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ARYLSUBSTITUTED HALOGEN(THIOCYANATO)AMIDES CONTAINING 4-ACETYLPHENYL FRAGMENT. SYNTHESIS, CYCLIZATION AND ANTIMICROBIAL PROPERTIES

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Abstract. 3-(4-Acetylphenyl)-(2-methyl)-2-chloro(bromo, thiocyanato)propanamides have been obtained *via* copper catalytic anionarylation of acrylic and methacrylic acids amides by 4-acetylphenyldiazonium salts. 5-(4-Acetylphenyl)substituted 2-aminothiazol-4(5*H*)-ones were synthesized by cyclisation of thiocyanatoamides. All synthesized compounds were tested for their antibacterial and antomycotic activity.

Keywords: anionarylation, acrylic and methacrylic acids amides, 4-acetylphenyldiazonium salts, 5-arylsubstituted 2-aminothiazol-4(5*H*)-ones, antimicrobial activity.

1. Introduction

Acetophenone was previously used as a hypnotic and anticonvulsant drug that undergoes metabolism in the human body to form benzoic and carbonate acids and acetone [1, 2]. Acetophenone is found in many foods (apples, cheese, apricots, bananas, beef, cauliflower) [3, 4]. Acetophenone derivatives are also reagents for the synthesis of many drugs, *e.g.* pyrrobutamine, dextropropoxyphene, trihexyphenidyl, pridinol, aspaminol, cycrimine, biperiden, procyclidine, acifran, amixetrine, mesuximide, and benmoxin [4-6].

Previously synthesized halogeno- and thiocyanatoarylation products [7, 8] have a sufficiently effective antibacterial and antimycotic activity [9-11]. 3-Aryl-(2-methyl)-2-thiocyanatopropanamides are characterized by pronounced anticandidiasis activity [9]. 3-[3-Amino-2-chloro(bromo, thiocyanato)-(2-methyl)-3-oxopropyl]-5-chloro(bromo, thiocyanato)benzoic acids have a pronounced effect on *E.coli* and *C.albicans* strains [12].

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Functionalized halogen(thiocyanato)amides and their cyclization products containing 4-acetylphenyl fragment were obtained and their antibacterial and antifungal properties were studied in order to find new bioactive compounds by the anionarylation reaction [13].

2. Experimental

2.1. Materials

IR-spectra of the compounds **I–IV** were recorded in vaseline oil using Specord M80 within the range of 4000–400 cm^{-1}. ^1H NMR spectra were obtained in DMSO-*d*6 using Varian Mercury device (400 MHz) and Bruker Avance DRX-500 (500 MHz). Tetramethylsilane was used as an internal standard. The elemental analysis was carried out according to the standard methods. The elemental analysis data correspond to the gross-formulas. The individuality of the synthesized compounds was established by TLC on Silufol UV-254 plates eluting with a hexane : methanol (3:1) and methanol : hexane : acetone (1:2:1) mixtures.

2.2. Synthesis

3-(4-Acetylphenyl)-2-chloropropanamide **(Ia)**. 5.2 g (0.022 mol) of 4-acetylphenyldiazonium tetrafluoroborate are added to 1.5 g (0.021 mol) of acrylamide, 0.8 g (0.0022 mol) of copper(II) tetrafluoroborate hexahydrate and 1.3 g (0.022 mol) of sodium chloride in 100 ml of water-acetone (1:3) mixture during 30 min. The nitrogen release was observed at 273–279 K for 1.5 h. Then 20 ml of water is added and 40 ml of methylene chloride is extracted. The extracts are washed by water and dried by anhydrous calcium chloride. After methylene chloride evaporation the residue is sustained at 253 K for 24 h for crystallization. The obtained solid phase is recrystallized from methanol and 2.2 g (46 %) of the compound **Ia** is obtained as yellow crystals with the melting point of 459 K. Found, %: N 6.09, Cl 15.64. $C_{11}H_{12}ClNO_2$. Calc., %: N 6.21, Cl 15.71.

The compound **Ib** is obtained according to the similar procedure.

