ISSN 1027-5495. Functional Materials, 28, No.2 (2021), p. 301-307.
doi:https://doi.org/10.15407/fm28.02.301

Prospective biologically active compounds based on 5-formylthiazole

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Received January 25, 2021

Thiazole cycle is a structural element of many compounds which have potential or already proven fungicidal, bactericidal and antiviral activity. A number of compounds and materials with promising antimicrobial effects can be functionalized by introducing the thiazole component into their composition. Among them, there are photoreactive materials, complexing agents, convenient building blocks for the synthesis of biologically active compounds etc. We have developed a number of synthetic approaches, as well as optimized conditions for obtaining new thiazole-containing compounds, which have the prospect of practical application based on their physicochemical properties and potential biological activity.

Keywords: thiazole, pyrimidine, benzimidazole, chalcone, amidine.

Перспективні біологічно активні сполуки на основі 5-формілтіазолу. *В.М.Котляр, О.О.Коломойцев, Д.О.Тарасенко, Є.Г.Бондаренко, С.В.Бутенко, О.В.Буравов, М.І.Котляр, О.Д.Рошаль.*

Тіазольний цикл є структурним елементом багатьох сполук, що мають як потенційну, так і доказану фунгіцидну, бактерицидну та противірусну дії. Багато перспективних сполук та матеріалів на їх основі можуть бути функціоналізованими за рахунок введення тіазольного компонента до їх складу. Серед них є фотореактивні матеріали, комплексоутворювачі, зручні білдинг-блоки для синтезу біологічно активних сполук, тощо. У даній роботі розроблено низку синтетичних підходів та оптимізовано умови одержання нових тіазол-вмисних сполук, які мають перспективу практичного застосування на основі їх фізико-хімічних характеристик і потенційної біологічної активності

Тиазольный цикл является структурным элементом многих соединений, имеющих как потенциальную, так и фунгицидное, бактерицидное и противовирусное действия. Многие перспективные соединения и материалы на их основе могут быть функционализированы за счет введения тиазольного компонента в их состав. Среди них есть фотореактивные материалы, комплексообразователи, удобные билдинг-блоки для синтеза биологически активных соединений, и тому подобное. В данной работе разработан ряд синтетических подходов и оптимизированы условия получения новых тиазольных соединений, которые имеют перспективу практического применения на основе их физико-химических характеристик и потенциальной биологической активности.

1. Introduction

Thiazole cycle is an element of many functional materials that are of practical interest to researchers due to their biological activity as well as their physicochemical characteristics. There were obtained, for example, promising triazole dendrimers [1] with interesting photophysical and electrochemical properties; flavonoid derivatives demonstrating pronounced anticancer action [2]; 1-formyl-, 1-acetyl- and 1-arylpyrazolines having biological activity of a fairly wide range [3]; various antibacterial azoles [4]; analogs of chalcones, which are promising as ligands for the determination of β-amyloid plaques in brain [5], etc. Among thiazole-containing compounds, there are also prospective fungicidal and bactericidal drugs [6], compounds with anti-inflammatory and anti-cancer properties. It should be noted that all these compounds are obtained based on carbonyl thiazoles and their derivatives – α,β-unsaturated ketones. Using such a synthetical way, various pyrazolines, pyrazoles, oxazoles, isoxazoles, diketones, and other promising compounds having practically important physicochemical and biological properties were synthesized.

Well-known and quite convenient approaches to synthesis of thiazole ring are intermolecular cyclocondensation reactions. In work [7], a synthetic approach to the assembly of thiazole nucleus based on thiosemicarbazides was presented. Another method is cyclocondensation of thiourea with various agents. Thus, the authors of research [4] obtained corresponding 2-amino-4-acetyl derivatives, using the chalcone analogs as an intermediate product which was further modified in several parallel directions: to pyrazolines, pyrazoles, oxazoles, isoxazoles, and the like.

