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*Organic Chemistry*

# Synthesis and Study of [4-Imidazole-1-yl-Thiazole-2-yl)] Naphthylamines

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**ABSTRACT. New heterocyclic system 4-imidazole-1-thiazole-2-naphthylamine was synthesized by staged transformation of aminophenylnaphthalene. Oxo- and halogen-containing thiazonaphthylamine systems were synthesized and characterized as intermediate products. Preparative method of delivering 1-naphthylthiocarbamide and 4-bromo-1-naphthylthiocarbamide was worked out and optimal conditions for these reactions were determined. The condensation of 1-naphthylthiocarbamide and 4-bromo-1-naphthylthiocarbamide with ethyl bromine of acetate was also conducted with formation of relevant products 2-(naphthylamine)thiazole-4-one and 2-(4-bromonaphthylamine)thiazole-4-on. The optimal conditions of the cyclization reactions were also determined. Reactions of chlorinating 2-(naphthylamine)thiazole-4-on and 2-(4-bromnaphthylamine)thiazole-4-on with phosphorus oxychloride were carried out. It has been established that productivity of chlorinating reaction is the highest for initial Oxy compounds phosphorus oxychloride and pyridine in case when taken in equimolar correlation. The structure of the final compound [4-(imidazole-1-yl)thiazole-2–yl)]naphthylamine has been defined on the basis of spectrum analysis.** *© 2019 Bull. Georg. Natl. Acad. Sci.*

**Key words**: naphthylamine, thiazole, cyclization reactions

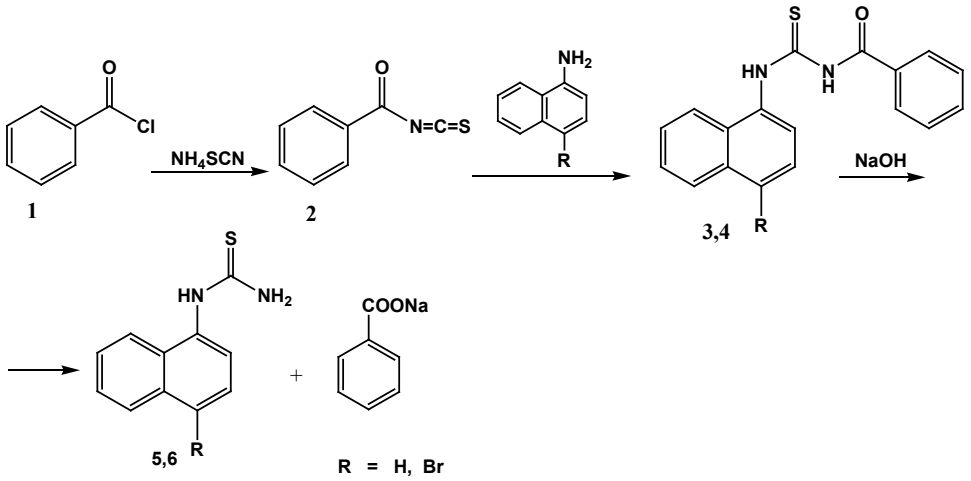
The synthesis of new naphthalene ring containing biologically active compounds, which consists of different heterocycles, was carried out by us. In particular, new thiazonaphthylamine containing imidazole ring, we synthesized by step transformation of aminophenylnaphthalenes. Thiazonaphthylamines, oxo- and halogen-containing systems are characterized as intermediate products, which in turn are interesting because of their structural likeness to other, well- known biologically active compounds [1-4].

Synthesis of target diheterocyclic systems containing thiazole ring represents four-step reaction. 1-Aminonaphthalene and 4-bromo-1-aminonaphthalene were chosen as initial substances.

Our goal on the first stage was to obtain naphthylen thiocarbamide. From publications we are aware of two ways of obtaining thiocarbamide from aromatic amines: one staged- and multistaged methods of synthesis [5]. We used both these ways.

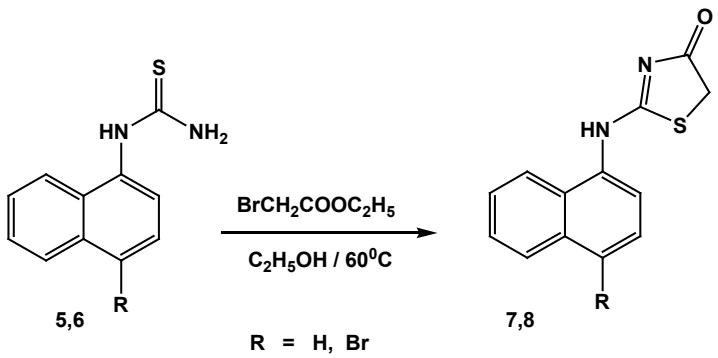
It turned out that in case of 1-aminonaphthalene the one-step reaction is characterized with low efficiency compared to the mentioned in publications substituted anilines. This can be explained, on the one hand, by weak basic nature of 1-aminonaphthalene in comparison with aniline ($pk_a$ 1-aminonaphthalene =3.92, $pk_a$ aniline=4.6 at 25 $^0$C). On the other hand, it might be the reason of steric hindrance of the large naphthalene ring.