3-(4-Acetylphenyl)-2-bromopropanamide **(IIa)**. The solution containing 4.6 g (0.021 mol) of 4-acetylphenyldiazonium bromide is added to 1.3 g (0.018 mol) of acrylamide and 0.5 g (0.002 mol) of copper(II) bromide dihydrate in 100 ml of water-acetone (1:3) mixture during 45 min. The nitrogen release was observed at 265–270 K for 1 h. The target product is extracted similar to the compound **Ia.** 3.1 g (62 %) of **IIa** is obtained as colorless crystals with the melting point of 450 K. Found, %: N 5.14, Br 29.47. $C_{11}H_{12}BrNO_2$. Calc., %: N 5.19, Br 29.58.

The compound **IIb** is obtained according to the similar procedure.

3-(4-Acetylphenyl)-2-thiocyanatopropanamide **(IIIa)**. 8.2 g (0.035 mol) of 4-acetylphenyldiazonium tetrafluoroborate are added to 2.4 g (0.034 mol) of acrylamide, 1.1 g (0.0035 mol) of copper(II) tetrafluoroborate hexahydrate and 3.4 g (0.035 mol) of potassium thiocyanate in 150 ml of water-acetone (1:3) mixture during 1 h. The nitrogen release was observed at 253–258 K for 2 h. The target product is extracted similar to the compound **Ia.** 6.4 g (76 %) of **IIIa** is obtained as colorless crystals with the melting point of 434 K. Found, %: N 11.31, S 12.99. $C_{12}H_{12}N_2O_2S$. Calc., %: N 11.28, S 12.91.

The compound **IIIb** is obtained in the similar way.

5-(4-Acetylbenzyl)-2-aminothiazol-4(5H)-one **(IVa).** 1.6 g (0.0064 mol) of 3-(4-acetylphenyl)-2-thiocyanatopropanamide **IIIa** are dissolved in 20 ml of dimethylformamide and 1 ml of triethylamine. The solution is boiled with a reflux condenser during 6 h. Then the reaction mixture is cooled to room temperature and extracted with 20 ml of diethyl ether. The extracts are washed by water and dried by anhydrous calcium chloride. After ether evaporation the obtained solid phase is recrystallized from methanol and 1.5 g (93 %) of the compound **IVa** is obtained as colorless crystals with the melting point of 488 K. Found, %: N 11.26, S 13.02. $C_{12}H_{12}N_2O_2S$. Calc., %: N 11.28, S 12.91.

The compound **IVb** is obtained in the similar way.

The yields, melting points and ^{1}H NMR spectra of 3-(4-acetylphenyl)-(2-methyl)-2-chloro(bromo, thiocyanato) propanamides **I–III** and 5-(4-acetylbenzyl)-2-amino-(5-methyl)thiazol-4(5*H*)-ones **IV** are represented in Table 1.

Table 1

Yields, melting points and ^{1}H NMR spectra of 3-(4-acetylphenyl)-(2-methyl)-2-chloro(bromo, thiocyanato)propanamides I–III and 5-(4-acetylbenzyl)-2-amino-(5-methyl)thiazol-4(5*H*)-ones IV