One of the classical approaches to synthesis of α,beta-unsaturated ketones is the Claisen-Schmidt condensation. Using this reaction, the authors of work [8] obtained series of α,beta-unsaturated ketones based on 2,4-disubstituted 5-formylthiazole derivatives, and then, described their physicochemical and spectral properties. In the same way, the authors of another research [2] synthesized chalcone analogs ongoing from 2-hydroxyacetophenone with further cyclization to the corresponding flavones in order to study the anticancer effect of the obtained compounds. Acetyl derivatives introduced into condensation with esters lead to obtaining corresponding diketones [9]. Condensation of the latter with hydrazine derivatives, as well as in the case of the above-mentioned analogs of chalcone [6], results in corresponding pyrazole derivatives, allowing thus to bypass the stage of obtaining the intermediate pyrazolines. This leads to increase in the total yield of the discussed multi-stage process. The pyrazole derivatives thus obtained were investigated for their inhibitory ability against 15-lipoxygenase. It should be noted that N-arylpyrazoles showed high selectivity and also proved to be promising dual inhibitors of cyclooxygenase.

One of the ways of synthesis of nitrogen-containing heterocyclic compounds is heterocyclization of chalcone derivatives with the participation of appropriate binucleophilic reagents. The classic approach of this kind is condensation of chalcones with formamide, which leads to the formation of pyrimidine nucleus [10]. It was also shown [11] that aliphatic unsaturated carbonyl compounds are quite suitable starting compounds for intermolecular cyclocondensation reactions with various amides. The series of compounds obtained demonstrate anti-cancer and anti-inflammatory effects whose activity is comparable to the known drugs colchicine and comBrestatin [12]. The authors of work [13] based on α,beta-unsaturated ketones obtained a number of pyrazoline, pyridine and pyrimidine analogues of 1,3,5-triazine, which were then tested for antibacterial activity. Pyrimidine derivatives showed the best results within the studied series of compounds.

A modified approach to heterocyclization was described in [14]: the interaction of guanidine with α,beta-unsaturated ketones resulted in 2-aminopyrimidines having quite interesting optical properties. An efficient synthetic route through condensation of amidines with unsaturated aliphatic carbonyl compounds was suggested in paper [15]. Such a condensation way can lead to the formation of both the corresponding pyrimidines and their derivatives – imidazoles. It should be noted that such diazaheterocycles are convenient building blocks due to introduction of amino group in the early stages of the synthesis; it is important that the temporary chemical protection of the amino group is critical under the conditions of all following transformations. An alternative approach to the synthesis of the pyrimidine ring based on heterocyclic polyacids was described in works [12, 16],

