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Synthesis and Supramolecular Organization of *para*-Carboxyhydrazinylidene Derivative of 3-Nitrophenylthiazolo[3,2-*a*]pyrimidine †

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Abstract: Synthesis of *para*-carboxyhydrazinylidene derivative of 3-nitrophenylthiazolo[3,2-*a*]pyrimidine was successfully performed in good yields. It was established different types of non-covalent intermolecular interaction may influence on supramolecular motif synthesized compound. Hydrogen- and chalcogen-bonding supramolecular driving forces collective impact results to two types of the centrosymmetric racemic dimeric self-assembly in crystalline phase.

Keywords: thiazolo[3,2-*a*]pyrimidines; arylhydrazone derivatives; crystal structure; crystalline phase; non-covalent interactions; racemic dimers; homochiral chains; X-ray diffraction

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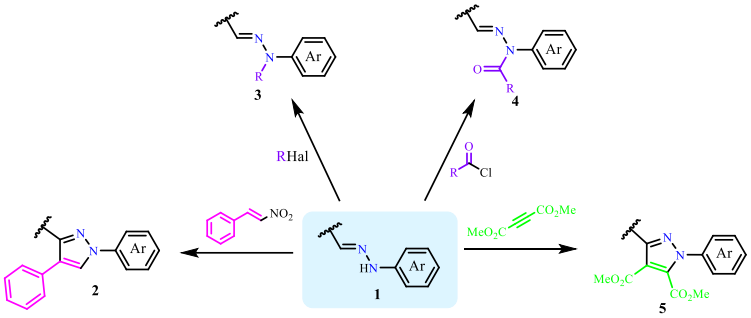
1. Introduction

The chemistry of heterocyclic compounds is one of the leading areas of organic chemistry. These compounds can serve as the basis for both natural biologically active substances and synthetic ones. In recent years, thiazolopyrimidines have been of interest because of their medicinal properties that can be used in medicine. These include antimicrobial [1], anti-inflammatory [2], analgesic [3], antiviral [4] and anti-tumor effects [3].

Due to their ability to react with electrophilic and nucleophilic reagents, hydrazones are widely used in organic synthesis, particularly in the preparation of heterocyclic compounds.

On the other hand, arylhydrazone derivatives are also promising building blocks for drug design. The chemical properties of the arylhydrazone derivatives **1** are quite diverse and the literature provides examples of interactions with reagents of different nature with C=N-NH fragment. These reactions can be divided into two types of chemical transformations, including (1) alkylation [5] and acylation [6] along the NH nucleophilic centre and (2) formation of new heterocyclic structures, namely the formation of a pyrazole ring in interaction with nitroolefins [7] and acetylenedicarboxylic acid esters [8] (Scheme 1).



Scheme 1. Chemical properties of arylhydrazone derivatives known in the literature.

The inclusion of functional groups into hydrazone molecules expands their range of applications in organic synthesis. Furthermore, the functionalization of the hydrazone group leads to the production of compounds with unique physical and chemical properties [9].

Hence, the combination of two pharmacophore blocks, namely the thiazolo[3,2-*a*]pyrimidine platform and arylhydrazone moiety, as part of a single compound is a promising direction for the development of medicinal products. This will expand the library of potentially important systems containing the thiazolopyrimidine fragment.

2. Materials and Methods

NMR experiments were performed on Bruker Avance 500 (Saarbrucken, Germany). Chemical shifts were determined relative to the signals of residual protons of the DMSO-d_6. MALDI mass spectra were obtained using an UltraFlex III TOF/TOF spectrometer in the linear mode; p-nitroaniline was used as the matrix. The melting points were determined on a BOETIUS melting table with an RNMK 05 imaging device. IR spectra in KBr tablets were recorded on a Bruker Vector-22.

The method of halogens determination is based on the combustion at 1200 °C of organic compound in oxygen in the presence of a platinum catalyst; the combustion products are adsorbed by the alkali and the halides formed were determined by mercurimetric titration with diphenylcarbazone as an indicator.

