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A new approach to 2,4,5-trisubstituted thiazoles from β-dicarbonylic compounds, arylglyoxals and thioamides

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Summary. A rapid and efficient one-pot three-component synthesis of 2-R-4-arylthiazoles containing a 4-hydroxycoumarin or dimedone fragment in the 5th position from β-dicarbonylic compounds, arylglyoxals and thioamides has been developed. 2-Amino-4,5-disubstituted thiazole derivatives were obtained by the reaction of bis-adducts based on CH-acids and arylglyoxals with thioureas.

Keywords: β-dicarbonylic compounds, thiazole, one-pot synthesis, thioamide, thiohydantoin.

Introduction. Thiazoles and their hydrogenated analogues are components of different types of drugs: antibiotics [1-3], cytoprotective [4], antimicrobial [5], growth regulatory [6], antiviral and antitumor drugs [7-9] and for treatment of central nervous system diseases [10, 11]. There is some data that antibiotics with a thiazole fragment can block cancer formation and 2,4-disubstituted thiazole derivatives have immunoregulatory and anti-inflammatory activities like Fanetizole [12]. On the other hand, one-pot multicomponent reactions have gained much attention because of many reasons such as time economy, simplicity, green conditions, and cost-effectiveness over a step-by-step procedure.

Thiazole is a very important skeleton, both in the field of natural products and also for medicinal chemistry. Thus, the preparation and transformation of nitrogen- and sulfur-containing compounds is an important step in the synthesis of pharmaceutical candidates and fine chemicals.

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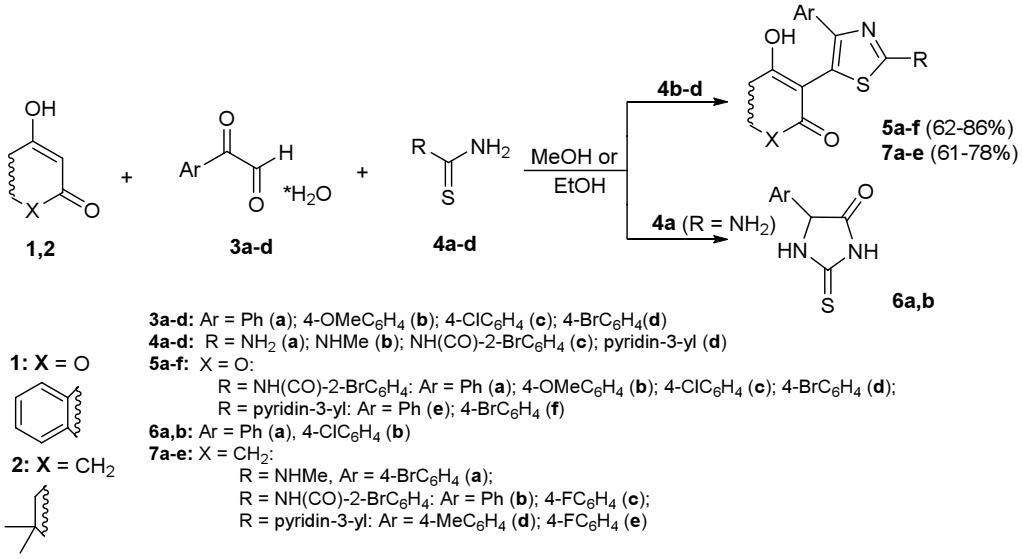
Previously, we reported the convenient one-pot condensation of thiazoles from reactions of 1,3-dimethylbarbituric (thiobarbituric) acid and arylglyoxals with several thioamides [13, 14]. This way is a simple, rapid and practical method of synthesis of thiazoles in good isolated yields and high purity.

A new simple and efficient method of thiazole cycle formation is described in this work. The proposed approach to the synthesis of thiazole derivatives can be used as a simple alternative to the Hantzsch reaction [15-17] and to some others methods of thiazole cycle generation [12, 18]. We selected the 4-hydroxycoumarin or dimedone as CH-acidic component of the discussed reaction. It should only be noted that dimethylbarbituric (thiobarbituric) acid is not prone to the formation of the enol form, whereas 4-hydroxycoumarin or dimedone are compounds in which enol form is fixed or its percentage is sufficiently high. In addition, the importance of thiazoles with interesting pharmacological activity has prompted many researchers to synthesize such derivatives.

