiadiazole (1.8 g, 0.01 mol) and 2-bromoacetophenone (0.01 mol) in alcohol (20 ml) was boiled with stirring for 2 h. Having cooled to room temperature, the precipitated solid was filtered off, washed with boiling alcohol (10 ml), and dried.

2-Bromo-6-phenylimidazo[2,1-*b*]-1,2,4-thiadiazole (2). A solution of salt **1** (0.1 mol) in alcohol (30 ml) was boiled with stirring for 13 h. The reaction mixture was cooled, and neutralized with sodium acetate (0.82 g). The precipitated solid was filtered off, washed with water, and recrystallized from dioxane.

2,5-Dibromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (3). Bromine (1.6 g, 0.01 mol) was added with stirring to a solution of 2-bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (0.01 mol) in glacial acetic acid (15 ml). The reaction mixture was left at room temperature for 60 min, then diluted with ice-water (50 ml), and neutralized with sodium acetate (0.82 g). The precipitated solid was filtered off, washed with water, and crystallized from dioxane.

2-Diethylamino-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (4) and 2-Morpholino-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole (5) (General Method). 2-Bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (0.01 mol) was dissolved in alcohol (15 ml) and amine (0.02 mol) was added with stirring. The reaction mixture was boiled with stirring for 5 h, then cooled, and diluted with ice-water (60 ml). The precipitated solid was filtered off, and washed with water.

2-Morpholino-5-morpholinomethyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (6). 2-Bromo-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole (0.01 mol) was dissolved in alcohol (15 ml) and morpholine (0.03 mol) was added with stirring. The mixture was boiled with stirring for 6 h, the reaction mixture was then cooled, and diluted with ice-water (60 ml). The precipitated solid was filtered off, washed with water, and recrystallized from dioxane.

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