In order to increase the yield of naphthylene thiocarbamide the reaction was conducted step by step (scheme 1). First intermediate product benzoyl thiocyanate (2) was synthesized by interaction of benzoyl chloride (1) and ammonium rhodanate in acetone medium. Then by interaction of benzoyl thiocyanate with aminonaphthalene (in molar correlation 1:1) and by alkaline hydrolysis of the obtained 1-benzoyl-(3-naphthylene-1-yl)thiocarbamide (3,4) the corresponding naphthylthiocarbamide (5) and 4-bromonaphthylen thiocarbamide (6) was isolated with corresponding yield 93 %, 89 %. The structure of the products obtained was determined by electronic spectra.




**Scheme 1.** Synthesis of naphthylene thiocarbamide.

The following stage of the synthesis was cyclization (scheme 2) of naphthalene thiocarbamide (5,6). Ethyl bromoacetate was used as cyclization agent. Reaction was conducted at temperature of 80$^0$C in absolute ethanol medium; oxo compounds (7,8) are obtained with 60% yield.




**Scheme 2.** Cyclization reaction of naphthalene thiocarbamide.

On the third stage of the work desoxychlorination was carried out. There are many descriptions of such cases in publications. As most of them are characterized with low outcomes, our aim was to find out optimal conditions of desoxychlorination reactions in order to increase the yield.

We carried out desoxychlorination experiment changing concentration of reacting substances, temperature and the time of the reaction (7,8). The outcome of the end product was still low in all cases.

By heating 7,8 substance and $POCl_3$ mixture at the presence of pyridine at 60 $^0$C with ratio 1:1:1, the end product (9,10) was obtained with 20% yield.

By heating the 7,8 substance and $POCl_3$ mixture at 140 $^0$C in soldered ampule for 8 hours at the presence of pyridine with an equivalent ratio there in the reactive mixture an initial substance appeared, the degree of resinizing increased causing problem in extraction of product due to its low yield. We were unsuccessful in increasing the yield even when we replaced pyridine with N, N-dimethylaniline.

It is known from publications that reactions of desoxychlorination are conducted in phosphorus oxychloride without base. In our case even in likewise conditions we got resinous mass and final product was formed only as a trace.

From our point of view above mentioned results can be explained by the fact that in case of exceeding amount of phosphorus oxychloride we may get an intermediate products o-phosphate as well as dimer (0,0)-phosphate [6]. Most probably resinous mass represents the mixture of above-mentioned substances.

Based on the results of experiments we may conclude that:

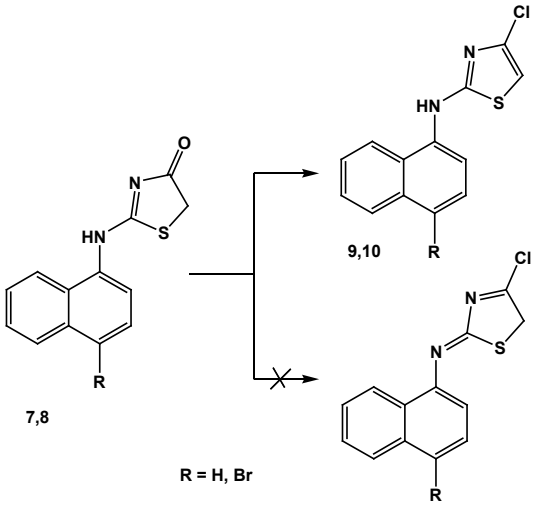
1. Rising temperature has negative impact on productivity of the given reaction;

2. Changing the base does not affect the yield;

3. Desoxychlorination without use of base do not increase productivity probably because of the production of accompanying products, due to creation of dimer.

It is known from the literature that the structure like 7, 8 can be characterized as amino-immune-tautomerism.

Therefore, it was to be expected that desoxychlorination reaction would go in two different ways (scheme 3). To establish the structure of synthesized compounds 9, 10 the nuclear magnetic resonance data were used.