Results and discussion. The synthesis of some new functionalized thiazoles from β-dicarbony-

Scheme 1

The formation of substituted thiazoles ***5a-f*** *and* ***7a-e*** *(method A)*



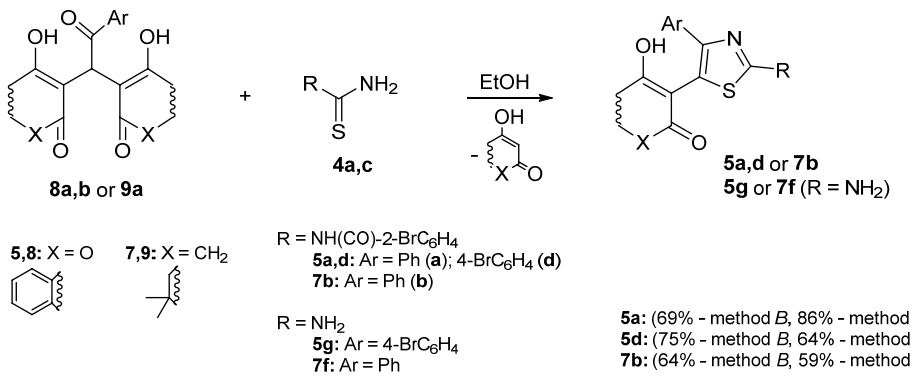
lic compounds (4-hydroxycoumarin **1** or dimedone **2**) and arylglyoxals **3a-d** with thioamides **4a-d** (Scheme 1) is the target of this research. A mixture of equimolar amounts of CH-acid **1** or **2**, arylglyoxal **3** and thiourea **4** with glacial acetic acid was refluxed in methanol or ethanol for 0.5-1 h up to the formation of a solid in the reaction mixture. It is interesting that the use of thiourea **4a** leads to the known thiohydantoines **6a,b** [19, 20] due to a rapid reaction of arylglyoxal and thiourea, while thioamides **4b-d** form 2-substituted 4-hydroxy-3-(4-arylthiazol-5-yl)-2*H*-chromen-2-ones (**5a-f**) in case of the use of coumarin **1** or 3-hydroxy-2-(4-arylthiazol-5-yl)-5,5-dimethylcyclohex-2-enones (**7a-e**) in case of dimedone **2** in good isolated yields.

The compounds **5a,d** and **7b** were obtained (with an impurity of **1** or **2**) in an alternative way — by heating bis-adduct **8a**(**b**) or **9a** [21] with thiourea **4c** (Scheme 2), but yields of the products were lower and common reaction time increased. However, the two-step reaction through Michael adducts gave the opportunity to prepare 2-aminosubstituted thiazoles. To obtain the compound **5g** or **7f**, the interaction was carried out in two stages using the corresponding bis-adducts **8b** or **9a** (Scheme 2) and thiourea **4a**.

The structures of compounds **5** and **7** were confirmed by microanalysis, ^{1}H NMR, ^{13}C NMR and mass spectra. There is a doublet of H-5 at 7.9 ppm (J=7.4-8.0 Hz), a triplet of H-7 near 7.7 ppm and multiplets of H-6 and H-8 protons at 7.30-7.45 ppm, a singlet of NH-proton near 12.85 ppm (for compounds **5a-d**); a broad singlet of OH-proton of lactone at 13.0-13.5 ppm with low intensity because of the fast exchange with

