SYNTHESIS AND STUDY OF ANTIFUNGAL AND ANTIBACTERIAL PROPERTIES OF 2-THIOCYANATO-1-ARYL-3-IODOPROPANES

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Previously, we have used the anionarylation reaction [1] to synthesize various allyl chloride, bromide, and isothiocyanate derivatives possessing antifungal and antibacterial properties [2 – 4]. In continuation of these investigations, we have used allyl iodide for the first time as initial compound in the anionarylation process.

It was found that aryldiazonium tetrafluoroborates intensively interact with allyl iodide in a water – acetone (1 : 3) medium in the presence of potassium rhodanide. The reaction leads to the formation of 2-thiocyanato-1-aryl-3-iodopropanes (I – III):

$$RC_6H_4N_2BF_4 + H_2C{=}CHCH_2I + NaSCN \longrightarrow$$

$$\longrightarrow RC_6H_4CH_2\underset{\underset{S{-}C{\equiv}N}{|}}{C}HCH_2I + N_2 + NaBF_4 + RC_6H_4NCS$$

I – III

R = H (I), *p*-CH_3 (II), *p*-CH_3O (III).

The thiocyanatoarylation of allyl iodide can be performed in the temperature interval from – 25 to – 15°C. The reaction proceeds only in the presence of a catalyst. In our work, the process was catalyzed by copper(II) acetate, whose amount was five times that usually employed [1]. The optimum reagent ratio diazonium salt – allyl iodide – sodium rhodanide – copper acetate is 1.0 : 1.2 : 1.3 : 0.5. Note that the allyl iodide thiocyanatoarylation is accompanied by a side reaction leading to the formation of isothiocyanatobenzenes with a yield of 12 – 15 %.

The thiocyanatoarylation products appear as cherry-red oils. Heating of the synthesized thiocyanates did not lead to isomerization with the formation of isothiocyanates.

Thus, the behavior of allyl iodide in the anionarylation reaction is much like that of allyl chloride (or bromide). The introduction of iodine into the allyl fragment did not affect regioselectivity of the thiocyanatoarylation process and was not accompanied by manifestations of an ambidentate character of the rhodan group. The experimental data agree with the radical-anion mechanism of anionarylation reactions described in [1, 5].

The proposed structures of the synthesized compounds were confirmed by the results of IR and ^1H NMR spectroscopic measurements. The IR spectra of compounds I – III contain narrow absorption bands due to thiocyanate groups in the 2160 – 2165 cm^{-1} region. The ^1H NMR spectra of 2-thiocyanato-1-aryl-3-iodopropanes display signals due to the protons of aromatic nuclei at 6.83 – 7.16 ppm. The signals from protons of the methylene groups bound to aromatic nuclei and iodine are manifested as doublets at 3.16 – 3.17 and 2.87 – 2.89 ppm, and the constants of the spin – spin coupling to methine protons, 6 and 8 Hz, respectively. The signals from methine protons are observed at 3.60 – 3.94 ppm.

Purity of the synthesized substances was checked by TLC on Silufol UV-254 plates eluted with a hexane – diethyl ether – chloroform (3 : 1 : 3) mixture.

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds I - III were recorded on an IKS-29 spectrophotometer using samples prepared as thin liquid films. The ^1H NMR spectra were recorded on a Varian VXR-300 spectrometer with a working frequency of 300 MHz using $(CD_3)_2CO$ as the solvent and HMDS as the internal standard.

