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Synthesis of New Hybrid Heterocycles Based on Transamination Reactions of 3-[(Dimethylamino)methylene]chromane-2,4-dione †

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Abstract

The transamination reaction of enamines is a convenient and selective method for structural modification, allowing the replacement of the dimethylamino group with various heterocyclic moieties, in particular, with the 1,2,4-triazol-3-ylamino group. Based on the results of quantum chemical calculations of the molecular geometry of the *E* and *Z* isomers, it is possible to make an assumption about the preferred isomer for each of the substances. It was found that the transamination reaction results in a change in conformation relative to the multiple bond of the product. Transamination under the action of 2-aminobenzimidazole proceeds via a stage of partial retro-cleavage of the enamine to the starting coumarin, followed by their condensation into a more complex condensed polycyclic system.

Keywords: coumarin; enamines; transamination

1. Introduction

Aminomethylidene derivatives of 4-oxochromen-2-one are polyfunctional synthons containing a conjugated enamine system, a lactone ring, and a carbonyl group in their structure [1,2]. Due to the presence of multiple reaction centers, such compounds are widely used in directed organic synthesis to obtain a variety of condensed and hybrid heterocycles, many of which possess potential biological activity. Transamination reactions of enamine derivatives of chromen-2-ones serve as effective structural modifications, enabling the introduction of various N-heterocyclic substituents.

2. Materials and Methods

The progress of the reaction, the composition of the basic mixtures, and the identification of individual isolated products were monitored and verified using thin-layer chromatography (TLC) and ^{1}H, ^{13}C NMR spectroscopy. TLC analysis was performed on Silufol UV-254 plates. The eluent consisted of ethyl acetate, hexane, and chloroform in a 2:2:1 ratio; the chromatograms were visualized using iodine vapor. For column chromatography, silica gel 60 was used as the sorbent, with the same eluent mixture (ethyl acetate:hexane:chloroform, 2:2:1). FT-IR spectra were recorded on a Nicolet 6700 spectrometer (Thermo Scientific, Waltham, MA, USA) using KBr pellets over the wavenumber range of 4000–400 cm^{-1}, with a spectral resolution of 4 cm^{-1}. ^{1}H NMR, ^{13}C NMR, and HSQC

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spectra were acquired on a Varian 400 spectrometer at 20–25 °C. The operating frequency was 400 MHz for ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra. TMS served as the internal standard, and the solvents used were $CDCl_3$ and dimethyl sulfoxide-d_6.

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 the hydrogen atom and d-ones for more heavy atoms as well as involving polarization functions (B3LYP/6-311G++ (d,p)).

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

*Synthesis and Characterization of Compounds **4a-c***

A mixture of 0.05 g (0.042 mmol) 3-(*Z*)-dimethylaminomethylene-4-(thio)oxochromen-2-one (**1a**-**b**) and 0.003 g (0.042 mmol) of 1,2,4-triazol-3-amine (**2**) refluxed for 40 min in 10 mL *i*-PrOH.

(Z)-3-(((4H-1,2,4-Triazol-3-yl)amino)methylene)chromene-2,4-dione (**4a**)

Yield 0.32 g. mp. 198–199 °C; FTIR, cm^{-1} 1716 (C=O), 1880 (C=O), 1580 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H, NH), 8.45 (s, 1H, =CH), 7.17–7.88 (m, 4H, Ar-H). Anal. Calcd. For $C_{12}H_8N_4O_3$ C: 56.25%; H: 3.15%; N: 21.87%; Found: C: 56.43%; H: 2.68%; N: 22.16%.

(E)-3-(((4H-1,2,4-Triazol-3-yl)amino)methylene)-4-thioxochroman-2-one (**4b**)

Yield 0.25 g. mp. 176–177 °C; FTIR, cm^{-1} 1718 (C=O), 1878 (C=O), 1576 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H, NH), 8.43 (s, 1H, =CH), 7.20–8.08 (m, 4H, Ar-H). Anal. Calcd. For $C_{12}H_8N_4O_3$ C: 52.93%; H: 2.96%; N: 20.58%; S: 11.77%; Found: C: 57.13%; H: 2.71%; N: 21.56%; S: 11.45%.

7-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-6a,7,9,14a-tetrahydro-6H-benzo[4,5]imidazo[1,2-a]chromeno[3,4-e]pyrimidin-6-one (**7**)

