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Mendeleev Commun., 2020, **30**, 765–767

Mendeleev Communications

New 1-hetarylfuropyridines and chromenes based on pyridoxal and 4-hydroxycoumarin

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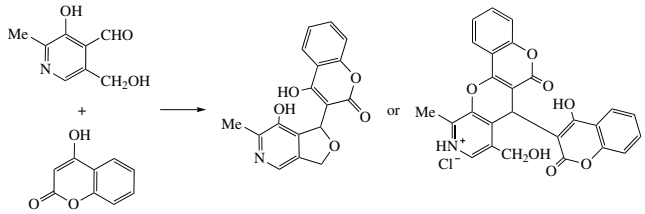
DOI: 10.1016/j.mencom.2020.11.025

Pyridoxal in the absence of catalyst forms furo[3,4-*c*]pyridine species (*ortho* aldehyde and hydroxymethyl groups are involved) which is further transformed into C–C hybrid with 4-hydroxycoumarin. Different products of chromeno-[3′,4′:5,6]pyrano[2,3-*c*]pyridine type are formed when pyridoxal hydrochloride or more sophisticated 2,4-dihydroxybenzaldehyde derivative are applied (herein, *ortho* aldehyde and hydroxy groups are involved into heterocyclization).



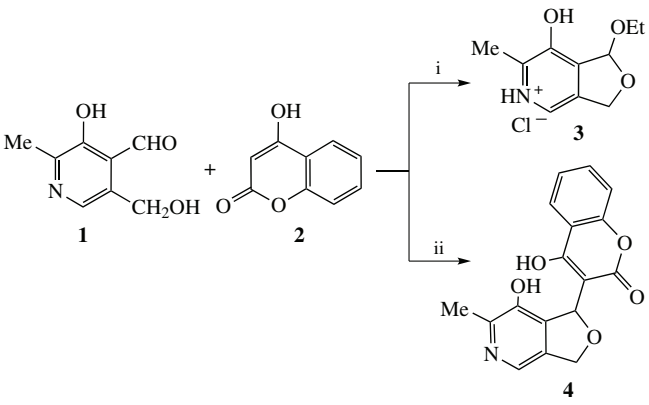
Keywords: heterocyclization, electrophilic substitution, furo[3,4-*c*]pyridines, chromeno[3′,4′:5,6]pyrano[2,3-*c*]pyridines, pyridoxal, chromenes.

At present, a strategy of 'hybrid' molecules is employed for design of new effective drugs.[1–3] We have previously carried out chemical modification of pyridoxal (vitamin B_6) through its new cascade reaction with phenols, polyphenols,[4,5] and pyrazol-5-one derivatives,[6] which allowed us to accees new types of fused heterocyclis systems such as furopyridines containing phenolic, polyphenolic and heterocyclic fragments. With the aim of expanding the series of heterocyclic compounds, which can participate in such transformations and form various 'hybrid' compounds, we studied herein the reactions of pyridoxal **1** and its derivatives with 4-hydroxycoumarin **2** whose derivatives are employed as anticoagulants, antitumor, anti-HIV, antipyretic, cosmetic, and antithrombotic drugs.[7–13] We supposed that new 'hybrid' compounds containing furopyridine and coumarin fragments, as well as the structures featuring phenolic group along with these fragments can result from such reactions.

Initially, the reaction between pyridoxal **1** and 4-hydroxycoumarin **2** was tried in the mixture of ethanol and concentrated hydrochloric acid by analogy with the synthesis of 1-arylfuropyridines.[4,5] However, under these conditions 1-ethoxyfuropyridine **3** as the product of intramolecular acetalization was mostly formed (Scheme 1, conditions i). The desired 1-hetarylfuropyridine **4** was not formed, and 4-hydroxycoumarin **2** remained unchanged.

Luckily, the reaction between **1** and **2** in absolute ethanol in the absence of HCl afforded new 1-hetarylfuropyridine **4** in 97% yield (see Scheme 1, conditions ii).

