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Synthesis and Quantum-Chemical Studies of New Hybrid Heterocyclic Molecules Derived from 3-(Thiocyanatoacetyl)Coumarin †

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Abstract: 3-(Thiocyanatoacetyl)coumarin, prepared by reaction of 3-(bromoacetyl)coumarin with KSCN, reacts with primary aryl amines to give new hybrid heterocyclic products, 3-(3-aryl-2-imino-2,3-dihydrothiazol-4-yl)-2H-chromen-2-ones. The structures and conformational features of the products have been studied by B3LYP-D3/6-311G(d,p) method.

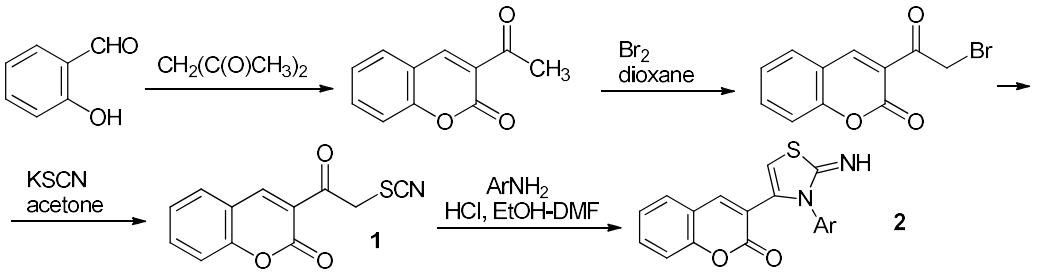
Keywords: 3-(bromoacetyl)coumarin; 3-(thiocyanatoacetyl)coumarin; heterocyclization; thiazolidines; DFT calculations

1. Introduction

Coumarins belong to privileged scaffolds useful as a starting point for preparation of druglike molecules [1]. We focused our interests on 3-thiocyanatoacetylcoumarins **1** are readily available through the bromination of 3-acetylcoumarins followed by subsequent nucleophilic substitution of bromine atom with SCN group [2–4]. Such thiocyanates have a high reactivity and useful as reagents for preparation of polyfunctional and polyheterocyclic structures. In general, α-thiocyanatocarbonyl compounds can be used in the synthesis of sulfur-containing heterocycles with potential biological activity (for reviews see [5–7]).

2. Results and Discussion

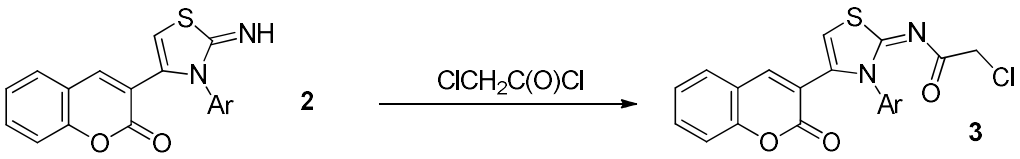
Thus, the reaction of compound **1** with anilines in an acidic medium lead to the formation of hybrid polycyclic systems **2** bearing the iminothiazoline fragment (Scheme 1). Such coumarin derivatives are of practical interest as perspective candidates for bioscreening [8–11].



Scheme 1. The synthetic pathway to hybrid molecules **2**.

The presence of the imino group in thiazole fragment provides very wide synthetic possibilities. Thus, the reaction of **2** with chloroacetyl chloride proceeds smoothly to give new chloroacetamides **3** (Scheme 2) useful as alkylating agents capable to introduce a hybrid polycyclic fragments into molecules.

The resulting compounds **2** were characterized using spectral methods (IR, NMR spectroscopy). Also, quantum-chemical DFT calculations of the most stable conformers of compound **2a** (R = H) were performed (Figure 1).



Scheme 2. The acylation of iminothiazolines **2**.

The preliminary conformational analysis of 3-(2-imino-3-phenyl-2,3-dihydrothiazol-4-yl)-2H-chromen-2-one using the semi-empirical RM1 method showed that this molecule can exist as two conformers (*s-trans* and *s-cis*) which are due to rotation around the C8– C11 bond (Figure 1). Since semiempirical methods in many cases led to incorrect results, further geometry optimization and energy DFT calculations were performed using the well-known functional B3LYP. The D3 Grimme's correction was used to describe the dispersion contribution to the energy to allow one to discuss the effect of the Van der Waals forces. The choice of the split valence basis set 6-311(d,p) was due to a compromise between the accuracy and the time of the calculation. The molecular structures of these conformers that were optimized using the B3LYP-D3 /6-311G (d, p) method are shown in Figure 1. According to the calculated data, the difference in energy between these conformations is 5.5 kJ/mol (the *s-trans* conformer is more stable). The C7-C8-C11-N12 torsion angle between the coumarin and thiazole fragments in the *s-trans* conformer is 24°, while the analogous C9-C8-C11-N12 angle in the *s-cis* conformer is 56°. It clearly points to the absence of conjugation between the heterocyclic cores. The C11-N12-C16-C21 torsion angle, which characterizes the mutual arrangement of thiazole ring and aromatic ring, in these conformers has somewhat closer values (45° and 55°, respectively).

