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SYNTHESIS OF 2-(1,2,3-THIADIAZOL-5-YL)-1H-BENZIMIDAZOLES

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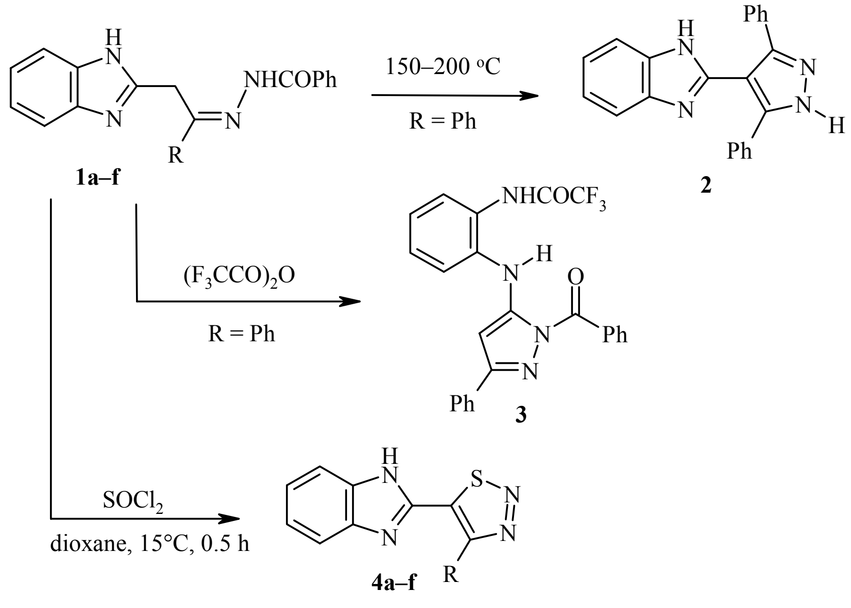
We have developed a convenient preparative method for synthesis of previously unknown 2-(1,2,3-thiadiazol-5-yl)-1H-benzimidazoles based on reaction of benzoylhydrazones of 2-acylmethyl-1H-benzimidazoles with thionyl chloride.

Keywords: benzimidazoles, hydrazones, 1,2,3-thiadiazoles, thionyl chloride.

Reaction of some acylhydrazones of methyl and methylene ketones with thionyl chloride is one of the methods for synthesis of 1,2,3-thiadiazoles [1]. In this work, we tested this reaction for the first time on benzoylhydrazones of 2-phenacyl-1H-benzimidazoles **1a-f**. The direction of the conversion was unpredictable since thionyl chloride has the properties of both a dehydrating and an acylating reagent [2], while the benzoylhydrazone of 2-phenacyl-1H-benzimidazole (**1a**), as established previously, when heated tends to undergo ring closure with liberation of water to form 2-(4-pyrazoyl)benzimidazole **2** [3], and when acylated with trifluoroacetic anhydride it undergoes recyclization to form anilinopyrazole **3** [4].



1, **4** **a** R = Ph, **b** R = 4-MeC_6H_4, **c** R = 4-$MeOC_6H_4$, **d** R = 3,4,5-$(MeO)_3C_6H_4$,
e R = 2-thienyl, **f** R = Me

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We have found that reaction of compounds **1a-f** with thionyl chloride occurs readily and highly selectively to form the previously unknown 1,2,3-thiadiazolyl-substituted compounds of benzimidazole **4a-f**.

The process is carried out by mixing the reagents in a 1:3 mole ratio in dioxane at 15-20°C, and goes to completion within 30 min. The products are isolated after treatment of the reaction mixtures with an aqueous solution of ammonia. The yields are as high as 80%-98%.

The synthesized compounds are colorless crystalline materials. They are light-sensitive and gradually decompose when exposed to light at 20-25°C, becoming various shades of yellow, orange, and red. However, when stored in a refrigerator at +8°C, they are quite stable for two years. The physicochemical characteristics of the compounds are given in Table 1. The structure of the compounds was confirmed by the ^{1}H NMR spectra (Table 2).

The ^{1}H NMR spectra of compounds **4** are characterized by signals from protons corresponding to the 4 and 7 positions of the benzimidazole system. The corresponding signals in most cases appear as two separate broadened multiplets, and for compound **4c** as a general broadened multiplet, which suggests hindered and fast migrations of the proton between the ring nitrogen atoms. A similar phenomenon was also observed earlier for benzimidazole derivatives containing substituted pyrazole or pyrimidine moieties in the 2 position [3, 5]. It is probably due to steric hindrances to this type of prototropism.

