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A New Rearrangement in the Thiazolopyrimidine Series: From 2-Arylmethylidenthiazolo[3,2-*a*]pyrimidines to 2,3-dihydrothiazolo[3,2-*a*]pyrimidine-2-carboxylates †

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Abstract: Microwave irradiation (MW) is one of the effective alternative activation method. The significant reduction in reaction time and higher yields of products made this alternative heating source an attractive tool in organic synthesis. It became possible to carry out the methanolysis reaction of 2-arylmethylidentiazolo[3,2-*a*]pyrimidine derivatives. This work is devoted to the stereoselective synthesis of 2,3-disubstituted-2,3-dihydrothiazolo[3,2-*a*]pyrimidine derivatives and the study of their structure.

Keywords: thiazolo[3,2-*a*]pyrimidines; 2-arylmethylidene derivatives of thiazolo[3,2-*a*]pyrimidine; 3,5-diaryl-2,3-dihydrothiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylates; microwave synthesis; nucleophilic addition; intramolecular rearrangement

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1. Introduction

The chemistry of heterocyclic compounds is one of the most important areas of organic chemistry. Such structures include 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives. These derivatives are among the promising structural fragments for the development of medicinal substances, including anticancer, anti-inflammatory and antifungal drugs [1–3].

At the same time, along with the task of searching for new antitumor drugs, the task of increasing the selectivity of synthetic processes has arisen. However, few methods of modification of 2-arylmethylidentiazolo[3,2-*a*]pyrimidine derivatives are known in the literature. This is due to the fact that all chemical properties are based either on interaction with sufficiently strong nucleophilic reagents (*CH*-acids and cyclic disulfides) [4–7] or on hydrolytic instability under acidic conditions [8]. Furthermore, information on reactivity with *O*-nucleophiles in the literature is present in the example of only one article from our research group (see Figure 1). The reaction of 2-arylmethylidene derivatives of thiazolo[3,2-*a*]pyrimidine **A** and methanol in the presence of base under MW conditions results in nucleophilic alcohol addition followed by intramolecular rearrangement into 3,5-diaryl-2,3-dihydrothiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylates **B** [9].

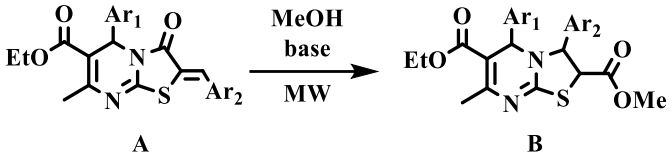


Figure 1. Synthesis of 3,5-diaryl-2,3-dihydrothiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylates.

In addition, until recently, the only known method for the preparation of 2,3-disubstituted-2,3-dihydrothiazolo[3,2-*a*]pyrimidine derivatives **D** was the interaction of 1,2,3,4-tetrahydropyrimidine derivatives **C** with acetylenedicarboxylic acid ethyl ester (see Figure 2). However, the reaction proceeds in the presence of poisonous 1-isocyanobutane, which is a potent respiratory and skin sensitizer [10].

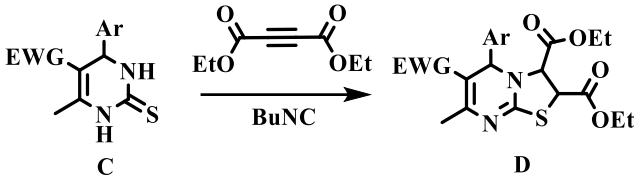


Figure 2. Synthesis of 2,3-disubstituted-2,3-dihydrothiazolo[3,2-*a*]pyrimidine derivatives.

Thus, single methods for the formation of 2,3-dihydrothiazolo[3,2-*a*]pyrimidine-2-carboxylates have been described in the literature. Therefore, the next step of this scientific study was to investigate the limits of applicability of the developed approach–methanolysis reaction of 2-arylmethylidene derivatives of thiazolo[3,2-*a*]pyrimidine under MW.

2. Materials and Methods

2.1. Synthesis and Characterisation

All reagents (AcrosOrganics (Belgium), AlfaAesar (USA))were usedwithout further purification. The ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1** [11], ethyl 7-methyl-3-oxo-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **2** [12] and ethyl (Z)-2-(4-bromobenzylidene)-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **3** [13] were synthesized according reported methods.

NMR experiments were performed on Bruker Avance instruments with an operating frequency of 400 and 600 MHz for shooting ^{1}H NMR spectra. Chemical shifts were determined relative to the signals of residual protons of the DMSO-d_6 solvent.