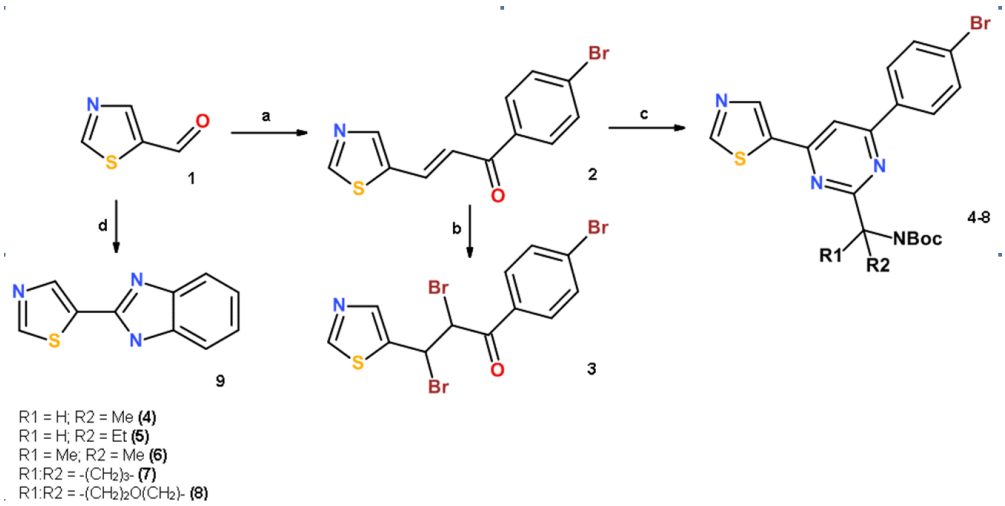

Fig. 1. General scheme of synthesis of derivatives 2-9. a) 4-Br-acetophenone, KOH, MeOH, r.t., 12h; (b) Br2, $CH_3COONa*3H_2O$, CH_3COOH, US, 1h; (c) amidine, pyridine, 100°C, 24h; (d) o-phenylenediamine, $Cu(CH_3COO)_2$, i-PrOH, reflux, 12h.

and a probable mechanism of cyclocondensation was suggested.

Thiazole derivatives of benzimidazole occupy a prominent place among the promising materials with biologically active properties based on nitrogen-containing heterocyclic compounds. The thiazole analog, 2-(thiazol-4-yl) benzimidazole, has been available under the trade name thiabendazole for more than half a century. Recently, both thiabendazole and its N-methyl analog have been studied as ligands in complexion with Iridium (III) ions [17]. Obtained complexes demonstrated interesting electrochemical and photophysical properties and were recommended as prospective electroluminescent materials.

Recently, our research group has proposed several synthetic approaches to preparation of the new compounds based on 5-formylthiazole 1. First, it is the Claisen-Schmidt condensation, the classical method of the synthesis of α,beta-unsaturated ketones. These compounds can be further undergone various chemical modifications at the propenone fragment. For this purpose, the obtained analog of chalcone 2 was reacted with bromine, which led to production of the corresponding diBromide 3 by the modified method. Obtaining α,beta-dibromopropanone 3 proved the possibility of synthesis of systematic series of unsaturated ketone derivatives based on 5-formylthiazole, which do not contain substituents in positions 2 and 4, without Bromination of the thiazole ring. Next, propenone 2 was introduced into a number of the intermolecular cyclocondensation reactions with various β-aminoamidines. Thus, we obtained several suitable pyrimidines 4-8 by the simple method without formation of by-products and with high yields. In addition, the starting aldehyde 1 was condensed with ortho-phenylenediamine to give the corresponding benzimidazole 9. The proposed approach proved to be quite simple and accessible for reproduction. Thus, we were able to develop significantly simpler and more efficient synthetic routes and to optimize the conditions for obtaining a number of promising derivatives based on 5-formylthiazole.

2.Experimental

Melting points of all synthesized compounds were determined with the Gallenkamp melting point apparatus in open capillary tubes. The reaction progress and chemical purity of the synthesized compounds were controlled using TL C Polychrom SI F254 plates. ^1H and ^{13}C NMR spectra were registered using DMSO-d6 on Bruker Avance 400 spectrometer. LC/M S spectra were recorded by Agilent 1100 L C MSD SL instrument, column SUPEL C O Ascentis Express C18. Ultrasonic activation was performed using an ultrasonic bath Bandelin DT 156 BH.

All commercially available starting materials were provided by Enamine Ltd, Kiev, Ukraine.

1- (4-bromophenyl) -3-thiazol-5-yl-prop-2-en-1-one (2).