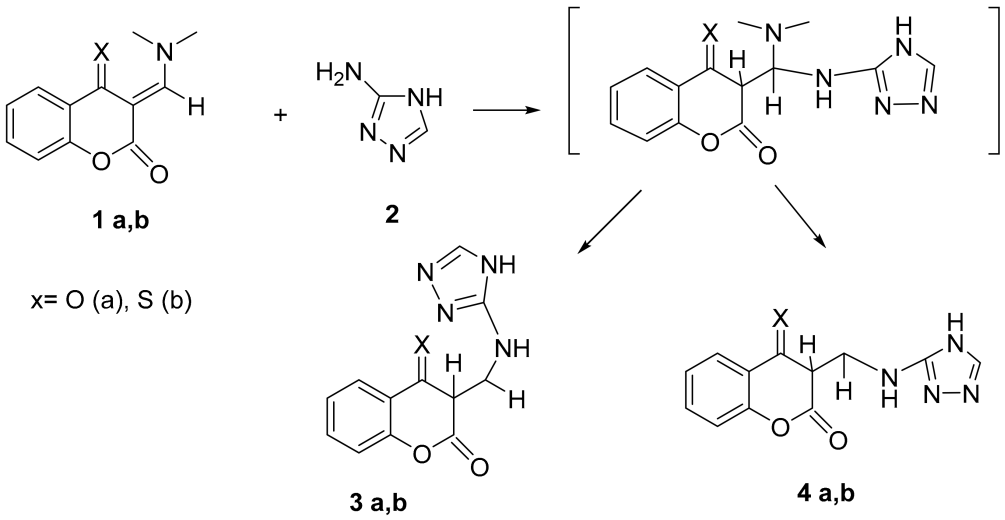
A mixture of 0.002 g (0.042 mmol) 3-(*Z*)-(dimethylamino)methylene)chroman-2,4-dione (**1a**) and 0.01 g (0.042 mmol) of 1H-benzo[d]imidazol-2-amine (**3**) refluxed for 80 min in 10 mL i-PrOH.

Yield 0.14 g. mp. 172–173 °C; FTIR, cm^{-1} 3350–3200 (NH), 1710–1680 (C=O), 1650–1620 (C=O), 1610–1580 (C=C), 1550–1500 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.5 (s, 1H, OH), 10.7 (s, 1H, NH), 8.60 (s, 1H, =CH), 7.25–8.02 (m, 8H, Ar-H). Anal. Calcd. For $C_{26}H_{15}N_3O_5$ C: 69.49%; H: 3.36%; N: 9.35%; Found: C: 64.43%; H: 2.88%; N: 8.96%.

3. Results and Discussion

Transamination reactions of enamine derivatives of chromen-2-ones serve as effective structural modifications, enabling the introduction of various N-heterocyclic substituents. Despite the numerous studies dedicated to the synthesis and properties of aminomethylidenechromenones, no systematic investigation into the transamination of their thio-analogs—conducted using Lawesson's reagent—has been carried out to date. The transamination reaction was carried out by reacting compounds **1a** and **1b** with 1,2,4-triazol-3-amine in ethanol at room temperature (Scheme 1).

Based on experimental data, a mechanism for the transamination reaction is proposed; it involves a step of nucleophilic attack by the triazole amino group on the C=C double bond of the aminomethylidene fragment, yielding an intermediate adduct that may possess either the R or S configuration at the asymmetric center. Subsequent elimination of dimethylamine leads to the formation of the final product as Z- and E-isomers. This process is analogous to a Michael addition followed by elimination, a conclusion supported by kinetic studies and spectroscopic data.



Scheme 1. Synthesis of 3-(*E*)-(((4H-1,2,4-triazol-3-yl)amino)methylene)-4-(thi)oxochroman-2-one (**4a,b**).

Calculated data regarding the molecular geometry (B3LYP functional with the 6-31G(d,p) basis set) and formation energies of the *E*- and *Z*-isomers indicate that isomers **4a** and **4b** are the preferred forms; they are stabilized by a hydrogen bond between the hydrogen of the exocyclic amino group and the lactone carbonyl (Figures 1 and 2).

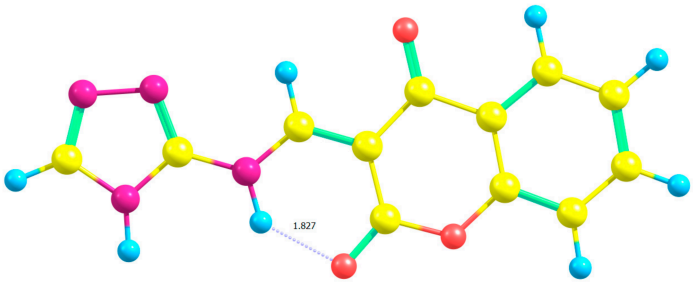


Figure 1. Optimized structure of compound **4a** (Z-isomer).