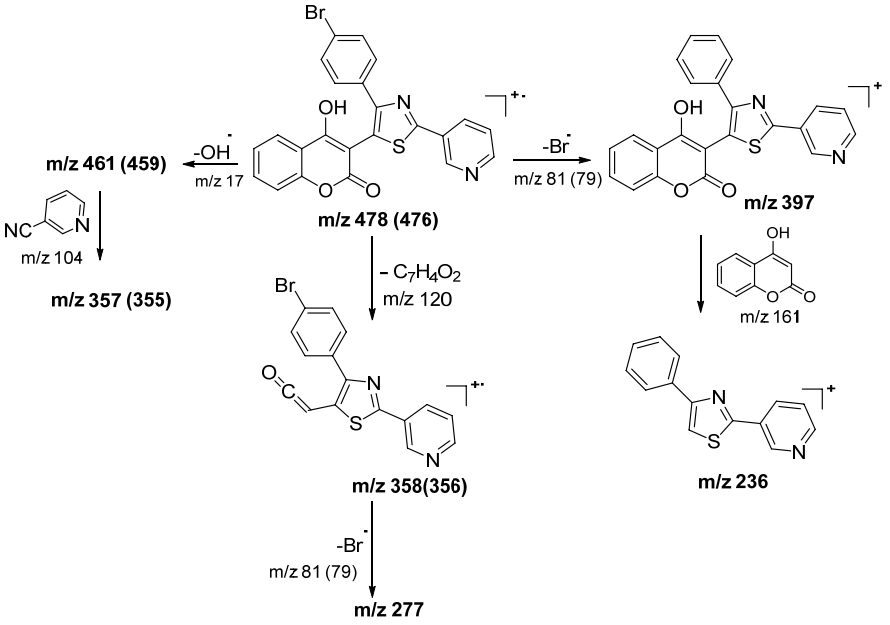
Scheme 2

Alternative way to thiazoles ***5*** *and* ***7*** *from Michael bis-adducts (method B)*



Scheme 3

*Fragmentation processes of compound **5f** in mass spectrum (EI)*



water (in solvent) in the ^{1}H NMR spectra of compounds **5**. There are singlets of two methyl (≈1 ppm) and two methylene groups (≈4 ppm), multiplets of the aromatic fragments at 7.2-9.1 ppm and a broad singlet, which disappeared when D_2O was added and was assigned to the OH-group of dimedone in the ^{1}H NMR spectra of compounds **7**. The stripe of the conjugated carbonyl group of dimedone presents itself at 1665-1675 cm^{-1} in the IR spectra. All corresponding signals of carbon atoms were observed in the ^{13}C NMR spectra. It was noted that the yields of compounds **7a-e** are lower than the yields of corresponding products **5a-f** by approximately 10 %.

The peaks of molecular ions have maximal intensities in mass spectra of the obtained compounds **5** and **7**. As a typical example, Scheme 3 illustrates some common decomposition processes of thiazole **5f**, molecular ions with m/z 478 (476) and intensity ratio near 1:1 are in the mass-spectrum. Fragmentation includes the elimination of an OH-group $[M\text{-}17]^+$; the pyrane ring opening with the following release of an benzocyclooxetane, ion (m/z 120), the elimination of a bromine radical $[M\text{-}81\ (79)]^+$, the peak of the 4-hydroxycoumarin ion (m/z 161) is present in this spectrum too.

The cyclization of thiazole can include a hydroxyketone **A** (or bis-adduct **A**) formation and, probably, this stage is a limited step of the discussed reaction. Further nucleophilic substitution of Y with an SH-group of thiourea (in major thiole form) leads to an intermediate **B** (Scheme 4), which forms the 5-membered thiazole cycle **5** (or **7**) after the elimination of water.

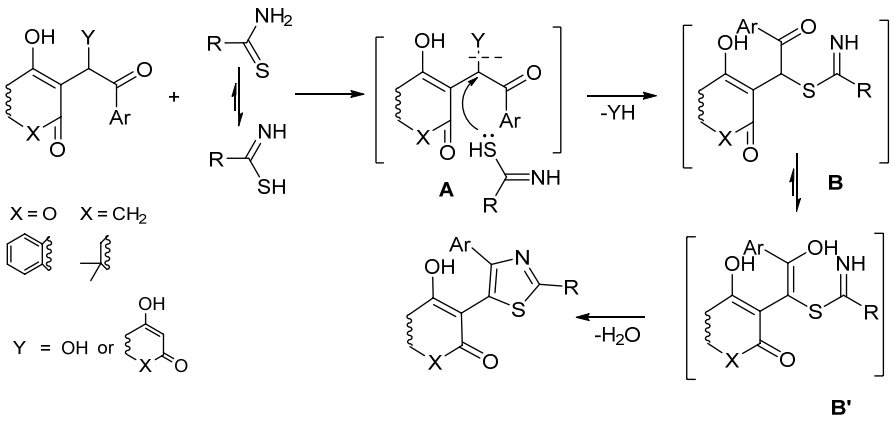
Thiohydantoines **6** were obtained only in the case of reaction with thiourea **4a**. This result can be explained either with a small fraction of the thiole form [22] or low rate of intermediate **A** formation. At the same time thiazoles **5** (**7**) were obtained by the reaction of bis-adducts **8** or **9** with thioureas **4**. Their formation passes through the stage of nucleophilic attack of an sp^3-carbon atom in the phenacyl fragment with the elimination of β-diketone and the further condensation of carbonyl and amino groups.

