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1,3-Dipolar Cycloaddition Reactions of 2-Arylmethylidentiazolo[3,2-*a*]pyrimidines with Azomethinylides, Studying the Supramolecular Organization of Products in the Crystalline Phase †

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Abstract: The [3+2]-cycloaddition of azomethinylides formed in situ to dipolarophiles is a promising approach for the synthesis of dispyroderivatives of oxindole and acenaphthenedione. In the course of our studies, it was shown that the cycloaddition of azomethinylides occurs specifically through the exocyclic double C=C bond resulting in the formation of a new pyrrolidine cycle as part of the molecule and, consequently, a dispyroheterocycle. This work is devoted to the synthesis and structural analysis of dispyrothiazolo[3,2-*a*]pyrimidine in the crystalline phase.

Keywords: thiazolo[3,2-*a*]pyrimidines; 2-arylmethylidene derivatives of thiazolo[3,2-*a*]pyrimidines; dispyrocompounds; [3+2]-cycloaddition; azomethinylides; supramolecular chemistry; crystal engineering; stereoselectivity

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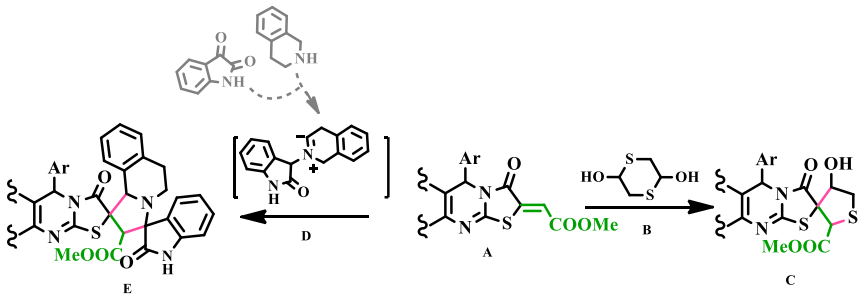
1. Introduction

The reactions of [3+2]-dipolar cycloaddition are interest to researchers due to the wide range of reagents and the ease of the reaction, and, consequently, the great synthetic potential for the development of fundamental chemical science, as well as for the preparative and industrial preparation of practically important compounds (pharmaceutical industry, agriculture, textile industry, etc.) [1–5].

Thiazolo[3,2-*a*]pyrimidine derivatives as a subject of research were selected not coincidence. Thiazolopyrimidine and oxindole frameworks are promising structural frameworks for the development of pharmaceutical compounds, since their derivatives are known to possess a range of pharmacological activities, including antipsychotic [6], anti-inflammatory [7] and analgesic [8–11] effects. Previously, our research group studied the anti-inflammatory activity of various 2-arylmethylidenethiazolo[3,2-*a*]pyrimidines in the relation to cancer cell lines, and identified leading compounds against M-Hela, that exhibited efficiency exceeding twice that of the to the reference drug *Sorafenib* [12,13].

Similar to 2-arylmethylidene derivatives of thiazolo[3,2-*a*]pyrimidine in structure, 2-methylidene carboxylates (Scheme 1, compound A) demonstrate a series of chemical transformations proceeding along the multiple double bond of the molecule, in some cases playing the role of a dipolarophile. These include interactions with such reagents as

cyclic disulfide B, azomethionylide D (generated from isatin and 1,2,3,4-tetrahydroisoquinoline), leading to the formation of spiroheterocyclic compounds C,E [14–17].



Scheme 1. 1,3-Dipolar cycloaddition of 2-methylidene carboxylates.

Hence, single examples of interaction of 2-substituted thiazolopyrimidines containing a C=C double bond with dipoles have been described in the literature, but the chemical conduct of 2-arylmethylidenethiazolopyrimidines has not been studied in the [3+2]-cycloaddition of the exocyclic double bond of the thiazolidine fragment. This fact allows us to expand the library of potentially important systems containing the thiazolopyrimidine fragment.

