ABSTRACT

Kolomoitsev O. O. Chemistry of 5-formylthiazole 2,4-disubstituted derivatives. Qualification scholarly paper: a manuscript.

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The dissertation is devoted to a series of 5-formylthiazole 2,4-disubstituted derivatives. Although to date, the study on the chemistry of thiazole, interest in these compounds is not declining. This is due to their physico-chemical, spectral, biological properties. These compounds have their place in chemistry, biology, pharmacy and materials science as a subject of practical application in many fields of science and technology.

Thiazole-containing compounds have been studied since the 19th century, but over time, interest in formylthiazole derivatives has only grown. Thus, many interesting properties of 5-formylthiazole derivatives have been discovered from both scientific and practical points of view.

Derivatives such as α,β-unsaturated systems based on 5-formylthiazole, are of interest due to the presence of an enone fragment that is part of them. Approaches to the modification of α,β-unsaturated systems to obtain diazaheterocyclic compounds containing two or more functions in their composition, significantly increase the variability of the functionalization of thiazole-containing compounds. For example, pyrimidines, 1*H*-imidazoles, 1*H*-pyrazolines, 1*H*-benzimidazoles with their interesting physicochemical, spectral, optical and biological properties are obtained, that opens a series of ways for their practical application.

The thesis is devoted to the study of the chemical nature of thiazole derivatives, namely the physicochemical and spectral properties of groups of thiazole analogues: 2,4-disubstituted 4-(1,3-thiazol-5-yl)but-3-en-2-ones, 5-aryl-1-(2-dialkylamino-4-chlorothiazol-5-yl)penta-1,4-diene-3-ones, 2-dialkylamino-4-chloro-5-[2-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)vinyl]thiazoles based on them and diazaheterocyclic

compounds ([4-(4-bromophenyl)-6-thiazol-5-yl-pyrimidin-2-yl]methylamines and 5-1*H*-benzimidazol-2-yl)thiazole).

Transformation by the carbonyl group that is a structural fragment of 5-formylthiazoles, by Claisen-Schmidt condensation reactions, as well as modified Horner-Wadsworth-Emmons and Wittig approaches, novel α,β-unsaturated ketones – 4-(1,3-thiazol-5-yl)but-3-ene-2-ones were obtained. Functionalization of positions 2 and 4 of the thiazole cycle allowed to investigate the effect of substituents in these positions on the properties of the obtained compounds.

The carbonyl component of 4-(1,3-thiazol-5-yl)but-3-en-2-ones through the Claisen-Schmidt reaction with aromatic aldehydes made it possible to obtain novel asymmetric dienone compounds – 5-aryl-1-(2-dialkylamino-4-chlorothiazol-5-yl)penta-1,4-diene-3-ones. Their properties were investigated by introducing these compounds into cyclocondensation with hydrazine, which also made it possible to obtain one of the two possible isomeric products of this interaction – 2-dialkylamino-4-chloro-5-[2-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)vinyl]thiazoles. The obtaining of one isomer of 1*H*-pyrazoline derivatives was confirmed by spectral research methods and quantum chemical calculations.

The effect of substituents at positions 2 and 4 of the thiazole cycle was studied for a series of 2,4-disubstituted derivatives of 5-formylthiazole: 4-(1,3-thiazol-5-yl)but-3-en-2-ones, 5-aryl-1-(2-dialkylamino-4-chlorothiazol-5-yl)penta-1,4-diene-3-ones and 2-dialkylamino-4-chloro-5-[2-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)vinyl] thiazoles.

A special place in the work is devoted to obtaining of thiazole analogues of chalcone, which was performed by the interaction of 5-formylthiazole with 4-bromoacetophenone. At this stage, a method of bromination of α,β-unsaturated systems containing thiazole nucleus with hydrogen atoms in positions 2 and 4 was developed, in which the formation of halogenation or hydrohalogenation by-products is practically eliminated and the yield of target compounds is close to quantitative.

Also, α,β-unsaturated ketone based on 5-formylthiazole has been proposed as an agent for heteroaromatization reactions with various 1,3-binucleophiles. As a result,

novel thiazole-containing 1,3-diazaheterocyclic compounds are formed. As such binucleophiles α-aminoamidines were used, for which a convenient synthetic approach has been proposed.

Possibilities of synthetic application of these compounds on the example of obtaining novel and interesting in terms of physicochemical properties and promising biological activity, imidazole and pyrimidine heterocyclic systems were demonstrated separately and a possible mechanism of intermolecular cyclocondensation reaction of 1,3-binucleophiles – α-aminoamidines with unsaturated carbonyl compounds was proposed.