The alternative way which included the condensation of aldehyde and amino groups as the first step was declined because in the cases of reactions of bis-adducts **8** or **9** with N-arylureas instead of 1,4-diarylsubstituted compounds 3,4-diarylimidazol-2-ones were obtained [23]. In our opinion, this data confirms the proposed mechanism of the described reaction.

Experimental. Starting materials were obtained from commercial suppliers. Melting points were determined on a Kofler apparatus. The ^{1}H NMR spectra were recorded at 200 MHz on a Varian VX-200R Mercury spectrometer and ^{13}C NMR spectra were recorded at 100 MHz on a

Scheme 4

The proposed mechanism of reaction



Bruker AM-400 spectrometer with $SiMe_4$ internal reference in DMSO-d_6. Mass spectra were taken on a Finnigan MAT 4651P instrument (EI, 70 eV). Elemental analysis data were obtained on instrument Vario MICRO cube Reactions were monitored by TLC (Silufol UV-254) in MeOH/toluene (1:1), toluene/EtOAc (1:1), and toluene/EtOAc (1:3), and visualized under UV light or iodine fume.

Synthesis of 3-(4'-aryl-2'-R-thiazol-5'-yl)-2-hydroxy-4H-chromen-4-ones, 5a-f. *General procedure*. Method *A («one-pot» way)*. A mixture of equimolar amounts (1 mmol) of CH-acid **1**, arylglyoxal **3** and thiourea **4b-d** in 15 ml MeOH or EtOH was refluxed for 0.5-1 h. The pale yellow precipitate was filtered off and recrystallized from ethanol or methanol.

Method *B (from Michael bis-adduct)*. Equimolar amounts of bis-adduct **8** (or **9**) and thiourea **4c** (1 mmol of each reactant) in 10 ml ethanol were heated for 1-1.5 h. The precipitate was filtered off and recrystallized from ethanol. The products **5g** and **7f** were synthesized and purified by this method using thiourea **4a**.

*2-Bromo-N-(5-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-phenylthiazol-2-yl)-benzamide (**5a**)*. Yield 86 % (0.45 g, method *A*), 69 % (0.36 g, method *B*); mp 246-248 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 7.22-7.53 (m, 7H, *p*-+2*m*-Ph+H-6+H_α+H_β+H_γ), 7.56-7.63 (m, 4H, 2*o*-Ph+H-8+H_δ), 7.71 (t, 1H, *J*=8.2 Hz, H-7), 7.89 (d, 1H, *J*=7.6 Hz, H-5), 12.89 (s, 1H, NH). NMR ^{13}C, δ, ppm: 97.1 (C-3), 116.4 (C-8), 117.2 (C-10), 119.3 (C-2, *o*-BrC_6H_4), 119.9 (C-5), 124.6 (C-6), 127.9 (2*o*-C, Ph), 128.2 (C-6, *o*-BrC_6H_4), 128.4 (*p*-C, Ph), 129.0 (C-7), 129.2 (2*m*-C, Ph), 130.0 (C-4, *o*-BrC_6H_4), 131.3 (C-5, *o*-BrC_6H_4), 133.4 (C-5'), 133.5 (C-3, *o*-BrC_6H_4), 133.8 (C-1, Ph), 135.7 (C-1, *o*-BrC_6H_4), 146.1 (C-9), 153.4 (C-4'), 162.0 (C-2'), 164.4 (C-2, C=O), 166.7 (C=O, amide), 169.7 (C-4, =C-OH). MS (EI, 70 eV): *m/z* (% intensity) =520/518 $[M]^+$ (75/74), 503/501 (30/29), 400/398 (18/17), 359/357 (34/33), 319 (12), 278 (26), 243 (11), 161 (43), 120 (22), 81/79 (20/19), 77 (8), 76 (13). Anal. Calcd for $C_{25}H_{15}BrN_2O_4S$: C 57.81; H 2.91; N 5.39. Found: C 57.90; H 2.87; N 5.43.