40% aqueous solution of KOH was added dropwise to a mixture of solutions of 5-formylthiazole (1) (1.13 g, 0.01 mol) in MeOH (20 mL) and 4-Br-acetophenone (1.99 g, 0.01 mol) in MeOH (20 mL) until the color stopped changing. The reaction mixture was stirred for 12 hours, after which the precipitate formed was filtered off, washed with 10 mL of MeOH and recrystallized from EtOH. Yield 2.49 g (84.7%), yellow powder, mp 133–135°C. ^{1}H NMR spectrum, δ, ppm: 7.65 (1H, d, J = 15.3 Hz); 7.78 (2H, d, J = 8.6 Hz); 8.02 (1H, d, J = 15.3 Hz); 8.06 (2H, d, J = 8.6 Hz); 8.43 (1H, s); 9.25 (1H, s). ^{13}C NMR spectrum, δ, ppm: 123.7; 127.5; 130.6; 131.9; 134.0; 135.2; 136.1; 148.2; 157.3; 187.7. Mass spectrum, m/z ($I_{rel.}$., %): 292(95), 293(15), 294(100), 295(14), 296(5). Found, %: C 49.04; H 2.71; Br 27.06; N 4.85; O 5.39; S 10.95. $C_{12}H_8BrNOS$. Calculated, %: C 48.99; H 2.74; Br 27.16; N 4.77; O 5.44; S 10.90.

2,3-Dibromo-1- (4-bromophenyl) -3-thiazol-5-yl-propan-1-one (3).

1-(4-bromophenyl)-3-thiazol-5-yl-prop-2-en-1-one (2) (2.94 g, 0.01 mol) was dissolved in CH_3COOH (40 mL), and then $CH_3COONa \cdot 3H_2O$ (1.36 g, 0.01 mol) was added. The resulting mixture was placed in an ultrasonic bath and Br2 (4.8 g, 0.03 mol) was added dropwise. After adding the entire amount of bromine, the reaction mixture was kept for another 1 hour in an ultrasonic bath. Then, the precipitate formed was filtered, washed with 20 ml of water, and dried in vacuum. Yield 4.4 g (96.7%), yellow powder, mp 142–143°C. ^{1}H NMR spectrum, δ, ppm: 6.35 (1H, d, J = 10.9 Hz); 6.65 (1H, d, J = 10.9 Hz); 7.87 (2H, d, J = 8.6 Hz); 8.21 (2H, d, J = 8.6 Hz); 8.34 (1H, s); 9.25 (1H, s).^{13}C NMR spectrum, δ, ppm: 43.4; 50.6; 128.4; 128.9; 132.1; 132.3; 135.3; 143.5; 153.0; 188.6. Mass spectrum, m/z ($I_{rel.}$., %): 450(14), 452(47), 453(8), 454(44), 455(6), 456(21), 457 (3). Found, %: C 31.86; H 1.73; Br 52.88; N 3.12; O 3.43; S 6.98. $C_{12}H_8Br_3NOS$. Calculated, %: C 31.75; H 1.78; Br 52.80; N 3.09; O 3.52; S 7.06.

Pyrimidines 4-8 synthesis.

General method. 1-(4-bromophenyl)-3-thiazol-5-yl-prop-2-en-1-one (2) (2.94 g, 0.01 mol) was dissolved in pyridine (30 mL), and the corresponding amidine was added to the solution. The reaction mixture was kept at 100° C for 24 hours. The solvent was then evaporated under reduced pressure, and the oily residue was dissolved in ethyl acetate (20 mL). The insoluble solid was filtered off, the filtrate was washed with saturated aqueous NaCl (3 x 20 mL), dried over anhydrous Na_2SO_4, and then the solvent was evaporated under reduced pressure. The solid residue was washed with hexane (20 mL).

Tert-butyl N-[1-[4-(4-bromophenyl)-6-thiazol-5-yl-pyrimidin-2-yl]ethyl]carbamate (4).