2. Materials and Methods

All chemicals were purchased from commercial suppliers and used without additional purification. The 1,2,3,4-tetrahydropyrimidin-2-thiones [18], thiazolo[3,2-*a*]pyrimidines [19,20] and 2-arylmethylidene derivatives of thiazolo[3,2-*a*]pyrimidine [21] were synthesized according to the described methods.

NMR experiments were performed on Bruker Avance 400 (Saarbrucken, Germany). Chemical shifts were determined relative to the signals of residual protons of the DMSO-*d6*. Electrospray ionization (ESI) mass spectra were obtained using a Bruker AmaZon X ion trap mass spectrometer.

General Method for the Preparation of Compounds **4**, **5**.

A mixture of 2-arylmethylidentiazolo[3,2-*a*]pyrimidine (200 mg, 1.0 mmol), 1,2-diketone (2.0 mmol), and sarcosine (80 mg, 2.0 mmol) in methanol (10 mL) was refluxed in an oil bath for appropriate time 8–12 h. After completion of the reaction as evident from TLC Hexane/EtOAc 4:1, the reaction was cooled at room temperature. Next, the reaction mixture was filtered off without any further purification.

Spiropyrrolidinoxindole derivative of (*Z*)-ethyl 2-benzylidene-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-6-carboxylate 4.

Yield 72%, yellow powder, mp 259–263 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δH ppm: 1.17 (t, *J* = 7.1 Hz, 3H, -CH2CH3), 2.24 (s, 3H, CH3), 2.29 (s, 3H, CH3), 3.43–3.47 (m, 1H, CH2), 4.02–4.10 (m, 2H, -CH2CH3), 4.13–4.18 (m, 1H, CH2), 5.18 (s, 1H, NH), 5.82 (s, 1H, CH-Ph), 6.80–6.83 (m, 3H, CH (Ph)), 7.12–7.16 (m, 1H, CH (isatin)), 7.20–7.21 (m, 3H, CH (Ph)), 7.29–7.32 (m, 3H, CH (isatin)), 7.34–7.37 (m, 3H, CH (Ph)), 7.49–7.51 (m, 1H, CH (Ph)). MS (ESI), m/z, [M+H]+: calcd. for C33H30N4O4S+: 578,68; found: 576,06. Anal. Calcd. for C33H30N4O4S, %: C 68.49; H 5.23; N 9.68; O 11.06; S 5.54. Found C 68.50; H 5.27; N 9.62; O 11.10; S 5.51

Spiroacenaphthenquinone derivative of (*Z*)-ethyl 2-benzylidene-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-6-carboxylate 5.

Yield 77%, orange crystals, mp 261–266 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δH ppm: 1.16(t, *J* = 7.2 Hz, 3H, -CH2CH3), 2.15 (s, 3H, CH3), 4.00–4.09 (m, 2H, -CH2CH3), 4.13–4.18 (m, 1H, CH2), 4.23–4.27 (m, 1H, CH2), 5.82 (s, 1H, CH-Ph), 7.23–7.25 (m, 3H, CH (Ph)), 7.29–7.30 (m, 2H, CH (Ph)), 7.36–7.37 (m, 3H, CH (Ph)), 7.74–7.78 (m, 2H, CH (Ph)), 7.85 (d, *J* = 6.8 Hz, 1H, CH (quinone)), 7.90 (d, *J* = 6.8 Hz, 1H, CH (quinone)) 7.96 (d, *J* = 8.0 Hz, 1H, CH (quinone)), 8.15 (d, *J* = 8.0 Hz, 1H,

CH (quinone)). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C) δC ppm: 14.59, 23.02, 35.58, 55.75, 58.62, 60.90, 72.76, 82.02, 108.66, 121.69, 125.10, 126.77, 128.33, 128.57, 129.25, 129.65, 130.69, 131.12, 131.63, 132.71, 134.47, 137.44, 140.39, 144.55, 152.95, 158.28, 165.92, 175.42, 207.30. MS (ESI), m/z, [M+H]+: calcd. for C37H31N3O4S+: 613,72; found: 614,32. Anal. Calcd. for C37H31N3O4S, %: C 72.41; H 5.09; N 6.85; O 10.43; S 5.22. Found C 72.35; H 5.10; N 6.80; O 10.42; S 5.33

