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Synthesis and mechanism of formation of hybrid structures comprising 2-oxochromene, thiazole and hydrazilidenechromene fragments

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Abstract: Molecules with a hybrid structure containing 1,3-, 1,5-dicarbonyl fragments, based on 2*H*-chromen-2-one, hold significant potential as biologically active substances. A direct method has been developed for the preparation of thiosemicarbazones 2-(7-(aryl)-10,10-dimethyl-6-oxo-7,9,10,11-tetrahydro-6*H*,8*H*--chromeno[4,3-*b*]chromen-8-ylidene)hydrazine-1-carbothioamides. Their further modification by reaction with 3-bromoacetyl-2*H*-chromen-2-one was carried out, involving the thioamide group to form hybrid structures comprising 2-oxochromene, thiazole and hydrazineylidenechromene fragments (yield 71–97%). It is shown that hydrazine-1-carbothioamides can be obtained from both the initial 1,5-dicarbonyl compound and the product of its intramolecular *O*-heterocyclization. A one-step method is preferable, because the one-step method is preferred over the more labour-intensive two-step approach (with a similar yield). A plausible reaction mechanism is presented, based on quantum chemical calculations of few possible tautomeric forms of the intermediates and the corresponding products. A comparative analysis of the ^{1}H NMR spectrum of the experimental sample and the spectra of several possible final products calculated by a quantum chemical method has also confirmed the chosen reaction pathway.

Keywords: 2*H*-chromen-2-one; hydrazine-1-carbothioamide; tautomeric system; DFT.

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INTRODUCTION

Nowadays, the interest in chromenone-containing systems is increasing due to their wide biological activity. Polyfunctional 4*H*-pyrans, most often used as antispasmodics,[1,2] have anti-HIV,[3] antioxidant[4] and antihistamine activities.[4] These compounds can also be used to treat neurodegenerative diseases, including Alzheimer's disease, schizophrenia and myoclonus. In addition, some 2-amino-4*H*--pyran derivatives can be used as photoactive materials. [5]

There are works[6–8] in the literature that demonstrate the possibility of carrying out a multi-component synthesis involving 3-substituted chromanone or 1,3-indanedione systems with urea derivatives and 3-bromomethylcoumarin. However, modifying the initial system by combining coumarin and a carbocyclic 1,3-diketone expands the synthetic capabilities to combine biologically relevant scaffolds.

In our previous studies, we found that 4-hydroxy-3-((2-hydroxy-4,4-dimethyl--6-oxocyclohex-1-en-1-yl)(aryl)methyl)-2*H*-chromen-2-ones **1a**, **b** and **d** (Fig. 1) exhibited anticoagulant activity, and Compound **1c** significantly reduced the rate of platelet aggregation. It has been also found that compound **1b** has a proplatelet effect, enhancing and accelerating platelet aggregation.[9]

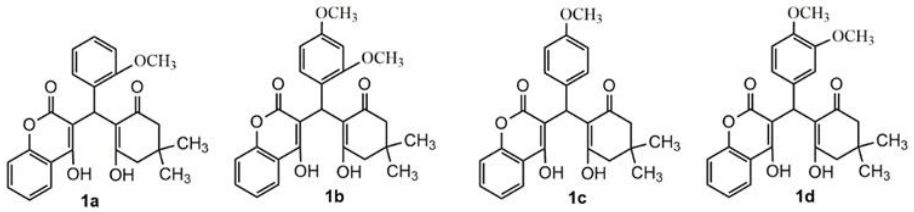

Fig. 1. Structures of biologically active 4-hydroxy-3-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(aryl)methyl)-2*H*-chromen-2-ones **1a**–**d**.

EXPERIMENTAL

General information

Thin-layer chromatography (TLC), Fourier IR and ^{1}H-NMR spectroscopy were used to monitor the reaction progress, to analyze the main mixtures and isolated individual products, and to identify them. TLC analysis was performed on Silufol UV-254 plates, eluent – ethyl acetate:hexane:chloroform (2:2:1), developer – iodine vapor. FTIR spectra were recorded on a Nicolet 6700 spectrometer (Thermo Scientific, USA) in KBr pellets (wavenumber range 4000––400 cm^{-1}) with a spectral resolution of 4 cm^{-1}. ^{1}H-, ^{13}C-NMR, HSQC and HMBC spectra were recorded on a Varian 400 MHz spectrometer (USA) at 400 MHz for protons (^{1}H) and at 100 MHz for carbons (^{13}C). Chemical shifts are given here in ppm from tetramethylsilane (TMS) as an internal standard in deuterated chloroform ($CDCl_3$). Coupling constants (*J*) are reported in Hz. All spectra were recorded at 25 °C, unless otherwise specified. Melting points were measured at a heating rate of 4 °C/min with no correction. Elemental analysis was performed on a Vario micro cube – C, H, N, S elemental analyzer (Elementar Analysensysteme GmbH, Germany).