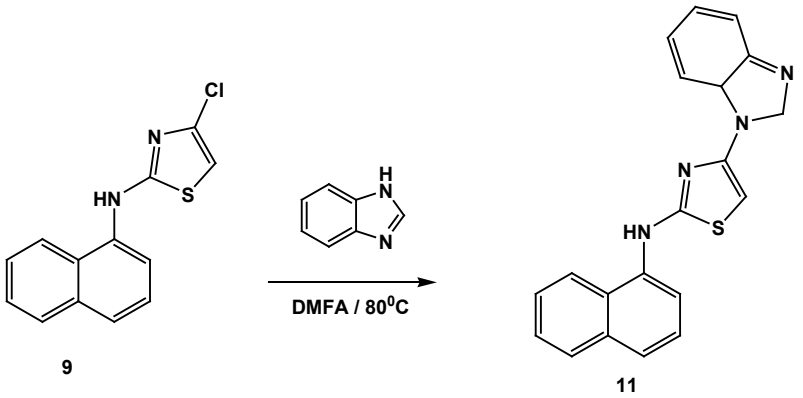



**Scheme 3.** Reaction of desoxychlorination.

On molecular diagram of nuclear magnetic resonance of excreted compound **10**, it is clearly visible that singlet signal 10.33 ppm corresponds to NH group of protons. Singletary signal 6.81 ppm corresponds to one proton in thiazole ring. Multiplet signal of spectrum in aromatic area 7.50-8.20 ppm belongs to the fragments of naphthalene protons.

Based on the spectrum analyses data we may conclude that structure of product obtained by us is in accordance with substance amino structure. In case of existence of amino structure on diagram there should not be fixation of a pick corresponding to protons of NH groups on weak area of field and at the same time, instead of one singlet signal of proton in ring of thiazole there should be two proton singlet signals.

On the last stage of synthesis, we conducted the process of condensation with Benzimidazole (9) according to scheme 4.




**Scheme 4.** Reaction of condensation of compound 9 with Benzimidazole.

The reaction was proceeding in dimethylformamide medium at temperature $80^0$C for 24 hours at constant mixing and resulted in reaching 73% yield of the end product (11).

## Experimental part

Chemical Procedures: general. NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer at 300 K, using TMS as an internal standard. IR spectra (KBr) were measured with a Bruker Tensor 27 spectrometer.

**Naphtylaminothiazole-4-ones (7-8). General Procedure**. The Naphthylthiocarbamides (27 mmol) were dissolved in 90 ml of ethanol pa at 45°C. To this solution ethyl bromoacetate (35 mmol) was added, and the mixture was stirred at this temperature for 2 h. After cooling to room temperature, the mixture was neutralized with aqueous ammonia. Dropwise addition of water when stirring led to precipitation of the product, which was removed by filtration and dried.

**2-(naphthylene-1-yl-amino)thiazole-4-one (7).** Yield: 46%, white crystals. Mp: 186-$189^0$C . $R_f$= 0,44 (Hexsane: diethyl ether 1:2). IR (KBr, ν, $cm^{-1}$) 3441, 1300 (N-H), 3122 (C-H), 1670 (C=O), 1549 (C=N), 1H NMR (DMSO-d6): δ (ppm) )11.97 (s, 1H), 7.91(trip, 2H, J= 7.8; J= 8.2), 7.70 (d, 1H, J=8.2 ), 7.55-7.45 (m, 3H), 7.05 (d, 1H, J=7.16), 3.97 (s, 1H). $^{13}$C-NMR (400 MHz, $CDCl_3$): 175.22; 126.44; 134.38; 128.41; 127.57; 126.88; 126.44; 126.26; 124.82; 123.45; 116.44; 34.78

**2-(4-bromonaphthylene-1-yl-amino)thiazole-4(5H)-one (8).** Yield: 49%, white crystals. Mp: 160-$164^0$C. $R_f$=0.7 (diethyl ether ). IR (KBr, ν, cm-1) 3453, 1288 (N-H), 3194 (C-H), 1670 (C=O), 1549 (C=N). 1H NMR (DMSO-d6): δ (ppm) )9.80 (s, 1H), 8.15 (d, H, J=7.76), 7.95(d, H, J= 7.96), 7.74-7.66 (m, 3H),

7.4 (d, H J=7.96), 3.97 (s, H). $^{13}$C-NMR (400 MHz, $CDCl_3$): 145.4; 135.40; 97.8; 94.79; 94.08; 92.85; 91.05; 90.25; 89.74; 88.90; 86.72; 83.03.

**4-chlor-n-(naphthylene-1-yl)thiazole-2-amines (9-10). General procedures.** A mixture of the appropriate Naphtylaminothiazole -4one (4.8 mmol), 3 ml of $POCl_3$, and 0.4 ml of pyridine was refluxed for 3 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in ether, and the solution was washed twice with 5% aqueous NaOH, brine, and water. The solvent was dried ($Na_2SO_4$) and removed under reduced pressure. The crude product was purified by column chromatography.