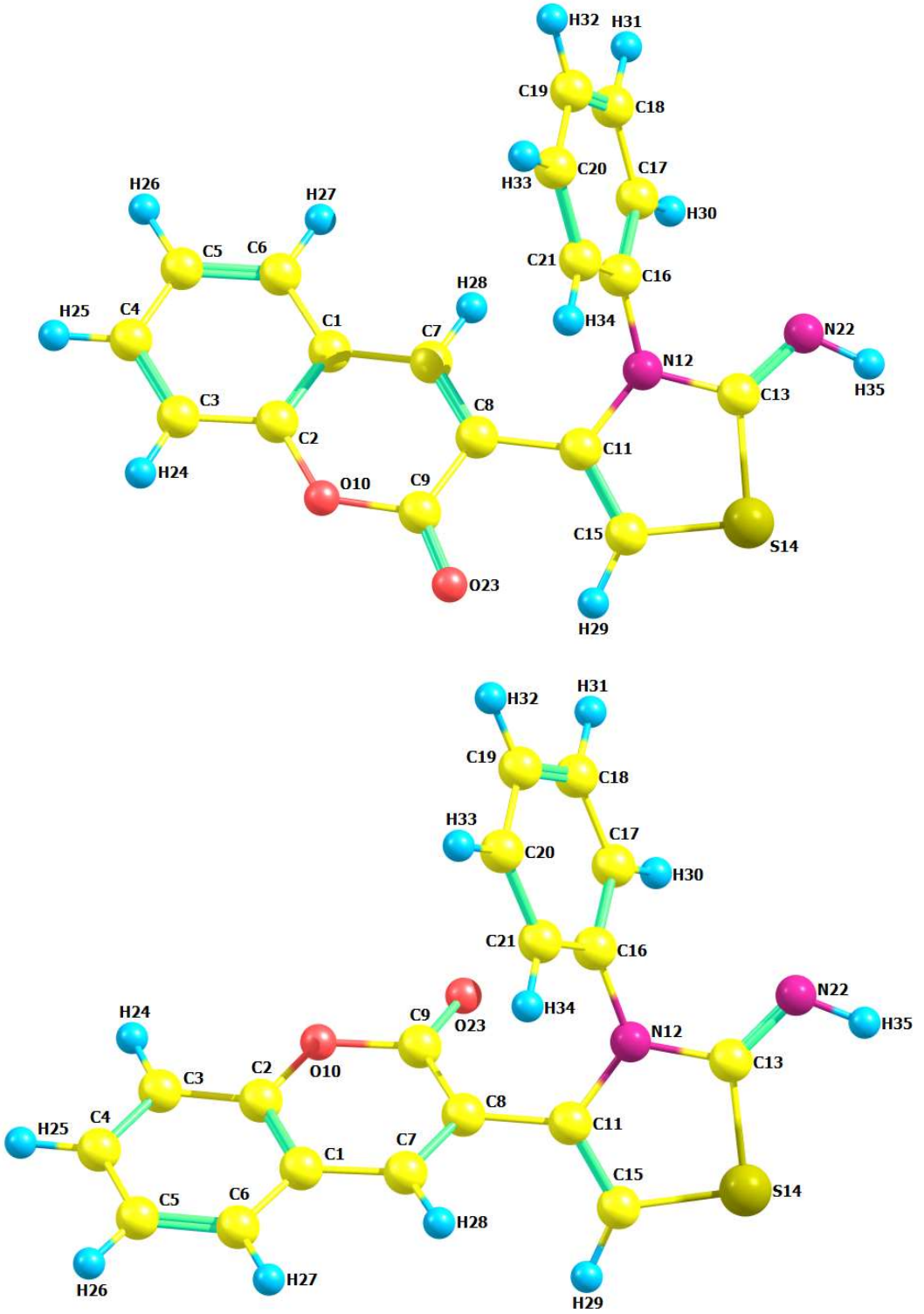


Figure 1. The structure of *s-trans* (upper) and *s-cis* (lower) conformers of 3-(2-imino-3-phenyl-2,3-dihydrothiazol-4-yl)-2H-chromen-2-one according to quantum-chemical studies.