*2-Bromo-N-(5-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(4-methoxyphenyl)-thiazol-2-yl)benz-amide (**5b**)*. Yield 80 % (0.44 g); mp 264-266 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 3.69 (s, 3H, OMe), 6.87 (d, 2H, *J*=8.8 Hz, *m*-Ar), 7.33-7.63 (m, 8H, 2*o*-Ar+H-6+H-8+H_α+H_β+H_γ+H_δ), 7.71 (t, 1H, *J*=7.8 Hz, H-7), 7.90 (d, 1H, *J* = 7.4 Hz, H-5), 12.85 (s, 1H, NH). MS (EI, 70 eV): *m/z* (% intensity) =550/548 $[M]^+$ (67/66), 533/531 (45/44), 443/441 (18/17), 429/427 (10/9), 348 (23), 322/320 (22/21), 272 (9), 203 (11), 120 (15), 107 (12), 81/79 (17/16). Anal. Calcd for $C_{26}H_{17}BrN_2O_5S$: C 56.84; H 3.12; N 5.10. Found: C 56.90; H 3.05; N 5.13.

*2-Bromo-N-(4-(4-chlorophenyl)-5-(4-hydroxy-2-oxo-2H-chromen-3-yl)-thiazol-2-yl)-benz-amide (**5c**)*. Yield 81 % (0.45 g); mp 258-260 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 7.32-7.61 (m, 10H, 2*o*-Ar+H-6+H-8+H_α+H_β+H_γ+H_δ+2*m*-Ar), 7.71 (t, 1H, *J*=8.0 Hz, H-7), 7.90 (d, 1H, *J* = 7.8 Hz, H-5), 12.83 (s, 1H, NH). Anal. Calcd for $C_{25}H_{14}BrClN_2O_4S$: C 54.22; H 2.55; N 5.04. Found: C 54.27; H 2.61; N 4.99.

*2-Bromo-N-(4-(4-bromophenyl)-5-(4-hydroxy-2-oxo-2H-chromen-3-yl)-thiazol-2-yl)-benz-amide (**5d**)*. Yield 75 % (0.45 g, method *A*), 64 % (0.38 g, method *B*); mp 272-274 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 7.33-7.64 (m, 10H, 2*m*-Ar+H-6+H-8+H_α+H_β+H_γ+H_δ+2*o*-Ar), 7.72 (t, 1H, *J*=7.6 Hz,

H-7), 7.90 (d, 1H, *J*=7.6 Hz, H-5), 12.92 (s, 1H, NH). Anal. Calcd for $C_{25}H_{14}Br_2N_2O_4S$: C 50.19; H 2.36; N 4.68. Found: C 50.12; H 2.43; N 4.59.

*4-Hydroxy-3-(4-phenyl-2-(pyridin-3-yl)thiazol-5-yl)-2H-chromen-2-on (**5e**).* Yield 65 % (0.26 g); mp 256-258 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 7.31-7.43 (m, 5H, *p*-+2*m*-Ph+H-6+H-8), 7.56-7.72 (m, 4H, H-7+2*o*-Ph+$H_β$), 7.91 (d, 1H, *J*=7.8 Hz, H-5), 8.39 (d, 1H, *J*=8.0 Hz, $H_γ$), 8.69 (d, 1H, *J*=3.2 Hz, $H_α$), 9.20 (s, 1H, $H_{α'}$). NMR ^{13}C, δ, ppm: 94.9 (C-3), 117.0 (C-8+C-10), 124.2 (C-5), 124.9 ($C_β$+C-6), 128.8 (2*o*-C, Ph+C-7), 130.1 (2*m*-C+*p*-C, Ph), 132.8 (C-1, Ph+$C_{β'}$+$C_γ$), 133.9 (C-5'), 134.2 ($C_α$+$C_{α'}$), 150.5 (C-9), 152.4 (C-2'), 154.2 (C-4'), 163.9 (C-2, C=O), 165.3 (C-4, =C-OH). Anal. Calcd for $C_{23}H_{14}N_2O_3S$: C 69.33; H 3.54; N 7.03. Found: C 69.42; H 3.48; N 7.09.