TABLE 1. Characteristics of Synthesized Compounds **4a-f**

Com-pound	Empirical formula	Found, % Calculated, %				mp, °C	Yield, %
		C	H	N	S		
4a	$C_{15}H_{10}N_4S$	64.77 64.73	3.85 3.62	20.05 20.13	11.34 11.52	235-236	95
4b	$C_{16}H_{12}N_4S$	65.84 65.73	4.25 4.14	19.07 19.16	10.85 10.97	247-249	94
4c	$C_{16}H_{12}N_4OS$	62.44 62.32	4.05 3.92	18.04 18.17	10.28 10.40	239-240	98
4d	$C_{18}H_{16}N_4O_3S$	58.74 58.68	4.49 4.38	15.16 15.21	8.57 8.70	204-205.5	94
4e	$C_{13}H_8N_4S_2$	54.97 54.91	2.97 2.84	19.58 19.70	22.46 22.55	236-237	80
4f	$C_{10}H_8N_4S$	55.63 55.54	3.91 3.73	25.76 25.91	14.89 14.83	229-230	85

TABLE 2. ^{1}H NMR Spectra of Synthesized Compounds **4a-f**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
4a	7.28–7.29 (2H, m, H-5,6); 7.51-7.53 (4H, m, H-7 + *m*- and *n*-protons C_6H_5); 7.72 (1H, br. m, H-4); 7.78-7.81 (2H, m, *o*-protons C_6H_5); 12.95 (1H, s, NH)
4b	2.38 (3H, s, CH_3); 7.27-7.30 (2H, m, H-5,6); 7.32 and 7.66 (2 × 2H, 2 d, *J* = 8.1, *n*-C_6H_4); 7.59 and 7.66 (2H, 2 br. m, H-4 and H-7); 12.80 (1H, s, NH)
4c	3.82 (3H, s, CH_3); 7.08 and 7.75 (2 × 2H, 2 d, *J* = 8.7, *n*-C_6H_4); 7.27-7.30 (2H, m, H-5,6); 7.63 (2H, br. m, H-4,7); 12.88 (1H, s, NH)
4d	3.71 (6H, s, 2CH_3); 3.75 (3H, s, CH_3); 7.26 (2H, s, C_6H_2), 7.29-7.34 (2H, m, H-5,6); 7.55-7.58 (1H, m, H-7); 7.72-7.75 (1H, m, H-4); 12.91 (1H, s, NH)
4e	7.22, 7.79 and 8.09 (3 × 1H, 3 m, 2-thienyl); 7.32-7.34 (2H, m, H-5,6); 7.62 and 7.78 (2H, 2 br. m, H-7 and H-4); 13.30 (1H, s, NH)
4f	3.08 (3H, s, CH_3); 7.32 (2H, br. m, H-5,6); 7.65 and 7.75 (2 × 1H, 2 br. m, H-7 and H-4); 13.22 (1H, s, NH)

Thus reaction of benzoylhydrazones of 2-acylmethyl-1H-benzimidazoles with thionyl chloride is a convenient and efficient preparative route to obtaining the previously unknown 2-(1,2,3-thiadiazol-5-yl)-1H-benzimidazoles.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Varian VXR-300 (300 MHz) in DMSO-d_6, internal standard TMS. The course of the reaction and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in the system benzene–ethanol, 9:1, visualization in UV light.

Compound **1a** was obtained by the method in [3]; compounds **1b-f** were obtained similarly and were used in the synthesis without preliminary purification.

2-(4-Phenyl-1,2,3-thiadiazol-5-yl)-1H-benzimidazole (4a). Thionyl chloride (0.22 ml, 3 mmol) was added all at once to a mixture of compound **1a** (0.354 g, 1 mmol) and anhydrous dioxane (1 ml) at 15-20°C. The mixture was stirred for 3-5 min and allowed to stand for 30 min. Water (1 ml) and a concentrated aqueous solution of ammonia (1 ml) were added and the mixture was stirred. After cooling, the precipitate was filtered out and then washed with water and 2-propanol. The product was purified by crystallization from a 2:1 pyridine–water mixture.

Compounds 4b-f were obtained similarly from the corresponding hydrazones **1b-f**.

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