SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF N-ALLYL-3-ARYL-2-THIOCYANATOPROPIONAMIDES

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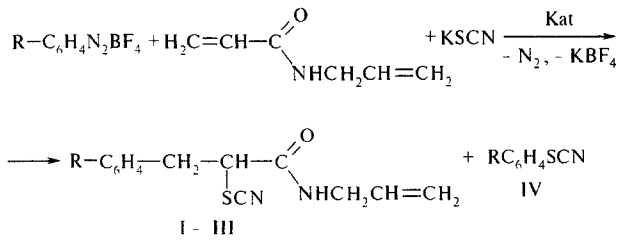
Previously, we have demonstrated that the anionarylation of alkenes [1] leads to functional derivatives belonging to various classes of organic compounds, many of which possessed antimicrobial properties. The most promising results in this respect were obtained for fatty-aromatic thiocyanates and isothiocyanates [2, 3].

The aim of this work was to obtain new thiocyanates using the reaction of N-allylacrylamide anionarylation. For this purpose we have studied for the first time the interaction of arenediazonium tetrafluoroborates with N-allylacrylamide under the conditions of anionarylation in the presence of potassium thiocyanate.

Taking into account our previous results on the thiocyanatoarylation of acrylamide [4] and allyl chloride and bromide [5], it was suggested that the interaction of aryldiazonium tetrafluoroborates with N-allylacrylamide may proceed by different pathways with participation of one or two multiple bonds. However, detailed investigation of the reaction products showed that only one of the possible directions is realized, namely, that leading to the formation of N-allyl-3-aryl-2-thiocyanatopropionamides (I – III); the main reaction was accompanied by the side formation of isothiocyanatobenzenes (IV) in amounts of 14 – 18 %.



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

The interaction of aryldiazonium tetrafluoroborates and potassium rhodanide with with N-allylacrylamide proceeds in a water – acetone (1 : 2) mixture at a temperature of 5 – 10°C in the presence of a catalytic amount of copper acetate. The presence of catalyst is a necessary condition for this reaction.

It should be also noted that no N-allyl-3-aryl-2-isothiocyanatopropionamides were found among the reaction products. The yields of N-allyl-3-aryl-2-thiocyanatopropionamides (I – III) amount to 52 – 61 %. The optimum reagent ratio diazonium salt – N-allylacrylamide – potassium rhodanide – copper acetate is 1.00 : 1.00 : 1.25 : 0.10.

The proposed structures of of N-allyl-3-aryl-2-thiocyanatopropionamides (I – III) were confirmed by the results of IR and ^{1}H NMR spectroscopic measurements. The IR spectra of these compounds contain absorption bands due to the carbonyl and NH groups (in the 1670 and 3240 cm^{-1} regions, respectively). The multiple bond of the allyl fragment is manifested by absorption in the 1640 cm^{-1} region. The nonplanar vibrations of CH bonds in this fragment can be assigned to the narrow absorption bands at 915 – 920 and 950 – 960 cm^{-1}. In addition, the IR spectra of compounds I – III show intense narrow absorption bands of the thiocyanate group in the 2140 – 2165 cm^{-1} region. The ^{1}H NMR spectra of compounds I – III (Table 1) contain signals due to the protons of aromatic nuclei and NH groups in the 6.85 – 7.85 ppm region (multiplets). The signals from protons of the methylene groups bound to the aromatic nuclei are manifested as two doublets with δ = 3.86 and 3.87 ppm, while the signals from methine protons, as two doublets with δ = 5.90 – 5.92 and a spin – spin coupling constant of J = 5 Hz.

EXPERIMENTAL CHEMICAL PART

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

The data of elemental analyses agree with the values calculated according to the empirical formulas.

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TABLE 1. Physicochemical Characteristics, Yields, and ^{1}H NMR Spectra of N-Allyl-3-arene-2-thiocyanatopropionamides I – III