*3-(4-(4-Bromophenyl)-2-(pyridin-3-yl)thiazol-5-yl)-4-hydroxy-2H-chromen-2-on (**5f**).* Yield 62 % (0.30 g); mp 271-273 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 7.31-7.43 (m, 2H, H-6+H-8), 7.52-7.68 (m, 6H, 2*m*-+2*o*-Ar+H-7+$H_β$), 7.92 (d, 1H, *J*=7.4 Hz, H-5), 8.39 (d, 1H, *J*=7.8 Hz, $H_γ$), 8.70 (d, 1H, *J*=3.4 Hz, $H_α$), 9.20 (s, 1H, $H_{α'}$). NMR ^{13}C, δ, ppm: 94.8 (C-3), 116.4 (C-8+C-10), 124.0 (C-5+*p*-C, Ar), 124.2 ($C_β$+C-6), 128.4 (2*o*-C, Ar), 128.7 (C-7), 129.1 (2*m*-C+C-1, Ar), 132.6 ($C_{β'}$+$C_γ$), 133.0 (C-5'), 133.7 ($C_α$+$C_{α'}$), 152.4 (C-9+C-2'), 152.9 (C-4'), 161.0 (C-2, C=O), 164.9 (C-4, =C-OH). Anal. Calcd for $C_{23}H_{13}BrN_2O_3S$: C 57.87; H 2.75; N 5.87. Found: C 57.93; H 2.81; N 5.92.

*3-(2-Amino-4-(4-bromophenyl)thiazol-5-yl)-4-hydroxy-2H-chromen-2-one (**5g**).* Yield 65 % (0.27 g); mp 283-285 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 7.28-7.61 (m, 6H, 2*m*-+2*o*-Ar+H-6+H-8), 7.69 (t, 1H, *J*=7.6 Hz, H-7), 7.88 (d, 1H, *J*=7.4 Hz, H-5), 8.70 (br. s, 2H, NH_2). MS (EI, 70 eV): *m/z* (% intensity) =416/414 $[M]^+$ (78/77), 293/295 (14/13), 255/253 (42/41), 214 (34), 161 (17), 120 (11), 81/79 (9/8). Anal. Calcd for $C_{18}H_{11}BrN_2O_3S$: C 52.06; H 2.67; N 6.75. Found: C 51.94; H 2.65; N 6.83.

3-Hydroxy-2-(4-arylthiazol-5-yl)-5,5-dimethylcyclohex-2-enones **7a-e** were obtained analogically to the synthesis of compounds **5a-f** by method *A*. Product **7b** was also obtained by method *B*.

*2-(4-(4-Bromophenyl)-2-(methylamino)thiazol-5-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**7a**).* Yield 68 % (0.28 g); mp 244-246 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 1.00 (s, 6H, 2Me), 2.29 (s, 4H, $2CH_2$), 2.80 (d, 3H, *J*=4.6 Hz, Me), 7.35 (d, 1H, *J*=4.6 Hz, NH), 7.43 (s, 4H, *m*-+*o*-Ar), 10.90 (s, 1H, OH). NMR ^{13}C, δ, ppm: 28.0 (2Me), 30.7 (Me), 32.1 (C-5), 56.1 (C-4+C-6, $2CH_2$), 107.0 (C-2), 111.3 (*p*-C, Ar), 120.8 (C-5'), 129.1 (2*o*-C, Ar), 130.6 (2*m*-C+C-1, Ar), 136.3 (C-4'), 146.3 (C-2'), 168.6 (C-1, C=O), 192.7 (C-3, =C-OH). NMR ^{13}C (Dept45), δ, ppm: 28.0, 30.7, 56.1, 129.1, 130.6. Anal. Calcd for $C_{18}H_{19}BrN_2O_2S$: C 53.08; H 4.70; N 6.88. Found: C 53.14; H 4.63; N 6.82.

*2-Bromo-N-(5-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-4-phenyl-thiazol-2-yl)-benz-amide (**7b**).* Yield 64 % (0.32 g, method *A*), 59 % (0.30 g, method *B*); mp 160-162 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 1.04 (s, 6H, 2Me), 2.34 (s, 4H, $2CH_2$), 7.22-7.34 (m, 3H, *p*-+2*m*-Ph), 7.43-7.56 (m, 5H, H-3+H-4+H-5+2*o*-Ph), 7.71 (d, 1H, *J*=8.0 Hz, H-6), 11.60 (br. s, 1H, OH), 12.65 (s, 1 H, NH). NMR ^{13}C, δ, ppm: 28.6 (2Me), 32.2 (C-5), 55.9 (C-4+C-6, $2CH_2$), 106.4 (C-2), 119.8 (C-Br, *o*-BrC_6H_4), 127.9 (2*o*-C, Ph), 128.3 (C-6, *o*-BrC_6H_4), 128.7 (*p*-C, Ph), 129.9 (2*m*-C, Ph), 132.5 (C-4+C-5, *o*-BrC_6H_4), 132.9 (C-3, *o*-BrC_6H_4+C-5'), 133.5 (C-1, Ph), 137.4 (C-1, *o*-BrC_6H_4), 156.7 (C-4'), 162.7 (C-2'+C=O, amide), 166.3 (C-1, C=O), 190.4 (C-3, =C-OH). Anal. Calcd for $C_{24}H_{21}BrN_2O_3S$: C 57.95; H 4.26; N 5.63. Found: C 57.86; H 4.17; N 5.71.