At the next stage, a convenient method for obtaining substituted pyrimidine derivatives based on thiazole-containing unsaturated compounds was developed, which allowed to synthesize novel [4-(4-bromophenyl)-6-thiazol-5-yl-pyrimidin-2-yl]methylamines, to investigate their properties, as well as to demonstrate the high potential of the obtained compounds in terms of their functionalization in different directions.

In the thesis for the first time: novel approaches to synthesis of 2,4-disubstituted 4-(1,3-thiazol-5-yl)but-3-en-2-ones based on 2,4-disubstituted 5-formylthiazoles have been developed, which have significant advantages over Claisen-Schmidt condensation and a series of previously unsaturated compounds was synthesized; a way to modify 2,4-disubstituted 4-(1,3-thiazol-5-yl)but-3-en-2-ones was developed to obtain a series of novel asymmetric 5-aryl-1-(2-dialkylamino-4-chlorothiazole-5-yl)penta-1,4-diene-3-ones; the chemical properties of asymmetric 5-aryl-1-(2-dialkylamino-4-chlorothiazol-5-yl)penta-1,4-diene-3-ones by their cyclocondensation with hydrazine were investigated, which led to the obtaining of novel 2-dialkylamino-4-chloro-5-[2-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)vinyl]thiazoles;
the influence of substituents in positions 2 and 4 of the thiazole cycle for the series of 2,4-disubstituted 4-(1,3-thiazol-5-yl)but-3-en-2-ones, 5-aryl-1-(2-dialkylamino-4-chlorothiazole-5-yl)penta-1,4-diene-3-ones and 2-dialkylamino-4-chloro-5-[2-(5-aryl-4,5-dihydro-1*H*-pyrazole-3-yl)vinyl]thiazoles was investigated; an effective method for the synthesis of 2,3-dibromopropanones based on thiazole-containing α,β-

unsaturated ketones was developed, novel 1-(4-bromophenyl)-3-thiazol-5-yl-prop-2-en-1-one and 2,3-dibromo-1-(4-bromophenyl)-3-thiazol-5-yl-propan-1-one were obtained; the optimal way of synthesis of functionalized α-aminoamidines for their use in heterocyclization reactions with α,β-unsaturated carbonyl compounds based on 5-formylthiazole was developed; the way of modification of thiazole-containing carbonyl compounds with obtaining of novel functionalized diazaheterocyclic systems containing thiazole structural fragment is proposed, their physicochemical and spectral properties are comprehensively studied; physicochemical and spectral properties are described for a series of novel thiazole-containing compounds: 2,4-disubstituted 4-(1,3-thiazol-5-yl)but-3-en-2-ones, 5-aryl-1-(2-dialkylamino)-4-chloro-thiazol-5-yl)penta-1,4-diene-3-ones, 2-dialkylamino-4-chloro-5-[2-(5-aryl-4,5-dihydro-1*H*-pyrazole-3-yl)vinyl] thiazoles based on them and diazaheterocyclic compounds ([4-(4-bromophenyl)-6-thiazol-5-yl-pyrimidin-2-yl]methylamines and 5-(1*H*-benzimidazol-2-yl)thiazole).

Practical significance of the obtained results: convenient approaches to the synthesis of novel asymmetric 2,4-disubstituted 4-(1,3-thiazol-5-yl)but-3-en-2-ones based on thiazole-containing substituted aldehydes have been developed; the advantages of the Horner-Wadsworth-Emmons condensation (HWE) in comparison with the classical Claisen-Schmidt condensation and the Wittig reaction have been demonstrated; convenient synthesis of novel asymmetric thiazole-containing penta-1,4-diene-3-ones is proposed; the direction of the cyclocondensation reaction of penta-1,4-diene-3-ones with hydrazine was investigated, which allows to obtain thiazole-containing 1*H*-pyrazolines on the basis of asymmetric thiazole-containing penta-1,4-diene-3-ones; bromination reaction conditions for 1-(4-bromophenyl)-3-thiazol-5-yl-prop-2-en-1-one were optimized, thus eliminating the formation of by-products of halogenation or hydrohalogenation; convenient approaches for obtaining and functionalizing pyrimidines and imidazoles based on 1,3-binucleophiles were developed.

Key words: thiazole, 5-formylthiazole, α,β-unsaturated compounds, Claisen-Schmidt condensation, Horner-Wadsworth-Emmons reaction, Wittig reaction,

intermolecular cyclocondensation reactions, pyrimidines, 1*H*-imidazoles, 1*H*-pyrazolines, 1*H*-benzimidazoles.