CHNS elemental analysis was carried out using a high-temperature one-/two-reactor analyzer (oxidation tube and reduction tube) EuroEA3028-HT-OM "Eurovector SpA".

Synthesis of 4-(2-(6-(Ethoxycarbonyl)-7-methyl-5-(3-nitrophenyl)-3-oxo-5H-thiazolo[3,2-a]pyrimidin-2(3H)-ylidene)hydrazineyl)benzoic acid **8**

A solution consisting of sodium nitrite (1 mmol), sodium hydroxide (1 mmol), *para*-aminobenzoic acid (1 mmol) in water (3 mL) was added drop by drop to a cooled hydrochloric acid (5 mmol) solution in water (5 mL) with stirring at 0–5 °C for 1 h. The resultant solution of aryldiazonium chloride (1 mmol) was added in portions with stirring at 0–5 °C to a cold solution of the corresponding thiazolo[3,2-*a*]pyrimidine 7 (1 mmol) and sodium acetate (1.1 mmol) in ethyl alcohol (10 mL). The mixture was stirred at room temperature for 2 h. Next, the reaction mixture was diluted with water, and the crude precipitate was collected by filtration, washed with water, and crystallized from ethanol.

4-(2-(6-(ethoxycarbonyl)-7-methyl-5-(3-nitrophenyl)-3-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-2(3*H*)-ylidene)hydrazineyl)benzoic acid **8**. Yield 78%, orange powder, mp 256–258 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ_H ppm: 1.11 (t, *J* = 7.1 Hz,3H, OCH2CH3), 2.43 (s, 3H, CH3), 4.00–4.08 (m, 2H, OCH2CH3), 6.16 (s, 1H, CH-Ar), 7.28 (d, *J* = 7.1 Hz, 2H, CH (Ar)), 7.67–7.71 (m, 1H, CH (Ar)), 7.79–7.80 (m, 1H, CH (Ar)), 7.89 (d, *J* = 7.1 Hz, 2H, CH (Ar)), 8.12 (m, 1H, CH (Ar)), 8.18–8.20 (m, 1H, CH (Ar)), 11.23 (s, 1H, NH), 12.62 (br. s, 1H, COOH). IR (KBr, cm^{-1}): 3429 (COOH), 3235 (NH); 1722 (C=O); 1704 (C=O); 1543 (C-C(Ph)). MS (MALDI-TOF), *m*/*z*, [M − H]$^-$: calcd. for $C_{23}H_{19}N_5O_7S^-$: 509.49; found: 507.8.

Anal. Calcd. for $C_{23}H_{19}N_5O_7S$, %: C 54.22; H 3.76; N 13.75; O 21.98, S 6.29. Found C 54.23; H 3.78; N 13.73; S 6.29.

Crystal of **8** suitable for X-ray diffraction study were obtained by slow evaporation of dimethylsulfoxide (DMSO) solution (20 mL) containing 0.02 mol of the dissolved compound after 5 days. All structures were solved by the direct method using the SHELXT program [10] and refined by the full-matrix least squares method over F^2 using the SHELXL program [11]. All calculations were performed in the WinGX software package [12], the calculation of the geometry of molecules and intermolecular interactions in crystals was carried out using the PLATON program [13], the drawings of molecules were performed using the ORTEP-3 [12] and MERCURY [14] programs.

Non-hydrogen atoms were refined in the anisotropic approximation. The positions of the hydrogen atoms H(O) were determined using difference Fourier maps, and these at-oms were refined isotropically. The remaining hydrogen atoms were placed in geometrically calculated positions and included in the refinement in the "riding" model. The crystallographic data of structure **8** was deposited at the Cambridge Crystallographic Data Center, and the registration number and the most important characteristics are given in Table 1.