*2-Bromo-N-(4-(4-fluorophenyl)-5-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-thiazol-2-yl)benzamide (**7c**).* Yield 61 % (0.31 g); mp 150-152 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 1.05 (s, 6H, 2Me), 2.36 (s, 4H, $2CH_2$), 7.16 (t, 2H, *J*=8.4 Hz, *m*-Ar), 7.45-7.56 (m, 5H, 2*o*-Ar+H-3+H-4+H-5), 7.72 (d, 1H, *J*=8.0 Hz, H-6), 11.63 (br. s, 1H, OH), 12.70 (s, 1H, NH). NMR ^{13}C, δ, ppm: 28.6 (2Me), 32.2 (C-5), 55.7 (C-4+C-6, $2CH_2$), 106.2 (C-2), 115.5 (2*m*-C, Ar), 119.8 (C-Br, *o*-BrC_6H_4), 128.3 (C-6, *o*-BrC_6H_4), 129.7 (C-1, Ar), 129.8+129.9 (2*o*-C, Ar), 132.6 (C-5+C-4, *o*-BrC_6H_4), 132.9 (C-5'), 133.5 (C-3, *o*-BrC_6H_4), 137.3 (C-1, *o*-BrC_6H_4), 146.9 (C-4'), 156.9 (C-F, Ar), 161.1 (C-2'), 162.5 (C=O, amide), 166.3 (C-1, C=O), 189.7 (C-3, =C-OH). MS (EI, 70 eV): *m/z* (% intensity) =516/514 $[M]^+$ (56/55), 499/497 (16/15), 435 (31), 421/419 (45/44), 290 (11), 282/280 (19/18), 145 (9), 139 (12), 95 (13), 81/79 (8/7). Anal. Calcd for $C_{24}H_{20}BrFN_2O_3S$: C 55.93; H 3.91; N 5.44. Found: C 55.84; H 4.00; N 5.50.

*3-Hydroxy-5,5-dimethyl-2-(2-(pyridin-3-yl)-4-p-tolylthiazol-5-yl)cyclohex-2-enone (**7d**).* Yield 62 % (0.24 g); mp 234-236 °C. NMR ^{1}H, δ, ppm (*J*, Hz): 1.05 (s, 6H, 2Me), 2.29 (s, 3H, Me),

2.37 (s, 4H, $2CH_2$), 7.16 (d, 2H, J=8.4 Hz, *m*-Ar), 7.53 (m, 3H, 2*o*-Ar+H_β), 8.29 (d, 1H, J=7.8 Hz, H_γ), 8.65 (d, 1H, J=4.2 Hz, H_α), 9.11 (s, 1H, $H_{\alpha'}$), 11.43 (br. s, 1H, OH). NMR ^{13}C, δ, ppm: 21.3 (Me), 28.6 (2Me), 32.4 (C-5), 47.0 (C-4+C-6, $2CH_2$), 106.0 (C-2), 115.6+115.8 (2*o*-C, Ar), 125.1 (C_β), 126.7 (C-1, Ar), 129.8 (C-Me), 130.1+130.4 (2*m*-C, Ar), 132.5 ($C_{\beta'}$), 134.1 (C_γ), 147.6 (C-5'), 151.6 (C_α), 152.3 ($C_{\alpha'}$), 161.2 (C-2'), 162.9 (C-4'), 163.5 (C-1, C=O), 190.8 (C-3, =C-OH). MS (EI, 70 eV): *m*/*z* (% intensity) =390 $[M]^+$ (82), 373 (13), 286 (52), 251 (17), 195 (31), 147 (14), 139 (9), 104 (11), 91 (9). Anal. Calcd for $C_{23}H_{22}N_2O_2S$: C 70.74; H 5.68; N 7.17. Found: C 70.65; H 5.73; N 7.09.