Yield 4.05 g (87.9 %), light grey powder, mp 178–180°C. ^{1}H NMR spectrum, δ, ppm: 1.42 (9H, s); 1.46 (3H, d, J = 7.3 Hz); 4.73 (1H, m); 7.26 (1H, bs); 7.81 (2H, d, J = 8.6 Hz); 8.32 (2H, d, J = 8.6 Hz); 8.54 (s, 1H); 9.02 (s, 1H); 9.30 (s, 1H).^{13}C NMR spectrum, δ, ppm: 20.1; 28.3; 52.2; 77.8; 125.2; 129.3; 131.9; 135.3; 138.2; 144.6; 155.5; 158.2; 162.7; 163.0. Mass spectrum, m/z ($I_{rel.}$., %): 459(82), 460(15), 461(100), 462(14), 463(7), 464(1). Found, %: C 52.01; H 4.51; Br 17.39; N 12.09; O 7.04; S 6.96. $C_{20}H_{21}BrN_4O_2S$. Calculated, %: C 52.07; H 4.59; Br 17.32; N 12.14; O 6.94; S 6.94.

Tert-butyl N-[1-[4-(4-bromophenyl)-6-thiazol-5-yl-pyrimidin-2-yl]propyl]carbamate (5).

Yield 4.08 g (85.9 %), light grey powder, mp 135–140°C. ^{1}H NMR spectrum, δ, ppm: 0.95 (3H, t, J = 7.4 Hz); 1.39 (9H, s); 1.79 - 1.73 (1H, m); 1.95 - 1.89 (1H, m); 4.55 (1H, m); 7.27 (1H, d, J = 8.0 Hz); 7.81 (2H, d, J = 8.6 Hz); 8.33 (2H, d, J = 8.6 Hz); 8.56 (1H, s); 9.03 (1H, s); 9.31 (1H, s).^{13}C NMR spectrum, δ, ppm: 27.1; 28.3; 58.2; 77.8; 109.7; 125.2; 129.4; 131.9; 135.3; 138.2; 144.6; 155.8; 158.0; 158.2; 162.6. Mass spectrum, m/z ($I_{rel.}$., %): 473(95), 474(22), 475(100), 476(22), 478(7). Found, %: C 53.01; H 4.99; Br 16.88; N 11.71; O 6.73; S 6.68. C2^{1}H23BrN4O2S. Calculated, %: C 53.06; H 4.88; Br 16.81; N 11.79; O 6.73; S 6.73.

Tert-butyl N-[1-[4-(4-bromophenyl)-6-thiazol-5-yl-pyrimidin-2-yl]-1-methyl-ethyl]carbamate (6).

Yield 4.27 g (89.9 %), light grey powder, mp 174–175°C. ^{1}H NMR spectrum, δ, ppm: 1.32 (9H, bs); 1.61 (6H, s); 7.27 (1H, m); 7.81 (2H, d, J = 8.6 Hz); 8.30 (2H, d, J = 8.6 Hz); 8.52 (1H, s); 9.01 (1H, s); 9.29 (1H, s).^{13}C NMR spectrum, δ, ppm: 27.8;

28.3; 77.4; 108.9; 125.0; 129.2; 131.9; 135.6; 138.6; 144.3; 154.6; 157.8; 158.0; 162.4. Mass spectrum, m/z ($I_{rel.}$., %): 473(100), 474(30), 475(95), 476(31), 477(8). Found, %: C 53.16; H 4.96; Br 16.76; N 11.73; O 6.66; S 6.73. $C_{21}H_{23}BrN_4O_2S$. Calculated, %: C 53.06; H 4.88; Br 16.81; N 11.79; O 6.73; S 6.73.

Tert-butyl N-[1-[4-(4-bromophenyl)-6-thiazol-5-yl-pyrimidin-2-yl]cyclobutyl]carbamate (7).