Quantum chemical calculations

Quantum chemical calculations were performed using the density functional theory (DFT) with Becke's three-parameter Lee–Yang–Parr (B3LYP) hybrid functional and the 6-311G(d,p) basis set, involving p-orbitals for hydrogen and d-orbitals for heavier atoms, as well as polarization functions (B3LYP/6-311G++ (d,p)).

The complete geometry was optimized for each possible isomer with a strict convergence criterion.

*General procedure for the synthesis of 7-aryl-10,10-dimethyl-7,9,10,11-tetrahydro-6*H,*8*H-*-chromeno[4,3-*b*]chromene-6,8-diones **2a**–**e***

A mixture of 4-hydroxy-3-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(aryl)methyl)-2*H*-chromen-2-ones **1a**–**e** (1.2 mmol) and acetyl acetate (3 mL, 31.8 mmol) was refluxed for 30–90 min. The liquid fraction was evaporated, and the crystals precipitated were filtered out.

*General procedure for the synthesis of 2-(7-aryl-10,10-dimethyl-6-oxo-7,9,10,11-tetrahydro-6*H,*8*H-*chromeno[4,3-*b*]chromen-8-ylidene)hydrazine-1-carbothioamides **3a**–**e***

Method 1. A mixture of 7-aryl-10,10-dimethyl-7,9,10,11-tetrahydro-6*H*,8*H*-chromeno[4,3-*b*]chromene-6,8-dione **2a**–**e** (0.6 mmol) and TSC (0.065 g, 0.7 mmol) in absolute ethanol (15 ml) was refluxed for 3 h. The liquid fraction was evaporated, and the crystals precipitated were filtered out.

Method 2. A mixture of 4-hydroxy-3-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)arylmethyl)-2*H*-chromen-2-one **1a**–**e** (0.6 mmol) and TSC (0.065 g, 0.7 mmol) in absolute ethanol (15 ml) was refluxed for 90 min. The liquid fraction was evaporated, and the precipitated crystals were filtered out.

*General procedure for the synthesis of 7-aryl-10,10-dimethyl-8-(2-(4-(2-oxo-2*H*-chromen-3-yl))-thiazol-2-yl)hydrazilidene)-8,9,10,11-tetrahydro-6*H,*7*H*-chromeno[4,3-*b*]chromene-6-ones **5a**–**e***

A mixture of carbothioamides **3a**–**e** (0.42 mmol) and 3-bromoacetyl-2*H*-chromen-2-one (0.11 g, 0.42 mmol) in absolute ethanol (15 ml) was refluxed for 2 h. The liquid fraction was evaporated, and the precipitated crystals were filtered out.

Analytical and spectral data of the compounds are given in the Supplementary material to this paper.

RESULTS AND DISCUSSION

In this work, we obtained polycyclic condensed compounds by reaction of the initial 4-hydroxy-3-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(aryl)methyl)-2*H*-chromen-2-ones **1a**–**e** with acetic anhydride (Fig. 2). As a result, *O*-heterocyclization products with sufficiently high yields were obtained, namely: 7-aryl-10,10-dimethyl-7,9,10,11-tetrahydro-6*H*,8*H*-chromeno[4,3-*b*]chromene-6,8-diones **2a**–**e** (Fig. 2), whose structure was confirmed by ^{1}H-, ^{13}C-NMR, HSQC and HMBC spectroscopy data.

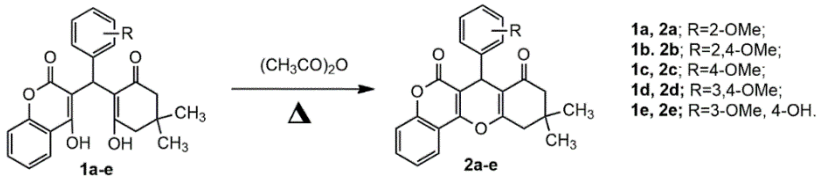

Fig. 2. *O*-Heterocyclization of 4-hydroxy-3-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1--yl)(aryl)methyl)-2*H*-chromen-2-ones **1a**–**e**.