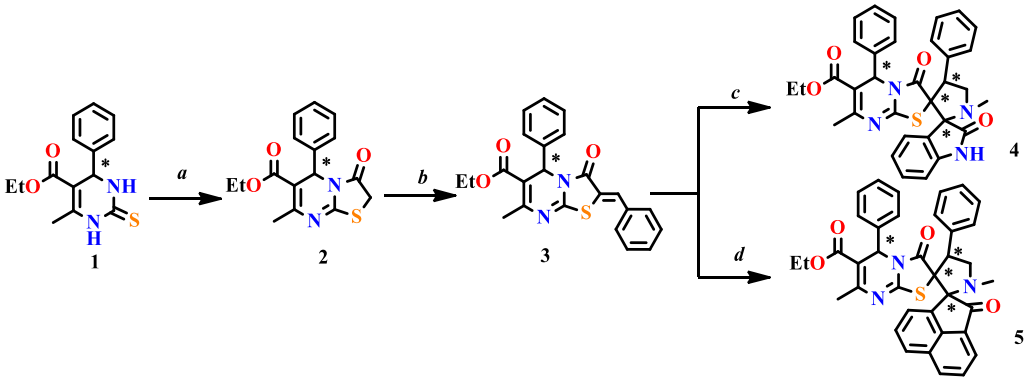
The crystals of 4 suitable for an X-ray diffraction study were obtained by slow evaporation of a solution in DMF/MeOH (3/1 mL) containing 0.02 mol of the dissolved compound after 7 days.

The structures of 4 were solved by the direct method using the SHELXT program [22] and refined by the full-matrix least squares method over F2 using the SHELXL program [23]. All calculations were performed in the WinGX software package [24], the calculation of the geometry of molecules and intermolecular interactions in crystals was carried out us-ing the PLATON program [25], the drawings of molecules were performed using the OR-TEP-3 [24] and MERCURY [26] programs.

3. Results and Discussion

3.1. Synthesis of the Dispyrothiazolo[3,2-a]pyrimidines **4**,**5**

Dispyrothiazolo[3,2-a]pyrimidines 4,5 were synthesized according to Scheme 2. The first step involved the reaction of the 1,2,3,4-tetrahydropyrimidine-2-thiones 1 with ethyl chloroacetate, resulting in the alkylation of the sulfur atom and subsequent cyclization with the formation of thiazolo[3,2-a]pyrimidine-3-one 2 [19,20]. Interaction of the CH-active derivative 2 with benzaldehyde under Knoevenagel reaction conditions led to 2-benzylidenetiazolo[3,2-a]pyrimidine 3 [21]. Finally, three-component condensation of compound **3** with azomethinylides generated in situ from 1,2-diketo derivative and sarcosine gave the target derivatives 4,5 in good yields (69–76%).



Scheme 2. Synthesis Dispyrothiazolo[3,2-*a*]pyrimidines 4,5. Reagents and conditions: (a) ClCH2CO2Et, 120 °C, no solvent; (b) benzaldehyde, EtOH, pyrollidine, 8 h, reflux; (c) 1,2-diketone, sarcosin, MeOH, 9 h, reflux, *—asymmetric carbon atom.

The target compounds were obtained in fairly high yields due to the regio- and diastereoselective reaction. The chemical structure was determined on the basis of a number of physicochemical analytical methods, including X-ray single crystal analysis as well as ^{1}H NMR and ^{13}C NMR spectral analysis. Only single set of signals was detected by ^{1}H NMR analysis, which confirms the selectivity of this method.