Yield 4.23 g (86.2 %), light grey powder, mp 159–163°C. ^{1}H NMR spectrum, δ, ppm: 1.37 (9H, s); 2.06 (2H, m); 2.39 (2H, m); 2.69 (2H, m); 7.68 (1H, bs); 7.82 (2H, d, J = 8.6 Hz); 8.33 (2H, d, J = 8.6 Hz); 8.54 (1H, s); 9.03 (1H, s); 9.30 (1H, s).^{13}C NMR spectrum, δ, ppm: 15.2; 25.5; 27.8; 28.3; 32.8; 60.4; 77.5; 108.9; 125.1; 129.2; 131.9; 135.6; 138.6; 144.4; 154.8; 157.9; 158.0; 162.4; 173.0. Mass spectrum, m/z ($I_{rel.}$., %): 485(82), 486(28), 487(100), 488(28), 489(9). Found, %: C 54.24; H 4,71; Br 16.39; N 11.56; O 6.62; S 6.48. $C_{22}H_{23}BrN_4O2S$. Calculated, %: C 54.21; H 4.76; Br 16.39; N 11.49; O 6.57; S 6.58.

Tert-butyl N-[3-[4-(4-bromophenyl)-6-thiazol-5-yl-pyrimidin-2-yl]tetrahydrofuran-3-yl]carbamate (8).

Yield 4.22 g (83.9 %), light grey powder, mp 164–166°C. ^{1}H NMR spectrum, δ, ppm: 1.36 (9H, s); 2.33 (1H, m); 2.66 (1H, m); 3.95 (1H, m); 4.01 (1H, m); 4.18 (1H, m); 4.30 (1H, m); 7.70 (1H, bs); 7.83 (2H, d, J = 8.6 Hz); 8.31 (2H, d, J = 8.6 Hz); 8.56 (1H, s); 9.03 (1H, s); 9.30 (1H, s).^{13}C NMR spectrum, δ, ppm: 26.0; 28.8; 67.8; 68.2; 78.1; 78.4; 109.7; 125.7; 129.8; 132.4; 135.8; 138.8; 145.1; 158.5; 158.7; 163.0. Mass spectrum, m/z ($I_{rel.}$., %): 501(92), 502(25), 503(100), 504(26), 505(8). Found, %: C 52.54; H 4.52; Br 15.97; N 11.01; O 9.54; S 6.42. $C_{22}H_{23}BrN_4O_3S$. Calculated, %: C 52.49; H 4.60; Br 15.87; N 11.13; O 9.54; S 6.37.

5-(1H-Benzimidazol-2-yl)thiazole (9).

A solution of 5-formylthiazole (1) (1.13 g, 0.01 mol) in 30 mL of isopropanol was mixed with 70 mL of aqueous solution of $Cu(CH_3COO)_2$ (1.82 g, 0.01 mol). Then o-phenylenediamine (1.08 g, 0.01 mol) was added to the resulting mixture. The reaction mixture was refluxed for 2 hours, and then chilled to room temperature. The precipitate was filtered off and immediately placed in i-PrOH (25 mL). Then H2 S was passed through the resulting suspension for 15 minutes. The resulting reaction mixture was filtered, the solution was evaporated under reduced pressure, and the residue was recrystallized from i-PrOH. Yield 1.87 g (92.6%), Brown-gray powder, mp 215–220° C dec. ^{1}H NMR spectrum, δ, ppm: 7.23 (2H, m); 7.59 (2H, m); 8.58 (1H, s); 9.23 (1H, s); 13.15 (1H, bs).^{13}C NMR spectrum, δ, ppm: 115.1; 118.5; 123.3; 123.6; 133.7; 135.5; 137.5; 137.7; 144.2; 152.1. Mass spectrum, m/z ($I_{rel.}$., %): 202(100), 203(10), 204(8). Found, %: C 59.80; H 3.44; N 20.79; S 15.97. $C_{10}H_7N_3S$. Calculated, %: C 59.68; H 3.51; N 20.88; S 15.93.