In the ^{1}H-NMR spectra of the isolated chromeno[4,3-*b*]chromen-6,8-diones **2a**–**e**, as compared with those of the initial compounds, there are no signals of hydroxyl groups in a weak field, while the methine proton signal has shifted to a higher field (4.87–6.15 ppm). The protons of the methylene groups are characterized by magnetic non-equivalence, so each methylene group is displayed in the spectrum as a doublet of doublets at 2.45–2.69 and 2.13–2.29 ppm. This is explained by fixation of the dimedonyl ring, whose rotation around the single C–C bond gets impossible, which leads to the possibility of implementing an asymmetric spatial structure of the fragment.

The HSQC spectrum shows a difference in the chemical shifts of the methyl groups along both axes, due to the dimedonyl ring fixation.

A difference in the nature of the protons in the methylene groups is clearly visible in the HMBC spectrum. The protons in the methylene group located at the carbonyl group correlate with the carbonyl carbon atom at 2.28/195.67 ppm and the cross peak at 2.63/163.55 ppm reflects interaction between the protons in the methylene group and the C-2 atom of the 4*H*-pyran moiety in the compound.

For the purpose of further functionalization and expansion of synthetic capabilities, the behavior of the initial polyoxo compounds in their nucleophilic transformations with TSC was studied. Our choice of this reagent was not accidental, since numerous studies have shown that thiosemicarbazones exhibit antimicrobial, antitumor properties and can inhibit the central nervous system activity.[10–15] It is believed that this is due to TSC being able to form various complex compounds with proteins and metal ions.[16] Therefore, of current interest is the preparation of polycondensed structures to combine the properties of semicarbazides and chromenochromenediones **2a**–**e** (polyfunctional compounds containing several electron--deficient centers).

This reaction was found to involve the dimedonyl carbonyl group of oxo compounds **2a**–**e** and the hydrazine fragment due to its greater activity compared to thioamide. The reaction produced carbothioamides **3a**–**e** in 44–51 % yields (Fig. 3).

A similar product was also obtained by direct reaction of the initial 2*H*--chromene-2-ones **1a**–**e** with TSC, which made it possible to bypass the isolation of the cyclization product into tetrahydrochromenochromendione **2** and, in general, significantly reduced the reaction time.

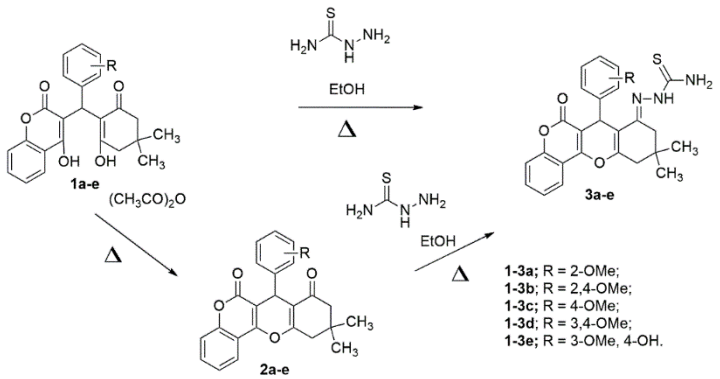

Fig. 3. Synthesis of chromeno[4,3-*b*]chromenhydrazine-1-carbothioamides **3a**–**e**.

Such a course of the process, namely, no products of nucleophilic attack at the competing reaction center in substrate **1**, allows us to conclude on the primary process of *O*-heterocyclization in compounds **2a**–**e**.

In the ^{1}H-NMR spectrum of carbothioamide **3** two protons of the thioamide group are located at 6.21–6.25 and 8.17–8.25 ppm, respectively; the NH proton singlet is located at 8.50–8.54 ppm, which is confirmed by the absence of correlation signals in the HSQC spectrum.

It is worth noting the signals at 8.52/178.6 ppm and 8.51/145.7 ppm in the HMBC spectrum, responsible for the interaction of the thioamide proton in the hydrazine fragment with the imine carbon atom, as well as with the α-carbon atom of the dihydropyran fragment, respectively; correlations of the protons of one of the methylene moieties at 2.24/145.2 ppm are also observed with the *α*-carbon atom and the tertiary proton of the dihydropyran heteroring at 5.48/145.2 ppm, which indicates the formation of thiosemicarbazone **3a**.