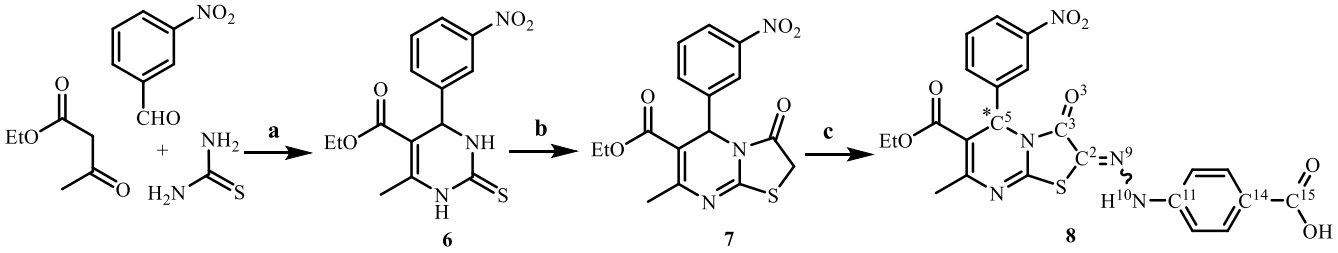
Table 1. Crystallographic data for compound **8**.

Compound	**3**
Molecular formula	$C_{23}H_{19}N_5O_7S \cdot C_2H_6OS$
Formula	$C_{23}H_{19}N_5O_7S$
Formula Weight	587.62
Crystal System	triclinic
Space group	P-1
Cell parameters	*a = 7.875 (3) Å,* *b = 17.716 (8) Å,* *c = 19.076 (7) Å;* *α = 95.852 (14)* ° *β = 90.594 (18)* ° *γ = 96.876 (12)* °
V [Å^3]	2627.7 (19)
Z and Z′	4 and 0
D(calc) [g/cm^3]	1.485
λ (Å)	0.71073
μ [/mm]	0.263
F(000)	1224
Theta Min-Max [Deg]	0.7178; 0.7457
Reflections measured	30,112
Independent reflections	12979
Observed reflections [I > 2σ(I)]	5734
Goodness of fit	1.024
R [I > 2σ(I)]	*R1 = 0.0720,* *wR2 = 0.1968*
R (all reflections)	*R1 = 0.1409,* *wR2 = 0.2347*
Max. and Min. Resd. Dens. [e/Å^{-3}]	0.339 and 0.376
Depositor numbers in CCDC	

3. Results and Discussion

4-Carboxyphenylhydrazinylidene derivative of thiazolo[3,2-a]pyrimidine was obtained according to the following Scheme 2. To obtain the initial 1,2,3,4-

tetrahydropyrimidine-2-thion **6**, a three-component Biginelli reaction was carried out between 3-nitrobenzaldehyde, thiourea and acetoacetic ether in a molar ratio of 1:1.5:1 by heating the reagents at 120 °C under solvent-free conditions, which led to almost quantitative yields of the product [15]. Precursor for the desired compound was obtained by the interaction of tetrahydropyrimidine-2-thion **6** with ethyl chloroacetate when heated at 110–120 °C [16]. The target product **8** was synthesized by reaction of converted to a base thiazolo[3,2-a]pyrimidine **7** with freshly prepared 4-carboxyphenyldiazonium salt in the presence of sodium acetate. The structure of the obtained compound was characterized by ^{1}H- and IR-spectroscopy, mass-spectrometry and single-crystal X-ray.



Scheme 2. Synthesis of 4-(2-(6-(ethoxycarbonyl)-7-methyl-5-(3-nitrophenyl)-3-oxo-5*H*-thiazolo[3,2-a]pyrimidin-2(3*H*)-ylidene)hydrazineyl)benzoic acid **8**. Reagents and conditions: (a) no solvent; (b) $ClCH_2CO_2Et$, 120 °C, no solvent; (c) 4-COOH-$C_6H_4N_2^+Cl^-$, AcONa, EtOH, 2h, 0–5 °C; *—asymmetric carbon atom.