3. Experimental

*3.1. 3-(Thiocyanatoacetyl)coumarin (**1**).*

3-Bromoacetylcoumarin (11.25 g, 0.05 mol) was placed in a flask and dissolved in 20 mL of acetone upon gentle heating. To the resulted solution, 5.8 g (0.06 mol) of potassium thiocyanate was added slowly with stirring. The formation of white precipitate (KBr) was observed. After 2 h, the reaction mixture was diluted with cold water, and the precipitated light yellow solid was filtered off and recrystallized from acetone-EtOH. Yield 7.7 g (67%). The purity of the product was checked by TLC (Sorbfil plates, "Imid Ltd." (Krasnodar)) using acetone: CCl_4 1: 1 mixture as an eluent.

IR spectrum (ν, cm^{-1}): 1708, 1673 (C = O), 1598 (C = C), 2156 (SCN) (Figure 2).

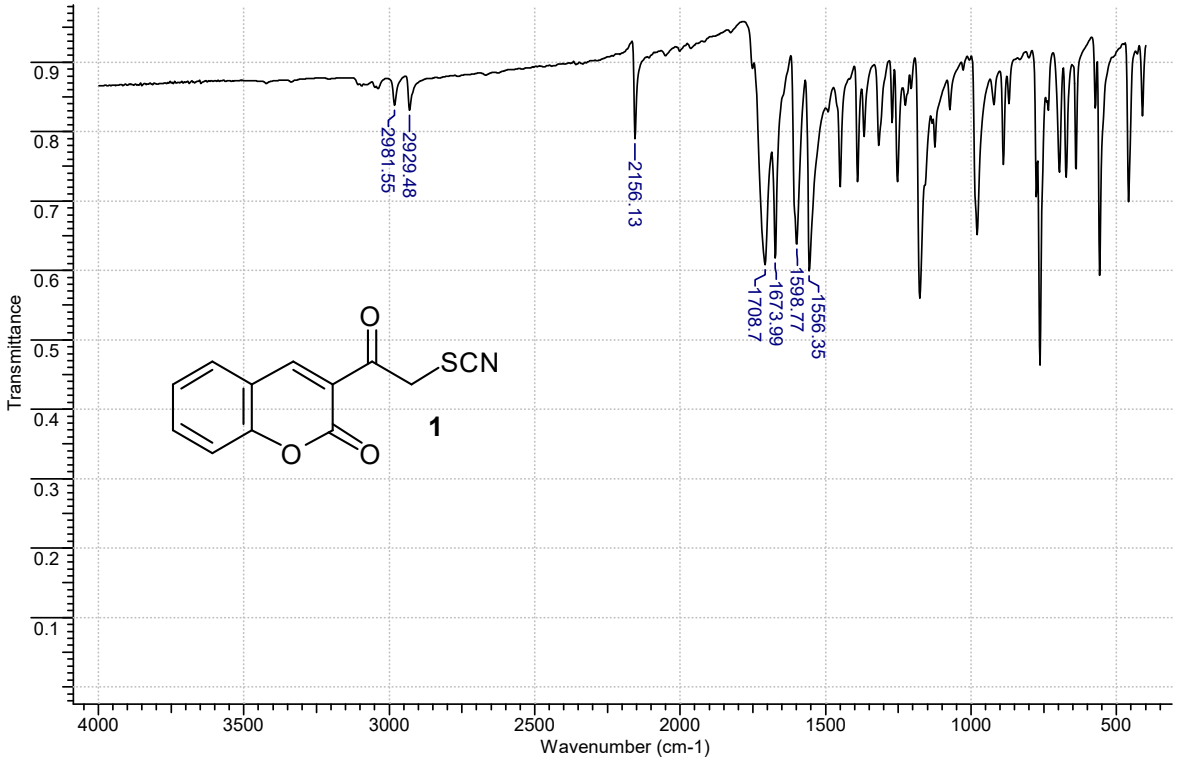


Figure 2. ATR-FT-IR spectrum of compound **1**.

3.2. Synthesis of 3-(2-imino-3-phenyl-2,3-dihydrothiazol-4-yl)-2H-chromen-2-one (2a)

Aniline (0.6 mL, 0.005 mol) was placed in a flask and neutralized with an equivalent amount of concentrated aq. HCl. The resultedg hydrochloride was dissolved in EtOH. To the solution of $PhNH_2$×HCl, a solution of 1.0 g (0.005 mol) of thiocyanatoacetylcoumarin (1) in a minimum volume of 1: 1 DMF–EtOH mixture was added. A gaseous HCl was passed through the reaction mixture for 2 h. Then the mixture was diluted with water to give a light yellow precipitate. The yield of product (**2a**) was 1.0 g (64%). The purity of the product was checked by TLC (Sorbfil plates, "Imid Ltd." (Krasnodar) using acetone: CCl_4 1:1 mixture as an eluent. IR spectrum (ν, cm-1): 3029 (N–H), 1724 (C=O), 1604 (C=N).

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