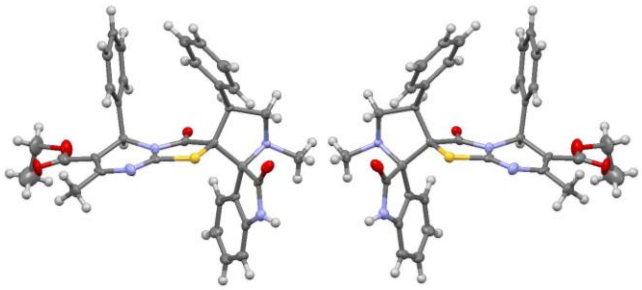
3.2. X-Ray Structure of **4**

The structure of compound **4**, crystallized in trigonal crystal system and space group R3c with one molecule per asymmetric unit and Z = 18, is represented by the only enantiomeric pair out of 4 possible ones, namely RSRR- and SRSS- isomers. The details of the structure and processing parameters are summarized in Table 1. The X-ray structure with 50% probability along with atom numbering is given in Figure 1 while the bonding

distances and angles are given in Table 1. It is worth to note that an anti-endo approach of the azomethynylide formed during the reaction to the exocylic double bond of 2-arylmethylidene derivative is carried out. Such regioselectivity is confirmed by NMR and PCA data. Curiously, pores with a diameter of 9 Å were observed during the analysis of the crystalline packaging. The additivity of structure-forming actions of hydrogen bonding of O-H...N type and weak Van-der-Waals interactions leads to the realization of porous supramolecular architecture in the crystalline phase (Figure 2).

Table 1. Experimental crystal dataset of the target molecule.

Compound	**4 (from DMF/MeOH)**
Molecular formula	C_{33} H_{30} N_4 O_4 S
Formula Weight	578.67
Crystal System	trigonal
Space group	R3c
Cell parameters	**a** 36.777(5) **b** 36.777(5) **c** 11.376(2) α 90 β 90 γ 120
V [Å^3]	13,325.2
Z and Z′	18 and 0
D(calc) [g/cm^3]	1.298
λ (Å)	MoK\α (0.71073)
μ [/mm]	0.154
F(000)	5472
Theta Min-Max [Deg]	1.918–27.489
Reflections measured	35,687
Independent reflections	6434
Observed reflections [I > 2σ(I)]	3725
Goodness of fit	0.935
R [I > 2σ(I)]	R1 = 0.0653 *w*R2 = 0.1269
R (all reflections)	R1 = 0.1477 *w*R2 = 0.1565
Depositor numbers in CCDC	



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

Figure 1. ORTEP view of molecule 4 in the crystalline phase (**a**) RSRR-isomer (**b**) SRSS-isomer; (C, O, N, S, and H-atoms are presented as grey, red, light-violet, yellow, and light grey ellipsoids with 50% probability, respectively).

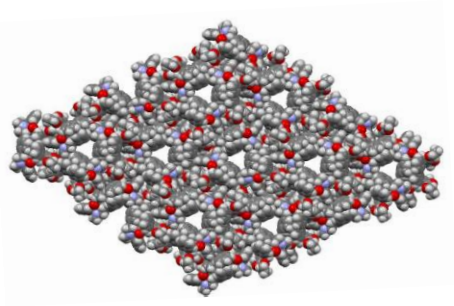


Figure 2. ORTEP view of crystal packing of molecule 4 in the crystalline phase (C, O, N, and H-atoms are presented as grey, red, light-violet, and light grey ellipsoids with 50% probability, respectively).

4. Conclusions

In this work, new dispyrothiazolo[3,2-*a*]pyrimidines have been synthesized. The use of NMR and X-ray spectroscopy has demonstrated that the reaction of 1,3-dipolar cycloaddition proceeds regio- and diastereoselectively with the formation of only one pair of enanthiomers, namely RSRR- and SRSS- isomers. The formation of a porous structure in crystalline samples of this compound makes them suitable for use as adsorption agents.

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