IR spectra in KBr tablets were recorded on a Bruker Vector-22.

Electrospray ionization (ESI) mass spectra were obtained using a Bruker AmaZon Xion trap mass spectrometer. Melting points were determined on a BOETIUS melting table with an RNMK 05 imaging device.

2.1.1. General Method for Compound **4** Preparation

A mixture of 2-arylmethylidentiazolo[3,2-*a*]pyrimidine (1.0 mmol) **3**, pyridine (0.1 mmol) and methanol (10 mL, 0.25 mol) was subjected to MW for 2 h and at a dynamic power of 100 W. The solvent was then removed at a rotary evaporator, the resulting yellow oil was recrystallized from the hexane/methanol mixture (1/1). The precipitate was filtered off, washed with cold methanol and dried.

6-Ethyl 2-methyl 3-(4-bromophenyl)-7-methyl-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarboxylate **4**. Yield 96%, white crystals, mp 192–194 °C. IR (KBr, cm^{-1}): 1746, 1734 (C=O); 1638 (C=N); 768 (C-S). ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) δH ppm: 0.96 (t, *J* = 7.0 Hz, 3H, OCH$_2$<u>CH$_3$</u>), 2.27 (s, 3H, CH$_3$), 3.49 (s, 3H, CO$_2$<u>CH$_3$</u>), 3.82–3.94 (m, 2H, O<u>CH$_2$</u>CH$_3$), 4.50 (d, *J* = 5.1 Hz, 1H, <u>CH</u>-CO$_2$CH$_3$), 4.88 (d, *J* = 5.1 Hz, 1H, <u>CH</u>-

Ar), 4.96 (s, 1H, CH-Ph), 7.12–7.13 (m, 2H, CH (Ar)), 7.32–7.39 (m, 5H, CH (Ar)), 7.70–7.72 (m, 2H, CH (Ar)). MS (ESI), *m*/*z*, $[M + H]^+$: calcd. for $C_{24}H_{24}BrN_2O_4S^+$: 516,42; found: 516,97. Anal. calcd. for $C_{24}H_{23}BrN_2O_4S$, %: C 55.93; H 4.50; Br 15.49; N 5.44; O 12.42; S 6.22; found: C 55.86; H 4.47; Br 15.58; N 5.40; O 12.38; S 6.31.

2.1.2. General Method for Compound 5 Preparation

A mixture of 2-arylmethylidentiazolo[3,2-*a*]pyrimidine (1.0 mmol) **3**, pyridine (0.1 mmol) and methanol (10 mL, 0.25 mol) was subjected to MW for 6 h and at a dynamic power of 100 W. The solvent was then removed at a rotary evaporator, the resulting yellow oil was dissolved in methylene chloride and purified by column chromatography using as eluent a solvent system of 1) hexane/ethyl acetate (4/1) and 2) methanol. The solvent was then removed at a rotary evaporator until a precipitate was formed.

3-(4-Bromophenyl)-6-(ethoxycarbonyl)-7-methyl-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid **5**. Yield 61%, white crystals, mp 218–220 °C. IR (KBr, cm^{-1}): 3418 (OH); 1698, 1676 (C=O); 1639 (C=N); 762 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δH ppm: 0.96 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.78–3.95 (m, 2H, OCH_2CH_3), 4.06 (d, *J* = 9.6 Hz, 1H, CH-COOH), 4.73 (d, *J* = 9.6 Hz, 1H, CH-Ar), 4.76 (s, 1H, CH-Ph), 6.99–7.01 (m, 2H, CH (Ar)), 7.26–7.33 (m, 5H, CH (Ar)), 7.63–7.65 (m, 2H, CH (Ar)). MS (ESI), *m*/*z*, $[M + H]^+$: calcd. for $C_{23}H_{22}BrN_2O_4S^+$: 502,40; found: 503,17. Anal. calcd. for $C_{23}H_{21}BrN_2O_4S$, %: C 55.10; H 4.22; Br 15.94; N 5.59; O 12.76; S 6.39; found: C 55.05; H 4.18; Br 16.00; N 5.57; O 12.80; S 6.40.

2.1.3. Crystallization Conditions

Crystals of compound **4** suitable for X-ray diffraction study were obtained by slow evaporation of a hexane (5 mL)/ethyl acetate (5 mL) solution containing 0.02 mol of the dissolved compound after 3 days.