*2-(4-(4-Fluorophenyl)-2-(pyridin-3-yl)thiazol-5-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**7e**).* Yield 78 % (0.31 g); mp 237-239 ˚C. NMR ^{1}H, δ, ppm (*J*, Hz): 1.04 (s, 6H, 2Me), 2.37 (s, 4H, $2CH_2$), 7.19 (t, 2H, J=8.4 Hz, *m*-Ar), 7.50-7.56 (dd, 1H, J=7.8 Hz, H_β), 7.68 (t, 2H, J=8.4 Hz, *o*-Ar), 8.29 (d, 1H, J=7.8 Hz, H_γ), 8.65 (d, 1H, J=4.2 Hz, H_α), 9.11 (s, 1H, $H_{\alpha'}$), 11.49 (br. s, 1H, OH). NMR ^{13}C, δ, ppm: 27.9 (2Me), 31.4 (C-5), 46.5 (C-4+C-6, $2CH_2$), 105.2 (C-2), 114.8+115.2 (2*m*-C, Ar), 124.2 (C_β), 125.8 (C-1, Ar), 129.4+129.5 (2*o*-C, Ar), 131.8 ($C_{\beta'}$), 133.2 (C_γ), 146.7 (C_α), 150.7 ($C_{\alpha'}$), 151.6 (C-5'), 159.7 (C-2'), 161.1 (C-4'), 162.8 (C-F, Ar), 168.5 (C-1, C=O), 192.5 (C-3, =C-OH). NMR ^{13}C (Dept45), δ, ppm: 27.9, 46.5, 114.8, 115.2, 124.2, 129.4, 129.5, 133.2, 146.7, 150.7. MS (EI, 70 eV): *m*/*z* (% intensity) =394 $[M]^+$ (76), 377 (12), 282 (47), 235 (31), 160 (16), 151 (33), 139 (23), 122 (8), 104 (11), 95 (9). Anal. Calcd for $C_{22}H_{19}FN_2O_2S$: C 66.99; H 4.85; N 7.10. Found: C 67.03; H 4.93; N 7.19.

*2-(2-Amino-4-phenylthiazol-5-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**7f**).* Yield 60 % (0.19 g); mp 278-280 ˚C. NMR ^{1}H, δ, ppm (*J*, Hz): 1.04 (s, 6H, 2Me), 2.36 (s, 4H, $2CH_2$), 7.22-7.34 (m, 3H, *p*-+2*m*-C_6H_5), 7.46-7.53 (m, 2H, 2*o*-C_6H_5), 8.78 (br. s, 2H, NH_2), 11.40 (br. s, 1H, OH). MS (EI, 70 eV): *m*/*z* (% intensity) =314 $[M]^+$ (79), 237 (46), 175 (23), 139 (17), 98 (19), 77 (8). Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C 64.94; H 5.77; N 8.91. Found: C 65.03; H 5.82; N 9.00.

Conclusion. So, the convenient one-pot synthesis of 2-*R*-4-aryl-5-*R*'-thiazoles in good isolated yields from β-dicarbonylic compounds, arylglyoxals and substituted thioureas has been developed. 2-*R* substituted products as well as 2-amino analogues were obtained by the reaction of Michael bis-adducts based on CH-acids and arylglyoxals with thioureas at the same experimental conditions, but with lower yields and the increased reaction time. One-pot reaction of CH-acids, arylglyoxals and thiourea led to 5-aryl-2-thioxoimidazolidin-4-ones only. Mechanisms of studied reactions were discussed. The structures of products were confirmed by physical and chemical data.

Moreover, thiazole is a very important skeleton, both in the field of natural products and also for medicinal chemistry. Thus, the preparation and transformation of nitrogen- and sulfur-containing compounds are important step in the synthesis of pharmaceutical candidates, fine chemicals and others.

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Новий підхід до синтезу 2,4,5-тризаміщених тіазолів за участі β-дикарбонільних сполук, арилгліоксалів і тіоамідів

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Резюме. Розроблено швидкий та ефективний однореакторний трикомпонентний метод синтезу 2-R-4-арилтіазолів, що містять у 5-му положенні фрагмент 4-гідроксикумарину або димедону на основі β-дикарбонільних сполук, гідратів арилгліоксалів і тіоамідів. 2-Аміно-4,5-дизаміщені похідні тіазолу одержано шляхом реакції бісадуктів на основі СН-кислот та арилгліоксалів із тіосечовинами.

Ключові слова: β-дикарбонільні сполуки, тіазол, однореакторний синтез, тіоамід, тіогідантоїн.

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