**4-chlor-n-(naphthylene-1-yl) thiazole-2-amine (9).** Yield: 20%, white crystals. Mp: 139$^0$C $R_f$ =0,4 (hexane : diethyl ether 1:1 ). 1H NMR (DMSO-d6): δ (ppm) )10.33 (s, 1H), 8.20-8.18 (m, H) 8.00(d, H, J= 7.28), 7.96-7.94 (m, H), 7.72 (d, H J=8.2), 7.57-7.50 (m, 3H), 6.81 (s, H). $^{13}$C-NMR (400 MHz, $CDCl_3$): 174.63; 143.91; 133.84; 127.87; 127.03; 126.35; 125.74; 124.33; 122.90; 115.97; 34.75.

**N-(4-bromonaphthylene-1-yl)-4-chlorthiazole-2-amine (10).** Yield: 21%, white crystals. Mp: 96-98$^0$C. $R_f$=0.7 (diethyl ether). 1H NMR (DMSO-d6): δ (ppm) )11.38 (s, 1H), 8.23(d, H, J= 7.28), 7.96-7.94 (m, H), 7.72 (d, H J=8.2), 7.55-7.32 (m, 3H), 6.44 (s, H). $^{13}$C-NMR (400 MHz, $CDCl_3$): 174.63; 143.91; 133.84; 127.87; 127.03; 126.35; 125.74; 124.33; 122.90; 115.97; 34.75.

**Synthesis of target derivates (11).** The appropriate (4-Chlor-N-(Naphthylene-1-yl) thiazole-2-amine (3.6 mmol) and the benzimidazole (18 mmol) were stirred in 7.5 ml of DMF at 80°C for 2-8 days (TLC control). The mixture was cooled to room temperature and poured into 300 ml of 5% aqueous $Na_2CO_3$. The crude product was filtered off, dried, and purified by column chromatography ($SiO_2$, ethyl acetate). Yield: 73%, white crystals. Mp: 196$^0$C. $R_f$=0.43 (diethyl ether:hexane ). 1H NMR (DMSO-d6): δ (ppm) ) 10.51 (s, 1H), 8.28 (s, 1H), 7.75 (s, 1H), 7.64 (d, 2H), 7.36 (t, 2H), 7.08 (s, 1H), 6.97 (m, 2H) 6.50 (s, 1H); 6.41 (s, 1H); 5.78 (s, 1H); 3.0 (s, 2H). $^{13}$C-NMR (400 MHz, $CDCl_3$): 174.63; 143.91; 134.67; 133.84; 130.50; 128.15; 127.87; 127.03; 126.35; 126.26; 125.90; 125.74; 124.33; 122.90; 120.47; 119.67; 115.97; 34.75.

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*ორგანული ქიმია*

# [4-(იმიდაზოლ-1-ილ)თიაზოლ-2-ილ)] ნაფთილამინების სინთეზი და კვლევა

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ამინოფენილნაფთალინების საფეხურებრივი გარდაქმნით სინთეზირებულია იმიდაზოლის ბირთვის შემცველი ახალი ჰეტეროციკლური სისტემა – [4-(იმიდაზოლ-1-ილ)თიაზოლ-2-ილ]ნაფთილამინი. შუალედური პროდუქტების სახით სინთეზირებული და დახასიათებულია თიაზო-ნაფთილამინის ოქსო- და ჰალოგენის შემცველი სისტემები. დამუშავებულია 1-ნაფთილენთიოშარდოვანას და 4-ბრომ-1-ნაფთილენთიოშარდოვანას მიღების პრეპარატული მეთოდი. დადგენილია რეაქციის მიმდინარეობის ოპტიმალური პირობები. ჩატარებულია 1-ნაფთილენთიოშარდოვანასა და 4-ბრომ-1-ნაფთილენთიოშარდოვანას კონდენსაცია ეთილბომაცეტატთან შესაბამისი 2-(ნაფთილამინო)თიაზოლ-4-ონისა და 2-(4-ბრომნაფთილამინო)თიაზოლ-4-ონის წარმოქმნით. დადგენილია ციკლიზაციის რეაქციის ოპტიმალური პირობები. ჩატარებულია 2-(ნაფთილამინო)თიაზოლ-4-ონისა და 2-(4-ბრომნაფთილამინო)თიაზოლ-4-ონის ქლორირების რეაქციები ფოსფორის ოქსიქლორიდით. დადგენილია, რომ ქლორირების რეაქციის გამოსავლიანობა საუკეთესოა საწყისი ოქსონაერთების, ფოსფორის ოქსიქლორიდისა და პირიდინის ეკვიმოლური თანაფარდობით აღების შემთხვევაში. მიღებული პროდუქტის, [4-(იმიდაზოლ-1-ილ)თიაზოლ-2-ილ)]ნაფთილამინის, სპექტრული ანალიზის საფუძველზე დადგენილია მიღებული ნაერთის აღნაგობა.

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