Compound	An	R	Yield, %	mp, K**	^{1}H NMR spectrum (*d*), ppm
Ia	Cl	H	46	459	7.84 d, 7.40 d (J = 8.2Hz) (4H, C_6H_4), 7.70 s, 7.27 s (2H, NH_2), 4.59 t (J = 7.6 Hz) (1H, CH(Cl)), 3.44 d.d, 3.22 d.d (J = 13.8 Hz) (2H, –C<u>H$_2$</u>–C_6H_4), 2.57 s (3H, $CH_3C(O)$)
Ib	Cl	CH_3	52	468	7.87 d, 7.42 d (J = 8.0Hz) (4H, C_6H_4), 7.69 s, 7.46 s (2H, NH_2), 3.48 d, 3.36 d (J = 13.2 Hz) (2H, –C<u>H$_2$</u>–C_6H_4), 2.56 s (3H, $CH_3C(O)$), 1.79 s (3H, CH_3)
IIa	Br	H	62*	450	7.89 d, 7.43 d (J = 8.4Hz) (4H, C_6H_4), 7.67 s, 7.25 s (2H, NH_2), 4.58 t (J = 7.4 Hz) (1H, CH(Br)), 3.42 d.d, 3.19 d.d (J = 14 Hz) (2H, –C<u>H$_2$</u>–C_6H_4), 2.56 s (3H, $CH_3C(O)$)
IIb	Br	CH_3	64*	418	7.89 d, 7.42 d (J = 8.4Hz) (4H, C_6H_4), 7.64 s, 7.49 s (2H, NH_2), 3.55 d, 3.45 d (J = 13 Hz) (2H, –C<u>H$_2$</u>–C_6H_4), 2.56 s (3H, $CH_3C(O)$), 1.75 s (3H, CH_3)
IIIa	SCN	H	76	434	7.92 d, 7.42 d (J = 7.6Hz) (4H, C_6H_4), 7.76 s, 7.48 s (2H, NH_2), 4.29 t (J = 7.8 Hz) (1H, CH(SCN)), 3.35 d.d, 3.18 d.d (J = 11.2 Hz) (2H, –C<u>H$_2$</u>–C_6H_4), 2.56 s (3H, $CH_3C(O)$)
IIIb	SCN	CH_3	81	441	8.01 s, 7.72 s (2H, NH_2), 7.98 d, 7.52 d (J = 8.4 Hz) (4H, C_6H_4), 3.53 d (J = 13 Hz), 3.45 d (J = 14 Hz) (2H, –C<u>H$_2$</u>–C_6H_4), 2.57 s (3H, $CH_3C(O)$), 1.48 s (3H, CH_3)
IVa	–	H	93	488	8.86 s, 8.64 s (2H, NH_2), 7.94 d, 7.48 d (J = 8.6 Hz) (4H, C_6H_4), 4.52 t (J = 8.2 Hz) (1H, CH), 3.39 d.d (J = 12.2 Hz), 3.09 d.d (J = 12.6 Hz) (2H, –C<u>H$_2$</u>–C_6H_4), 2.59 s (3H, $CH_3C(O)$)
IVb	–	CH_3	96	501	8.19 s, 7.94 s (2H, NH_2), 7.92 d, 7.38 d (J = 8.4 Hz) (4H, C_6H_4), 3.54 d (J = 15 Hz), 3.19 d (J = 14 Hz) (2H, –C<u>H$_2$</u>–C_6H_4), 2.57 s (3H, $CH_3C(O)$), 1.85 s (3H, CH_3)

Notes: *under Meerwein reaction conditions; **the compounds are recrystallized from methanol.

2.3. Microbiological Investigations

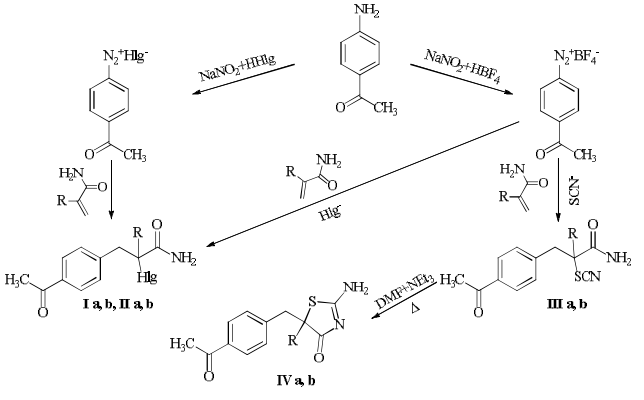
The antimicrobial activity of the synthesized compounds was determined using the method of serial dilutions in a liquid nutrient medium – meat peptone broth (MPB). At first 1% mother waters of the compounds in ethanol were prepared. Directly before the experiments they were dissolved in MPB from 1:10 to 1:320. The investigated bacterial suspension in the amount of 0.2 ml was brought in the test-tube with microbes' concentration of 10^5 in 1 ml according to McFarland. Germs were incubated at 310 K for 18–24 h and then the presence or absence of microorganisms' growth was observed. The least quantity of the compounds in the presence of which the culture growth was depressed we accepted as a minimum inhibitory concentration (MIC). Non-growing germs we put on meat peptone agar in Petri dishes and thus determined the minimum bactericidal concentration (MBC). For the control we used test tubes with the equivalent amount of ethanol.