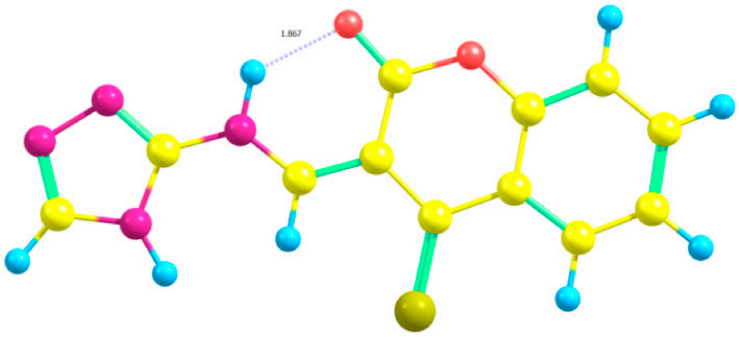
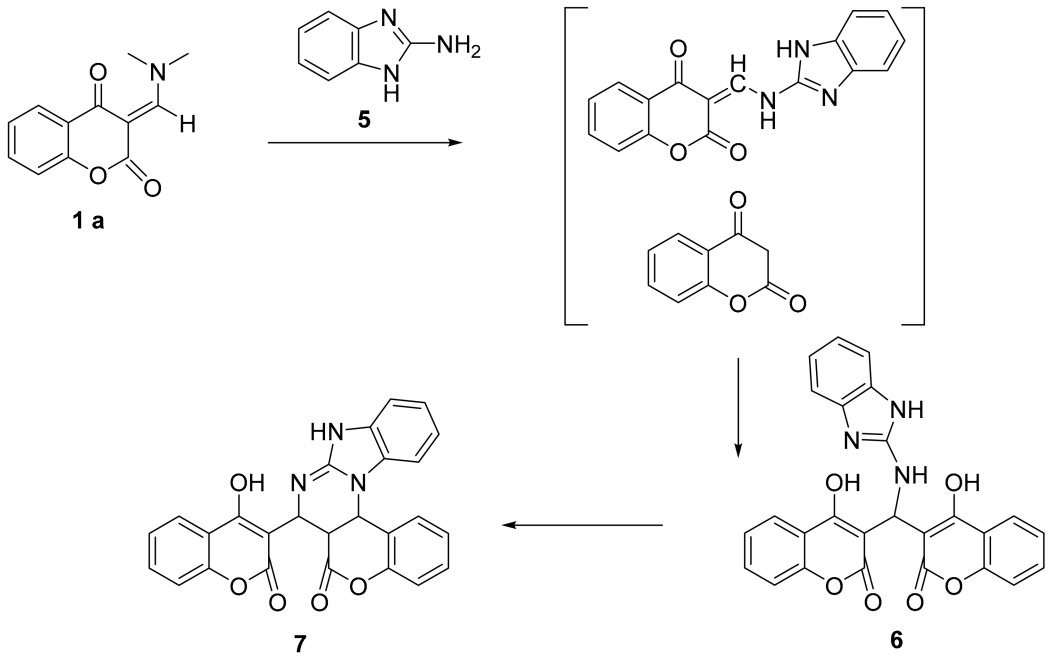


Figure 2. Optimized structure of compound **4e** (E-isomer).

The reaction of 3-((*E*)-((dimethylamino)methylene))-4-oxo-3,4-dihydro-2H-chromen-2-one (1) with 2-aminobenzimidazole involves a transamination step—comprising the nucleophilic attack of the 2-aminobenzimidazole amino group on the β-carbon atom of the enamine system and partial deaminomethylation of the resulting intermediate [3] (Scheme 2). In the subsequent stage, the resulting adducts undergo a Michael-type reaction, leading to the formation of an aminomethyl-bis-chromene structure (7).



Scheme 2. Synthesis of 7-(4-hydroxy-2-oxo-2H-chromen-3-yl)-6a,7,9,14a-tetrahydro-6H-benzo[4,5]imidazo[1,2-a]chromeno[3,4-e]pyrimidin-6-one (**7**).

^{1}H NMR spectroscopy data (solvent: DMSO-d_6) provide the most compelling evidence that the transamination reaction has occurred. In the spectrum of product (**7**), the characteristic intense singlet corresponding to the six protons of the dimethylamino group of the starting material (at $\delta \approx 3.10$ ppm) disappears completely, indicating its total replacement.

Instead, two broad singlets corresponding to the NH protons of the benzimidazole moiety appear downfield in the δ 11.80–12.70 ppm range. The appearance of a singlet for the methine proton at 5.12 ppm serves as a characteristic signal indicating the formation of the bis-system.

4. Conclusions

Modification of 3H-4-oxo-chromen-2-one was carried out by transamination reaction with 1,2,4-triazol-3-amine and 2-aminobenzimidazole; in the case of benzimidazole, subsequent cycloaddition with the formation of a new condensed tetracyclic system was revealed. Using DFT calculation methods (B3LYP/6-31G(d)), using the example of [(4H-1,2,4-triazol-3-ylamino)methylene]-chroman-2,4-dione, the preferential formation of the E-isomer stabilized by intramolecular hydrogen bonds was shown.

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Abbreviations

The following abbreviations are used in this manuscript. NMR—Nuclear Magnetic Resonance; HMBC—Heteronuclear Multiple Bond Correlation; DMSO—Dimethyl Sulfoxide; TMS—Tetramethylsilane (NMR standard); DFT—Density Functional Theory; B3LYP—Becke, 3-parameter, Lee–Yang–Parr

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