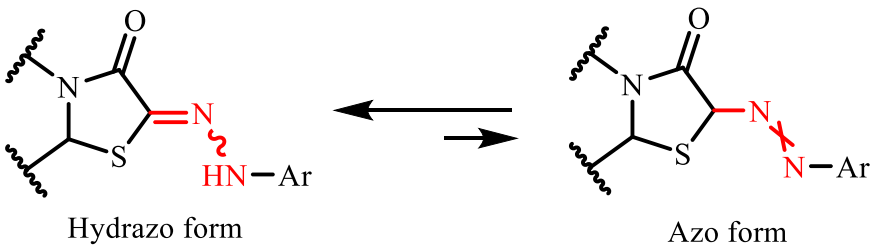
The target arylhydrazone is characterized by the possibility of the existence of azo-hydrazone tautomerism (Scheme 3). A proton signal in the form of a singlet in the weak-field region was registered by ^{1}H NMR spectroscopy (Table 2).

Table 2. Chemical shifts (ppm) of proton signals in ^{1}H NMR spectra of compound **8.**

$OCH_2\underline{CH_3}$	CH_3	$O\underline{CH_2}CH3$	<u>CH</u>-Ar	CH (Ar) *	NH	COOH
1.11 (t)	2.43 (s)	4.00-4.08 (m)	6.16 (s)	7.27-8.20	11.23 (s)	12.62 (br. s)

* The signals of these protons are in the presented region as a number of doublets and multiplets.

This signal relates to the proton of the NH hydrazone form rather than the proton of the CH azo form, which indicates the formation of only one tautomeric form – the hydrazone.



Scheme 3. Azo-hydrazo-tautomerism.

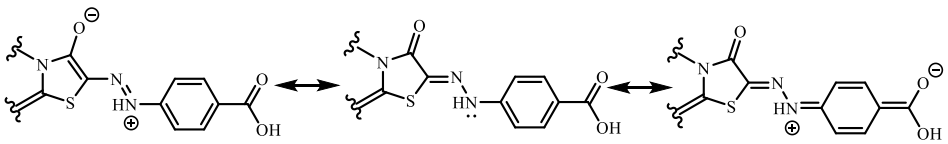
Crystal for single-crystal X-ray diffraction analysis was obtained by slow evaporation of a solution of **8** in dimethylsulfoxide (DMSO). The bond lengths of the arylhydrazone fragment are shown in Table 3.

Table 3. The bond lengths of the arylhydrazone fragment.

Bond	Length (Å)
O^3-C^3 *	1.202 (5)
C^2-C^3	1.491 (6)
C^2-N^9	1.289 (6)
N^9-N^{10}	1.323 (5)
N^{10}-C^{11}	1.371 (5)
C^{14}-C^{15}	1.469 (6)

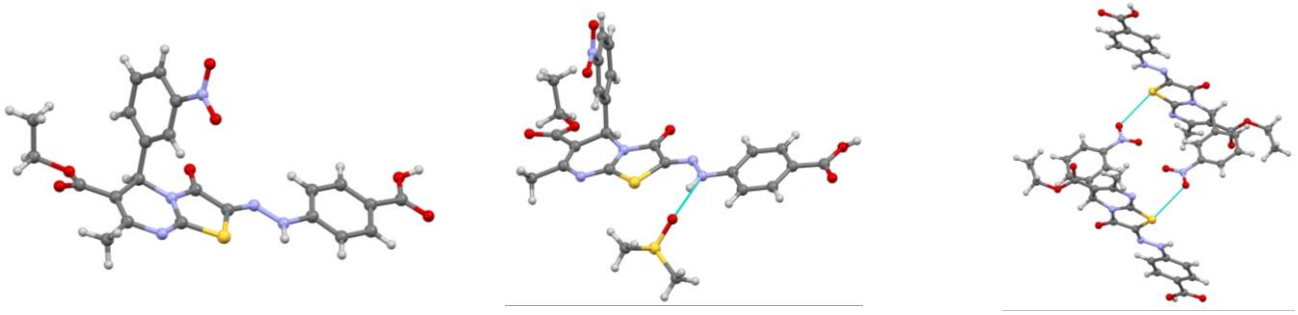
* See the numbering of atoms in Scheme 1.