In order to obtain a series of novel complex polycyclic structures, carbothioamides **3** were reacted with 3-bromoacetylcoumarin. As a result of the reaction, the thiol group of compounds **3a**–**e** initially interacted with the haloalkyl fragment of the reagent to eliminate hydrogen bromide, which led to the formation of hydrazinecarbimidothiolate **4a**–**e** and its respective tautamers **4'a**–**e** and subsequent cyclization into either thiazoles **5a**–**e**, which can be tautomerized to **5'a**–**e** or **6a**–**e**, or mixture thereof.

In order to evaluate the reactivity of the nucleophilic centers of tautomers **4** and **4'**, the Fukui indices were calculated (Table I).

Quantum chemical calculations were carried out in the Firefly 8.2.0 program within the framework of density functional theory (DFT) using the B3LYP hybrid functional and the 6-31G(d,p) basis set.[17–20]

Full geometry optimization was done for neutral molecules; the energies of radical cations and radical anions were calculated based on the geometry of the

neutral molecule in accordance with Koopmans' theorem. From these values, ionization energies (I) and electron affinities (A) were calculated. For an N-electron system, the Fukui indices (FI) were calculated using the Mulliken populations (q) by the following equations:

$$FI^{+} = q(N+1) - q(N) \quad (1)$$

$$FI^{-} = q(N) - q(N-1) \quad (2)$$

where $q(N)$ is the population of the atom in a neutral molecule (cluster), and $q(N-1)$ and $q(N+1)$ are the population of the atom in the cation and anion of the molecule (cluster), respectively.

TABLE I. Reactivity indices of hydrazinecarbimidothioate **4'a** and carbamohydrazonothioate **4a**

Compound	Reactivity indices (FI^{-}/FI^{+})	
	N (27)	N (29)
4a	0.049118/−0.0028	0.062148/0.002623
4'a	0.026116/0.019385	0.030662/−0.02827

According to the calculated Fukui indices, N (29) is more nucleophilic in both tautomeric forms **4** and **4'a**, which suggests its nucleophilic attack at the free carbonyl group in compounds **5a**–**e** or its tautamer forms **5'a**–**e**. Then, the attack of compound **4'a** with hydrazine N (27) to form adduct **6** would not be beneficial (Fig. 4).

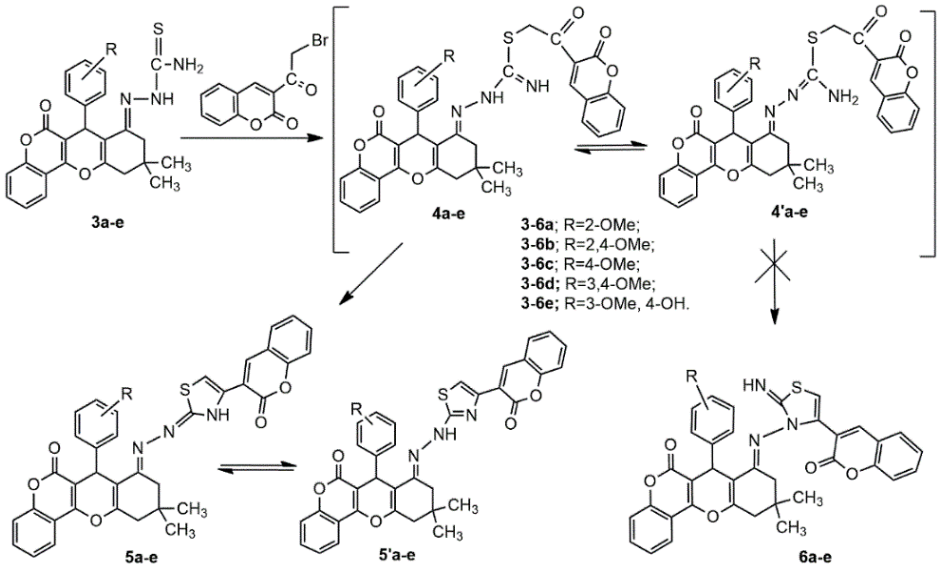

Fig. 4. Synthesis of thiazolehydrazonotetrahydrochromeno[4,3-*b*]chromen-6(7*H*)-ones **5a**–**e**.