2.1.4. Single Crystal X-Ray Diffraction

Single-crystal X-ray diffraction (SC XRD) study was performed on a Bruker D8 QUEST automated three-circle diffractometer with a PHOTON III area detector and an IμS DIAMOND microfocus X-ray tube at a temperature of 100(2) K for compound **4**: λ(Mo *Kα*) = 0.71073 Å, ω/ϕ-scanning mode with a step of 0.5°. *APEX3* software package was used to index the diffraction data and to determine and refine the unit cell parameters. Numerical absorption correction based on the crystal shape, additional spherical absorption correction, and systematic error correction were performed using the *SADABS*-2016/2 software [14]. Structures were solved by direct methods using the *SHELXT*-2018/3 program [15] and refined by full-matrix least-squares on F^2 using the *SHELXL*-2018/3 program [16]. Nonhydrogen atoms were refined anisotropically. The positions of hydrogen atoms of methyl groups were inserted using the rotation of the group with idealized bond angles; the remaining hydrogen atoms were refined using a riding model. Most calculations were performed using the *WinGX* software package [17]. Crystallographic data for structures are listed in Table 1.

Table 1. Crystallographic data and X-ray experimental parameters for the single crystals of compound **4.**

Compound	4 (from Hexane/EtOAc)
Molecular formula	C_{24} H_{23} Br N_2 O_4 S
Formula Weight	515.42
Crystal System	triclinic
Space group	P-1 (No. 2)
Cell parameters	**a** 8.9860(6) **b** 9.9645(7) **c** 13.6972(8) **α** 104.984(2) **β** 107.461(2) **γ** 90.864(2)
V [Å3]	1124.44(13)

Z and Z′	2 and 0
D(calc) [g/cm^3]	1.519
λ (Å)	MoK\α (0.71073)
μ [/mm]	1.955
F(000)	526
Theta Min-Max [Deg]	2.127–31.999
Reflections measured	45823
Independent reflections	7800
Observed reflections [I > 2σ(I)]	6638
Goodness of fit	1.029
R [I > 2σ(I)]	R1 = 0.0401 wR2 = 0.1022
R (all reflections)	R1 = 0.0497 wR2 = 0.1065

3. Results and Discussion

2,3-Disubstituted-2,3-dihydrothiazolo[3,2-*a*]pyrimidines 4,5 were synthesized according to Figure 3. The first step was a three-component Biginelli condensation between acetylacetone, thiourea and benzaldehyde carried out in sulfuric acid [11]. The obtained 1,2,3,4-tetrahydropyrimidine-2-thiones **1** were involved in the reaction of sulfur atom alkylation by ethyl chloroacetate followed by cyclization with the formation of thiazolo[3,2-*a*]pyrimidine-3-one **2** [12]. Knevenagel condensation between *CH*-active component of thiazolo[3,2-*a*]pyrimidine **2** and 4-brombenzaldehyde carried out in boiling ethanol in the presence of piperidine as a base leads to 2-arylmethylidentiazolo[3,2-a]pyrimidine **3** [13]. Finally methanolysis reaction of 2-arylmethylidene derivative **3** in the presence of pyridine under MW for 2 h gave the target 2,3-disubstituted-2,3-dihydrothiazolo[3,2-*a*]pyrimidine **4** in almost quantitative yields (96%) [9]. When the reaction was carried out in aqueous methanol for six hours, the hydrolysis product **5** was detected. Only the methoxycarbonyl group in the second position of the thiazolopyrimidine scaffold was hydrolyzed, while the ethoxycarbonyl group in sixth position remained unaffected. The successful separation of the reaction mixture by column chromatography led to the identification of 3,5-diaryl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acid **5**, with a yield of 61%.