Each experiment was repeated ten times. The results were statistically analyzed using Microsoft Excel computer programs.

3. Results and Discussion

3.1. Synthesis and Cyclization of 3-(4-Acetylphenyl)-(2-methyl)-2-chloro (bromo, thiocyanato)propanamides

3-(4-Acetylphenyl)-(2-methyl)-2-chloro(bromo, thiocyanato)propanamides **I-III** are obtained *via* interaction between 4-acetylphenyldiazonium salts and acrylic and methacrylic acids amides in the presence of chloride, bromide and rodanide anions. Halogenamides **I, II** are also synthesized under Meerwein reaction conditions (Scheme).



Hlg = Cl (**I**), Br (**II**); R = H (a), CH_3 (b)

Scheme

The reactions proceed in water-acetone (1:3) medium at 253–278 K in the presence of a catalyst – copper(II) tetrafluoroborate. The yields of halogen (thiocyanato)arylation products are 46–81 %. The yields of bromamides **II** are higher under Meerwein reaction conditions. The reactions are accompanied by the formation of 1-[4-chloro(bromo, isothiocyanato)phenyl] ethanones in the amount of 10–25 % to calculate for diazonium salt and resinoid compounds of undetermined structure.

It is known, that 2-thiocyanatoamides are useful reagents for 2-aminotiazol-4 (5*H*)-one synthesis. 5-(4-Acetylbenzyl)-2-amino-(5-methyl)thiazol-4(5*H*)-ones **IV** were obtained by cyclization of thiocyanatoamides **III** with boiling in DMF-triethylamine (10: 1) mixture. The yields of aminothiazolones **IV** under those conditions are approaching to quantitative.

3.2. Structure of Obtained Halogen(thiocyanato)amides and 2-Aminothiazol-4(5*H*)-ones

The structure of the products **I–IV** is in agreement with the data of IR- and ^{1}H NMR spectroscopy. In IR-spectra of the compounds **I–IV** we observe the absorption bands of carbonyl and amide groups at 1652–1680 and 3378–3404 cm^{-1}, respectively. Thiocyanatoamides **III** are additionally characterized by absorption bands of thiocyanate groups at 2152–2156 cm^{-1} which disappear after cyclization to 2-aminothiazole derivatives.

^{1}H NMR-spectra of halogen(thiocyanato)amides **I–III** (Table 1) contain signals of aromatic protons (two doublets in the region of 7.98–7.25 ppm) and acetyl group protons (singlets in the region of 2.59–2.56 ppm). Methylene group protons bounded with aromatic nuclei (compounds **Ia–IVa**) form two double doublets at 3.44–3.09 ppm and for the compounds **Ib–IVb** – two doublets at 3.55–3.19 ppm. Protons of NH_2-groups are characterized by two singlets at 8.86–7.25 ppm, protons of methenyl group (compounds **Ia–IVa**) – by triplets at 4.59–4.29 ppm, and protons of methyl groups (compounds **Ib–IVb**) – by singlets at 1.85–1.48 ppm.

3.3. Antimicrobial Activity of 3-(4-Acetylphenyl)-(2-methyl)-2-chloro (bromo, thiocyanato)propanamides and 5-(4-Acetylbenzyl)-2-amino-(5-methyl)thiazol-4(5*H*)-ones

We investigated the antimicrobial properties of 3-(4-acetylphenyl)-(2-methyl)-2-chloro(bromo, thiocyanato) propanamides **I–III** and 5-(4-acetylbenzyl)-2-amino-(5-methyl) thiazol-4(5*H*)-ones **IV** relative to bacteria *S.aureus* ATCC

6538, *B.subtilis* ATCC 6633, *E.coli* ATCC 25922, *P.aeruginosa* ATCC 9027 and fungus *C.albicans* ATCC 885-653.