The bond length between the thiazolidine carbon atom C^2 and the nitrogen atom N^9 is 1.289 (6) Å for crystal **8**, the length of the double C=N bond from the literature data is 1.280 Å. This fact confirms the formation of only the hydrazone form. The bond lengths of C^2-C^3 and N^9-N^{10} of the hydrazone fragment are 1.491 (6) Å and 1.323 (5) Å. Both lengths are shorter compared to the literature for the appropriate single bonds. While the lengths double C=N bond are slightly longer than the classical C=N bond. It may be concluded about the conjugation and electron density delocalization in this fragment, and two canonical structures contribute to the structure (Scheme 4). The N^{10}-C^{11} and C^{14}-C^{15} bond lengths are also shortened, which indicates the conjugation of N^{10} nitrogen atom lone electron pair with double C=N bond and with 4-carboxyphenyl substituent. The cross-conjugation and hence a planar form of this fragment including the thiazolidinone cycle and the arylhydrazone fragment is confirmed by the presented arguments.



Scheme 4. Canonical structures of arylhydrozone fragment.

Compound **3** was found to be in the Z-configuration with relation to a multiple C=N double bond in the crystalline phase (Figure 1a). Furthermore, only one set of signals is observed in the ^{1}H NMR spectra of **8**, indicating the presence of a single geometric isomer in solution. Thus, the diastereoselectivity of the azo-combination reaction with aryldiazonium salt with the formation of the Z-isomer has been proved.



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

Figure 1. ORTEP view of: (**a**) molecule **8** in the crystalline phase (C, O, N, S, and H-atoms are presented as grey, red, blue, yellow, and light grey ellipsoids with 50% probability, respectively); (**b**) hydrogen-bonded crystallosolvates **8**-DMSO; (**c**) chalcogen-bonded centrosymmetric racemic dimers of crystal **8** (H-bonds and chalcogen bonds is presented by light blue dotted lines).

Analyzing the crystal packaging, it was found that two different enantiomers self-organize to form racemic dimers (Figure 2). The driving force of this process was the

intermolecular hydrogen OH...O bonding ($d_{O...O}$ = 2.613 Å) due to the interaction of two carboxyl groups of the para-carboxyhydrazinylidene fragment.

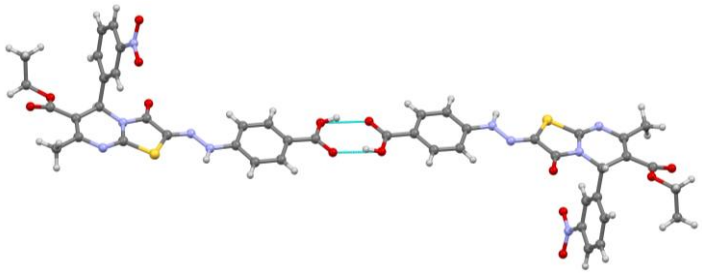


Figure 2. Hydrogen-bonded centrosymmetric racemic dimers of crystal **8**. H-bonds is presented by light blue dotted lines.

Another type of hydrogen bonding was found in crystal **8**. It was shown that the formation of a crystalline solvate occurs due to intermolecular hydrogen NH...O type bonding ($d_{N...O}$ = 2.776 Å) with a solvate molecule (Figure 1b).

An interesting fact was the formation of chalcogen S...O bonds between the thiazolidine ring's sulfur atom and the nitro-group. This supramolecular synthon was the reason for the realization of racemic dimers (Figure 1c).

4. Conclusions

Synthesis of 4-(2-(6-(ethoxycarbonyl)-7-methyl-5-(3-nitrophenyl)-3-oxo-5*H*-thiazolo[3,2-a]pyrimidin-2(3*H*)-ylidene)hydrazineyl)benzoic acid was successfully performed in good yields. The combined influence of all the above supramolecular driving forces leads to the implementation of three types of crystal self-assembly, namely racemic hydrogen-, chalcogen-bonded (O-H...O, NH…O, S…O types) dimers. Thus, by controlling intermolecular interactions, it is possible to influence the supramolecular motif of self-assembly in the crystalline phase. This can play a key role in chiral discrimination for further enantio-separation, the biological activity study and production of new supramolecular complexes with promising magnetic and/or adsorption properties.

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