3. Results and discussion

The Claisen-Schmidt condensation applied to 5-formylthiazole and 4-Br-acetophenone occurred by usual way, although the nature of thiazole cycle, its reactivity, and even the ability to be open under certain conditions do not preclude complications during the reaction with methylene-active compounds under alkaline catalysis. α,β-unsaturated ketone 2 was obtained in high yield. At the next stage, the synthesis of dibromo derivative 3 from ketone 2, we attempted to carry out the reaction under classical conditions: both in CCl_4 and in CH_3COOH according to the methods [18]. Bromination reaction did not always go smoothly: in the reaction in CCl_4, it was difficult to achieve complete conversion of the starting propenone into the dibromo-containing product. The reactions in CH_3COOH led to the formation of a mixture of products: monobromopropenone (α-Br) and dibromopropanone. Thus, the attempts to achieve complete bromination by a multiple bond and to obtain only the dibromo-substituted product resulted in formation of a number of by-products. Tougher reaction conditions led to the tarring and formation of a salt form (hydrobromide) of α-Br derivative. We tried to neutralize the salt form, but its reactivity was insufficient to interact with the classical bases: triethylamine, $NaHCO_3$, pyridine, and so on.

Ultrasonic activation at room temperature in acetic acid with direct addition to the reaction medium of the base, sodium acetate, was further used for the synthesis of the target product. In this case, we managed to obtain the target product with almost quantitative yield without the presence of by-products.

α,β-unsaturated ketone 2 was used as a cyclizing agent in heteroaromatization reac-

tions, and introduced into a number of the intermolecular cyclocondensation reactions with various α-aminoamidines. This allowed obtaining the target pyrimidine derivatives, although initially we isolated products of unsatisfactory degree of purity containing 5-7% w/w by-products in the amount. Similar result was obtained when boiling an equimolar mixture of reactants in pyridine (~ 115–116°C). Under these rather harsh conditions, the possibility of tarring or polymerization of the reagents involved was not excluded. After several unsuccessful attempts, we somewhat relaxed the conditions of the reaction under discussion: the temperature was reduced to 100° C that avoided formation of the by-products.

Under the optimal conditions described above, we obtained a number of thiazole derivatives with pyrimidine ring 4-8, which were functionalized with a chemically protected amino group. If necessary, the protecting tert-butoxycarbamate group could be removed, and the obtained products would be introduced into the reaction with the participation of the free amino group. That would allow expanding the functions of the obtained compounds beyond the traditional heterocyclization reactions.

In addition, on the example of benzimidazole derivative 9, we showed the possibility of obtaining the perspective thiazole-containing compounds in terms of their biological activity and subsequent functionalization. We also used a simple and affordable method of benzimidazole cycle synthesis based on aldehyde and o-phenylenediamine. The synthesis with Copper (II) acetate is economically more attractive than the Suzuki and Kumada reactions using valuable Palladium compounds or toxic organophosphorus reagents, as well as it is simpler and safer than organolithium or silylation reactions. It provides high yields and low probability of formation of the unwanted by-products. The studied cyclocondensation reaction opens opportunities for the synthesis of compounds of thiazolyl-benzimidazole series as thiabendazole congeners, which are promising in terms of their high biological activity.

4.Conclusions

We have analyzed modern synthetic approaches to obtaining a number of substituted derivatives of thiazole, chalcone, pyrimidine, and benzimidazole. An optimized method for the synthesis of substituted pyrimidine derivatives based on thiazole-containing unsaturated compounds is proposed. The appropriate conditions for carrying out the bromination reaction of α,beta-unsaturated systems containing thiazole moiety non-substituted in positions 2 and 4 are found. At these conditions, the formation of by-products of halogenation or hydrohalogenation is practically excluded, and the total yield of target products is close to the quantitative one. The optimal synthetic approach to the formation of benzimidazole cycle based on aldehydes is proposed. It is much simpler and cheaper than known alternative methods. As a result, a series of new functionalized products promising both in terms of their physicochemical properties and biological activity were synthesized.

Acknowledge

The authors thank Enamine Ltd., Kyiv, Ukraine for providing reagents, measuring the required spectra and other types of support.

This work was supported by the Scientific Grant of the National Research F oundation of Ukraine 2020.02/0016 "Indicators based on chromone derivatives for fluorescent determination of β-glucosidase activity".

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