Compound	Yield, %	B.p., °C (1 Torr)	n_D^{20}	d_4^{20}	MR_D found	MR_D calcd	Empirical formula	^{1}H NMR spectrum: δ, ppm
I	61	90 – 91/1	1.5230	1.0856	69.22	69.54	$C_{13}H_{14}N_2OS$	7.85 – 7.45 (m, 5H, C_6H_5; 1H, NH), 6.35 (dd, J_{H-H} 10 Hz), 6.21 (dd, 2H, J_{H-H} 2 Hz, NH–CH_2-), 5.91 (dd, 1H, J_{H-H} 5 Hz, –CH), 5.60 (dd, 1H, J_{H-H} 2 Hz, -CH=), 5.12 (dd, 2H, J_{H-H} 14 Hz, $=CH_2$), 3.86 (dd, 2H, J_{H-H} 5 Hz, -CH_2-Ph)
II	56	95 – 96/1	1.5288	1.0876	73.70	74.19	$C_{14}H_{16}N_2OS$	7.64 – 7.30 (m, 4H, C_6H_4; 1H, NH), 6.33 (dd, J_{H-H} 10 Hz), 6.21 (dd, 2H, J_{H-H} 2 Hz, NH–CH_2-), 5.90 (dd, 1H, J_{H-H} 5 Hz, –CH), 5.59 (dd, 1H, J_{H-H} 2 Hz, -CH=), 5.11 (dd, 2H, J_{H-H} 14 Hz, $=CH_2$), 3.87 (dd, 2H, J_{H-H} 5 Hz, -CH_2-Ph), 2.37 (s, 3H, *p*-CH_3-Ph)
III	52	79 – 80/1	1.5235	1.1153	75.66	75.97	$C_{14}H_{16}N_2O_2S$	7.16 – 6.85 (m, 4H, C_6H_4; 1H, NH), 6.35 (dd, J_{H-H} 10 Hz), 6.22 (dd, 2H, J_{H-H} 2 Hz, NH–CH_2-), 5.92 (dd, 1H, J_{H-H} 5 Hz, –CH), 5.60 (dd, 1H, J_{H-H} 2 Hz, -CH=), 5.13 (dd, 2H, J_{H-H} 14 Hz, $=CH_2$), 3.86 (dd, 2H, J_{H-H} 5 Hz, -CH_2-Ph), 3.71 (s, 3H, *p*-CH_3O-Ph)

N-Allyl-3-phenyl-2-thiocyanatopropionamide (I). To a mixture of 0.1 mole of N-allylacrylamide, 0.125 mole KSCN, and 0.01 mole $Cu(CH_3COO)_2 \cdot 2H_2O$ in 150 ml of a water – acetone (1 : 2) mixture was gradually added (over 1.5 h) with stirring 0.1 mole of benzenediazonium tetrafluoroborate. The reaction was conducted within the temperature interval from 5 to 10°C for 3 h. When the nitrogen evolution ceased, the reaction mixture was treated with 200 ml of ether. The ether extract was washed with water and dried over magnesium sulfate. Then the solvent (ether) was evaporated and the residue was distilled in vacuum to obtain 1.9 g (15.5%) of isothiocyanatobenzene and 7.25 g (61%) of compound I.

Compounds II and III were obtained by similar procedures.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of compounds I – III was tested on both museum-stored (3 species) and freshly isolated (27 species) strains of *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. The museum cultures were represented by *St. aureus* ATCC 2022, *E. coli* ATCC 25922, and *P. aeruginosa* ATCC 9027.

The antimicrobial activity was determined by the method of double serial dilutions in liquid nutrient media.

The working 1% solutions of compounds I – III were prepared in 70% aqueous ethanol. Immediately before experiments, the samples were diluted in a nutrient medium in the ratio 1 : 500 or 1 : 256,000. A bacterial culture suspension (0.2 ml) with a microbial cell concentration of 10^5/ml was introduced into every test cell and the samples were incubated at 37°C for 18 – 24 h. Then the presence or absence of microbial growth was visually assessed and the minimum bacteriostatic concentration evaluated.

By passaging the cultures from tubes with no evidence of growth onto Petri dishes with a meat-broth agar medium, we have also estimated the minimum bactericidal concentrations.

The control tubes contained an equivalent amount of 70% aqueous ethanol.

The experimental results were processed by the method of variational statistics.

It was established that all the compounds studied in this work (I – III) exhibited antimicrobial activity with respect to *St. aureus*, *E. coli*, and *P. aeruginosa*

The most pronounced activity was observed for compound II, which suppressed the growth of microbial cultures when diluted to 1 : 64,000. Compounds I and III showed approximately equal antimicrobial properties and inhibited the growth of museum cultures being diluted to 1 : 16,000 – 1 : 32,000. The activity of compound II with respect to *St. aureus* and *P. aeruginosa* was approximately four times that of compounds I and III.

The minimum bactericidal concentrations of compounds I – III were 2 – 4 times their minimum bacteriostatic concentrations.

REFERENCES

1. B. D. Grishchuk, P. M. Gorbovoi, N. I. Ganushchak, and A. V. Dombrovskii, *Usp. Khim.*, **63**(3), 269 – 273 (1994).
2. B. D. Grishchuk and P. M. Gorbovoi, *Nauch. Zap. Ternopol. Pedagog. Univ., Ser. Khim.*, **1**(6), 3 – 18 (1997).
3. B. D. Grishchuk, L. I. Vlasik, A. V. Blinder, et al., *Abstracts of Papers. The 17th Ukrainian Conf. on Organic Chemistry* [in Ukrainian], Kharkov (1995), p. 576.
4. B. D. Grishchuk, P. M. Gorbovoi, E. Ya. Kudric, N. I. Ganushchak, et al., *Zh. Obshch. Khim.*, **63**(10), 2335 – 2341 (1993).
5. B. D. Grishchuk, P. M. Gorbovoi, N. I. Ganushchak, et al., *Zh. Obshch. Khim.*, **63**(7), 1655 – 1658 (1993).