To prove the above, the energy profile of the *N*-heterocyclization reaction was computed. Hydrazinecarbimidothiolate **4** can be considered as a common intermediate in the process of formation of all three possible products. The energy barrier for the reaction, calculated using DFT/B3LYP/6-31G(d) in vacuum, was thus estimated to be 11.70 kcal*/mol. Regardless of the choice of the reaction center, a new thiazole ring is formed as a result of intramolecular nucleophilic attack of the carbonyl carbon atom by the nitrogen atom. Considering the geometry optimization of the molecules of all three hypothetical products using 7-(2-methoxy)-phenyl derivatives as an example, it should be noted that chromenylthiazole-2(3*H*)--ylidene)hydrazono)tetrahydrochromeno[4,3-*b*]chromen-6(7*H*)-one (**5**) has turned out to be stabilized due to the formation of a hydrogen bond (1.983 Å) between the hydrogen atom of the NH group of the thiazole ring and the oxygen of the lactone carbonyl group, which ensures the coplanarity of the chromene and thiazole rings and the entire structure as a whole and reduces the overall energy of the molecule (Fig. 5).

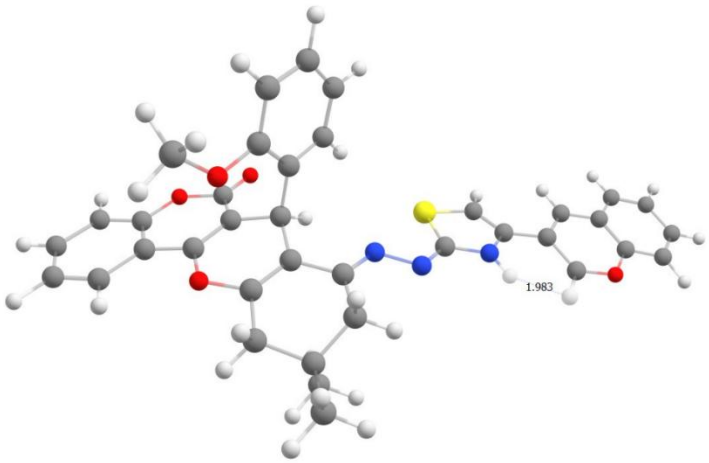

Fig. 5. Optimized geometry of 10,10-dimethyl-8-((4-(2-oxo-2*H*-chromen-3-yl)thiazol-2(3*H*)--ylidene)hydrazono)-7-(2-methoxyphenyl)-8,9,10,11-tetrahydrochromeno[4,3-*b*]chromen-6(7*H*)-one (**5a**).

As for the third option of *N*-heterocyclization due to nucleophilic attack by the hydrazine nitrogen in chromenylthiazol-3(2*H*)-ylimino-tetrahydrochromeno[4,3--*b*]chromen-6(7*H*)-one (**6a**), having considered the optimized geometry of the adduct, where in addition to the lack of coplanarity of the cycles, their proximity is observed, which determines an unfavorable spatial structure reaction. Moreover, having computed its formation energy, we can definitely state the impossibility of

* 1 kcal = 4184 J

its formation in the course of this reaction, since it significantly exceeds even the energy of the selected intermediate.

The energy diagram of the proposed simplified *N*-heterocyclization scheme was computed using the example of 2-methoxy derivative (**a**) within the framework of DFT/B3LYP/6-31G(d) in vacuum with complete optimization of the geometry of all proposed structures (Fig. 6). According to these calculations, a probable pathway of the process can be deduced as the transition of tautomer **4** to the energetically more favorable carbamohydrazonothiolate **4'**, followed by cyclization to thiazolehydrazonotetrahydrochromenochromenone (**5**).

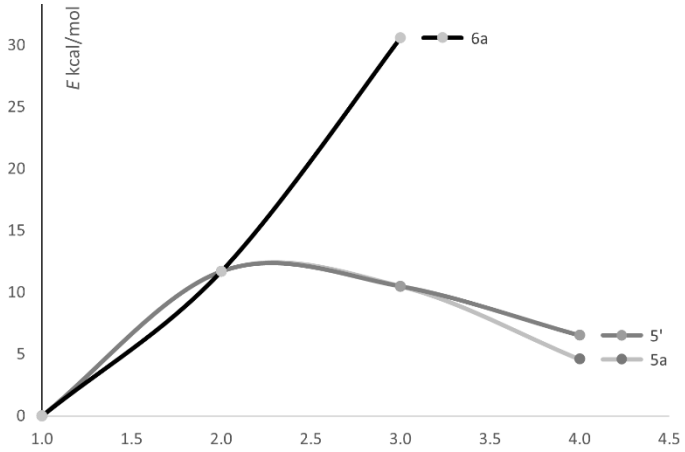

Fig. 6. Energy diagram of the reaction of hydrazinecarbothioamide (**3a**) with 3-bromoacetylcoumarin.