2-Thiocyanato-1-aryl-3-iodopropane (I). To a mixture of 0.12 mole of allyl iodide, 0.05 mole of copper acetate, and 0.13 mole of NaSCN in 160 ml of a water – acetone (1 : 3) mixture was gradually added (over 90 min) with stirring 0.1 mole of phenyldiazonium tetrafluoroborate at a temperature of – 25 to– 15°C. When the nitrogen evolution ceased (~ 3.5 h), the reaction mixture was treated with 200 ml of diethyl ether. The ether extracts were washed with water and

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TABLE 1. Yields, Physicochemical Characteristics, and ^{1}H NMR Chemical Shifts of 2-Thiocyanato-1-aryl-3-iodopropanes I – III

Compound	Yield, %	B.p., °C (1 Torr)	d_4^{20}	n_d^{20}	Empirical formula	IR spectrum: ν(SCN), cm^{-1}	^{1}H NMR spectrum: δ, ppm
I	28	51 – 53	1.5738	1.5908	$C_{10}H_{10}INS$	2163	2.89 (dd, 2H, J_{H-H} 8 Hz, CH_2-I); 3.17 (dd, 2H, J_{H-H} 6 Hz, CH_2-Ar), 3.60 – 3.88 (m, 1H, CH); 7.08 (s, 5H, C_6H_5)
II	32	60 – 62	1.5644	1.6016	$C_{11}H_{12}INS$	2160	2.87 (dd, 2H, J_{H-H} 8 Hz, CH_2-I); 3.17 (dd, 2H, J_{H-H} 6 Hz, CH_2-Ar); 3.61 – 3.90 (m, 1H, CH); 7.12 (s, 4H, C_6H_4); 2.24 (s, 3H, p-CH_3)
III	26	64 – 66	1.5552	1.5817	$C_{11}H_{12}INOS$	2165	2.88 (dd, 2H, J_{H-H} 8 Hz, CH_2-I); 3.16 (dd, 2H, J_{H-H} 6 Hz, CH_2-Ar), 3.67 – 3.94 (m, 1H, CH), 6.83, 7.16 (d, 4H, C_6H_4), 3.71 (s, 3H, p-CH_3O)

TABLE 2. Antimicrobial Properties of Compounds I – III

Compound	MIC, μg/ml						
	S. typhimurium No. 1534 *his D* 3052	*P. mirabilis* No. 410	*St. aureus* ATCC No. 25923 F-49	*P. aeruginosa* ATSS No. 27853 F-51	*B. subtilis* No. 8236 F-800	*C. albicans* TsShVI	*S. cerevisiae* No. 61
I	500	NA	NA	NA	500	250	62.5
II	500	NA	NA	NA	NA	500	125
III	500	NA	NA	NA	500	250	62.5

* NA = No activity.

dried over magnesium sulfate. Then diethyl ether was evaporated and the residue was distilled in vacuum to obtain 1.62 g (12%) of isothiocyanatobenzene and 8.49 g (28%) of compound I; b.p., 51 – 53°C (1 Torr); d_4^{20}, 1.5738; n_D^{20}, 1.5908.

Compounds II and III were obtained by similar procedures (Table 1).

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the synthesized compounds was studied by the method of double serial dilutions in liquid nutrient media (a beef-infusion broth for bacteria, a modified Sabouraud liquid medium for fungi) using 96-well immunological plates and a Takachi microtitrator.

The working solutions were prepared by dissolving 10 mg of each compound in 0.25 ml DMF, followed by adding 9.75 ml of distilled water. The solutions were thoroughly stirred immediately before experiment. The activity of a substance was considered as high if the growth of a microbial strain was inhibited at a sample solution concentration of 15.6 μg/ml or below.

The tests were performed on Gram-positive (*St. aureus* ATCC No. 25923 F-49), Gram-negative (*P. mirabilis* No. 410, *S. typhimurium* No. 1534 his D 3052, *P. aeruginosa* ATSS No. 27853 F-51), and spore-forming (*B. subtilis* No. 8236 F-800) bacteria and yeast fungi (*C. albicans* TsShVI and *S. cerevisiae* No. 61) species.

As is seen from the data presented in Table 2, compounds I – III showed no antibacterial properties. Compounds I and III exhibited moderate antifungal effects. A comparison of the results obtained in this work with the previous data indicates that the substitution of iodine for chlorine (bromine) atoms in molecules of functionalized allyl derivatives leads to the loss of antibacterial properties, while the antifungal activity is retained.

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