The results show that the compounds **I–IV** have pronounced antimicrobial activity relative to the investigated test-microorganisms (Table 2).

The most sensitive to the investigated compounds are gram-positive bacteria *S.aureus*. Bromamides **IIa, b**, thiocyanatoamides **IIIa, b** and 2-aminothiazol-4(5*H*)-ones **IVa,b** have the bactericidal activity at minimum concentrations of 3.9–15.6 μg/ml. The cultures of gram-negative bacteria *E.coli* and spore-forming gram-negative bacillus *P.aeruginosa* are found to be the most stable ones.

The culture *B.subtilis* is the most sensitive toward the compounds **Ia** and **Ib** (MIC is 7.8 μg/ml). The similar activity of the mentioned compounds is observed relative to yeasts *C.albicans*. Other tested compounds have slight antimycotic activity with the concentrations of 31.2–62.5 μg/ml.

Table 2

Antibacterial and antimycotic activity 3-(4-acetylphenyl)-(2-methyl)-2-chloro(bromo, thiocyanato)propanamides I–III and 5-(4-acetylbenzyl)-2-amino-(5-methyl)thiazol-4(5*H*)-ones IV

Compound	An	R	Investigated microorganisms				
			S.aureus	*E.coli*	*C.albicans*	*B.subtilis*	*P.aeruginosa*
			MIC, μg/ml				
Ia	Cl	H	62.5	62.5	7.8	7.8	62.5
Ib	Cl	CH_3	31.2	31.2	15.6	7.8	62.5
IIa	Br	H	3.9	31.2	62.5	125.0	62.5
IIb	Br	CH_3	7.8	31.2	31.2	62.5	31.2
IIIa	SCN	H	15.6	62.5	62.5	31.2	62.5
IIIb	SCN	CH_3	7.8	62.5	62.5	62.5	125.0
IVa	–	H	15.6	31.2	62.5	62.5	62.5
IVb	–	CH_3	15.6	62.5	62.5	31.2	31.2

4. Conclusions

4-Acetylphenyldiazonium salts are suitable and high-reactive arylation agents for the reactions of diedia-zonation in the presence of unsaturated compounds and nucleophiles. This fact allows the introduction of reactive acetyl groups into the structure of anionarylation products.

The analysis of antimicrobial activity of the synthesized 3-(4-acetylphenyl)-(2-methyl)-2-chloro (bromo, thiocyanato)propanamides **I–III** and 5-(4-acetylbenzyl)-2-amino-(5-methyl)thiazol-4(5*H*)-ones **IV** shows the insignificant increase in their antibacterial and antomycotic activity compared with 2-halogen (thiocyanato)-(2-methyl)-3-phenylpropanamides [10, 11]. This regularity is caused most of all by the modification of aromatic nucleus *via* introducing the acetyl group.

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АРИЛЗАМІЩЕНІ ГАЛОГЕНО(ТІОЦІАНАТО)АМІДИ, ЩО МІСТЯТЬ 4-АЦЕТИЛФЕНІЛЬНИЙ ФРАГМЕНТ. СИНТЕЗ, ЦИКЛІЗАЦІЯ ТА ПРОТИМІКРОБНІ ВЛАСТИВОСТІ

Анотація. *Купрокаталітичним аніонарилюванням амідів акрилової і метакрилової кислот солями 4-ацетилфенілдіазонію синтезовані 3-(4-ацетилфеніл)-(2-метил)-2-хлоро (бромо, тіоціанато)пропанаміди. Циклізацією тіоціанатоамідів одержані арилзаміщені 2-амінотіазол-4(5H)-они з ацетофеноновим фрагментом. Досліджено протибактеріальну та протигрибкову активність синтезованих сполук.*

Ключові слова: *аніонарилювання, аміди акрилової і метакрилової кислот, солі 4-ацетилфенілдіазонію, 5-арилзаміщені 2-амінотіазол-4(5H)-они, протимікробна активність.*