There is only one set of signals in the ^{1}H-NMR spectra of the products **5a**–**e**. This suggests that only one of the tautomeric forms is stabilized (at least in deuteronchloroform). Compared with the spectrum of the precursor, there are no signals from the thioamide group protons. A signal is observed of the vinyl proton in the thiazole heteroring at 7.87–7.93 ppm. The vinyl proton of the chromenone ring is located at 8.48–8.56 ppm, the broadened signal of the NH group is at 10.61–10.93 ppm. But since the resulting set of signals, in general, could correspond to any of the tautomeric forms of the final thiazole **5** or **5'**, to clarify the structure of the final product, we calculated the chemical shifts of protons in the putative tautomers both in vacuum and in the solvent, which was most close to deuterochloroform (which the spectra were experimentally recorded in) according to its characteristics. The calculated chemical shifts of the vinyl, methine protons and amino group protons correlate well with the experimental data. A distinctive feature of this type of compounds is the shift of the key signal of the amine proton to a weak field, which is probably explained by the formation of an intramolecular hydrogen bond with its participation, which is consistent with the structure of compounds **5a**–**e**.

In the 2D correlation HSQC spectrum of chromenylthiazol-2(3*H*)-ylidene)-hydrazono)-tetrahydrochromeno[4,3-*b*]chromen-6(7*H*)-one (**5a**), the previously absent signals are noted at 7.91/110.55 ppm, belonging to the vinyl proton of the newly formed thiazole heteroring, as well as a signal from the vinyl proton of the chromenone fragment at 8.50/139.0 ppm.

In the HMBC spectrum, the key correlation signal means contact of the vinyl proton of the thiazole heterofragment H62 with the carbonyl carbon of the lactone fragment of chromenone C38 at 7.82/167.89 ppm. As the HMBC spectrum lacks any correlation between the protons of the hydrazine group and the carbon atom of the methylene unit of the dimedone ring, characteristic of structure **5'**, this finally confirms the formation of tautomer **5**.

CONCLUSION

Thus, as a result of a series of chemical transformations, it is possible to derivatize the molecules of oxocyclohexenyl(aryl)methyl-2*H*-chromen-2-ones **1a**–**e** by introducing pharmacophoric fragments (thiazole and chromen-2-one) therein. Using calculated and experimental data, a probable pathway of the transformations, the structure of the intermediates and final reaction products are shown.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12976, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА И МЕХАНИЗАМ ФОРМИРАЊА ХИБРИДНИХ СТРУКТУРА КОЈИ КАО СТРУКТУРНЕ ДЕЛОВЕ САДРЖЕ 2-ОКСОХРОМЕН, ТИАЗОЛ И ХИДРАЗИЛИДЕНХРОМЕН

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Хибридни молекули која садржи 1,3- и 1,5-дикарбонилне фрагменте, засновани на 2*H*-хромен-2-ону, имају значајан потенцијал као биолошки активне супстанце. Развијена је директна метода за припрему тиосемикарбазона 2-(7-(арил)-10,10-диметил-6-оксо-7,9,10,11-тетрахидро-6*H*,8*H*-хромено[4,3-*b*]хромен-8-илиден)хидразин-1-карботиоамида. Извршена је њихова даља модификација реакцијом са 3-бромоацетил-2*H*-хромен-2-оном, која укључује тиоамидну групу, ри чему су добијене хибридне структуре које садрже 2-оксохроменске, тиазолне и хидразинилиденхроменске фрагменте (принос 71–97 %). Показано је да се хидразин-1-карботиоамиди могу добити и из почетног 1,5-дикарбонилног једињења и из производа његове интрамолекуларне *O*-хетероциклизације. Једностепени метод је пожељнији, јер је једностепени метод пожељнији у односу на радно интензивнији двостепени приступ (са сличним приносом). Представљен је вероватан

механизам реакције, заснован на квантно-хемијским прорачунима неколико могућих таутомерних облика интермедијера и одговарајућих производа. Упоредна анализа ^{1}H--NMR спектра експерименталног узорка и спектара неколико могућих финалних производа израчунатих квантно-хемијском методом такође је потврдила изабрани реакциони пут.

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