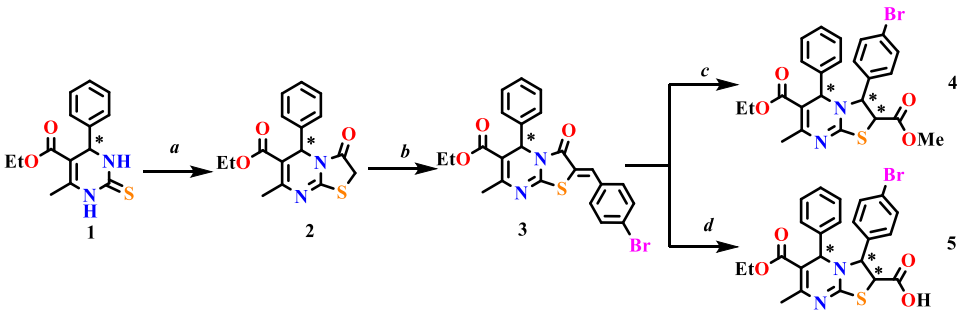
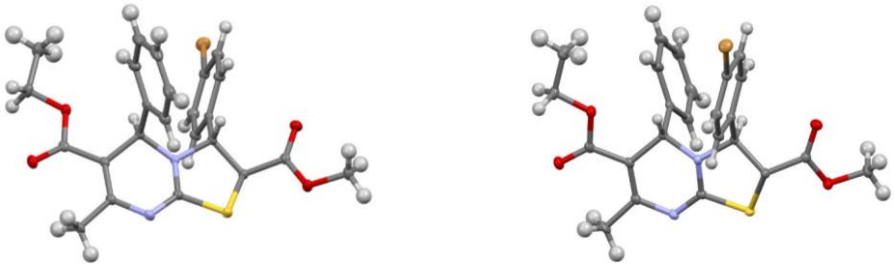


Figure 3. Synthesis 2,3-Disubstituted-2,3-dihydrothiazolo[3,2-*a*]pyrimidines **4** and **5**. Reagents and conditions: (*a*) $ClCH_2CO_2Et$, 120 °C, no solvent; (*b*) 4-brombenzaldehyde, EtOH, piperidine, reflux, 6 h; (*c*) MeOH, pyridine, MW, 2 h; (*d*) MeOH, pyridine, MW, 6 h; *—asymmetric carbon atom.

The obtained derivatives were characterized by a complex of physicochemical methods. As a result of ^{1}H NMR analysis of compound **4**, only one set of signals was detected. At the same time, the structure of compound **4** was confirmed by X-ray diffraction analysis (see Figure 4). The investigation revealed that a single pair of stereoisomers is formed during the reaction. The formation of *S*-,*R*-,*R*- и *R*-,*S*-,*S*- isomers with *trans*-orientation between substituents at asymmetric carbon atoms was observed. Thus, these observations

demonstrate that the methanolysis reaction proceeds diastereoselectively. The details of the structure of compound **4** and processing parameters are summarized in Table 1.



(**a**) (**b**)

Figure 4. ORTEP view of molecule **4** in the crystalline phase (**a**) *S*-,*R*-,*R*-isomer (**b**) *R*-,*S*-,*S*-isomer; (C, O, N, S, Br, and H-atoms are presented as grey, red, blue, yellow, brown, and light grey ellipsoids with 50% probability, respectively).

4. Conclusions

In this work, new 2,3-disubstituted 2,3-dihydrothiazolo[3,2-*a*]pyrimidine derivatives in almost quantitative yields were obtained. Additionally, a method for obtaining previously unavailable 3,5-diaryl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxylic acids in good yields was also described. The investigation revealed that the methanolysis reaction of the 2-arylmethylidentiazolo[3,2-*a*]pyrimidine derivatives under MW proceeded diastereoselectively, namely with the formation a single pair of enantiomers (*S*-,*R*-,*R*- и *R*-,*S*-,*S*-isomers).

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: ^{1}H NMR spectrum of compound **4** (DMSO-d_6, 600 MHz, 25 °C); Figure S2: ESI MS spectrum of compound **4** (ion polarity: positive); Figure S3: IR spectrum of compound **4** (KBr tablet); Figure S4: ^{1}H NMR spectrum of compound **5** (DMSO-d_6, 400 MHz, 25 °C); Figure S5: ESI MS spectrum of compound **5** (ion polarity: positive); Figure S6: IR spectrum of compound **5** (KBr tablet).

Author Contributions: Conceptualization A.K. and A.A.; methodology, A.O. and I.L.; validation, A.K., A.A. and I.L.; formal analysis, I.L.; investigation, A.K. and A.N.; resources, I.L.; data curation, A.K. and A.A.; writing—original draft preparation, A.K.; writing—review and editing, A.K. and A.A.; visualization, A.K.; supervision, A.K., A.A., S.S. and I.A.; project administration, S.S. and I.A.; funding acquisition, S.S. and I.A. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are contained within the article or in Supplementary Materials, or are available on request from the corresponding author Andrey Kozhikhov.

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Conflicts of Interest: The authors declare no conflict of interest.

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