A broad variety of catalysts was previously used for the derivatization of coumarins, in particular, LiCl, propane-1,2,3-triyl tris(hydrosulfate),[14] $[PySO_3H]Cl$,[15] $Bi(NO_3)_3 \cdot 5H_2O$,[16] choline hydroxide,[17] TsOH,[18,19] and piperidine.[20–22] With the aim to synthesize bis-coumarins with pyridoxal fragment, we tried the reactions at a **1/2** ratio of 1 : 2 in the presence of TsOH or piperidine, as well as without them. However, the product of 1 : 2 ratio was not formed while the yield of compound **4** formed

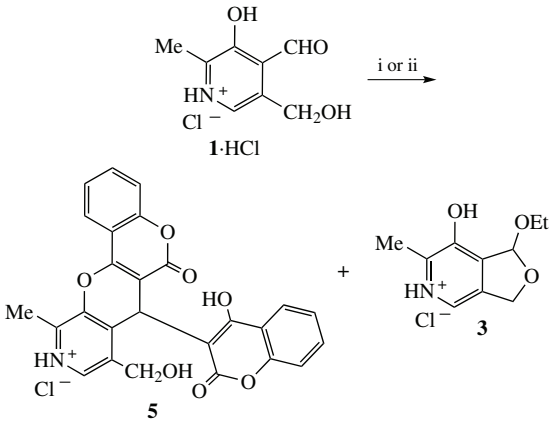


Scheme 1 *Reagents and conditions*: i, **2** (1 equiv.), EtOH (abs.)/HCl, reflux, 10 h; ii, **2** (1 equiv.), EtOH (abs.), reflux, 10 h, yield of **4** 97%.

in the course of the reaction, decreased. Thus, the non-catalytic reaction of pyridoxal **1** with 4-hydroxycoumarin **2** can afford only 1 : 1 adducts in nearly quantitative yield.

The reaction of pyridoxal hydrochloride **1** · HCl with 1 mol of 4-hydroxycoumarin **2** in EtOH without catalysts gives the product of 1 : 2 composition **5** being the first representative of benzochromenopyranopyridines (Scheme 2, conditions i). Comparable amounts of side 1-ethoxyfuropyridine **3** were also formed. Changing the **1** · HCl/**2** reactant ratio to 1 : 2 provided the preparation of target chromene **5** in high yield (see Scheme 2, conditions ii). Application of TsOH or piperidine as catalysts caused little effect on the reaction outcome.

We suggest that the reaction occurs according to the cascade mechanism and compound **5** is formed through electrophilic substitution in the position 3 of coumarin, with the formation of an intermediate biscoumarin derivative of pyridoxal and subsequent intramolecular dehydration with the participation of



Scheme 2 *Reagents and conditions*: i, **2** (1 equiv.), EtOH (abs.), 78 °C, 10 h, yield of **5** 46%, yield of **3** 54%; ii, **2** (2 equiv.), EtOH (abs.), 78 °C, 10 h, yield of **5** 67%, **3** is not formed.

the hydroxyl groups of coumarin and pyridine. The structure of this compound was confirmed by MALDI mass spectrometry, ^{1}H NMR spectroscopy, elemental analysis and X-ray analysis data (Figure 1).

According to X-ray data, compound **5** crystallizes in monoclinic space group *C*2/*c* and there is one independent molecule of compound **5** and Cl-counterion at axis 2, as well as DMSO solvent molecule in the unit cell. The bond lengths are within the range of standard values for this type of bonds. A six-membered oxygen-containing heterocycle O(20)C(3)C(4)C(9)C(10)C(19) adopts a 'C(9)-sofa' conformation; five-atomic fragment C(4)C(3)O(20)C(19)C(10) is planar within the range of 0.085 Å and C(9) atom deviates at 0.129(6) Å from the plane. Other heterocycles are planar within the experimental measurement error.†

At the next stage of this study, 4-hydroxycoumarin **2** was reacted with previously[4] prepared polycyclic aldehyde **6** based on pyridoxal and 2,4-dihydroxybenzaldehyde (Scheme 3). The application of TsOH as the catalyst provided the highest yield of chromene derivative **7** being a 2 : 1 adduct of **2/6** reactants. Its

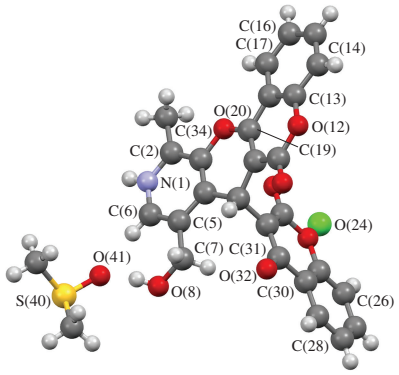
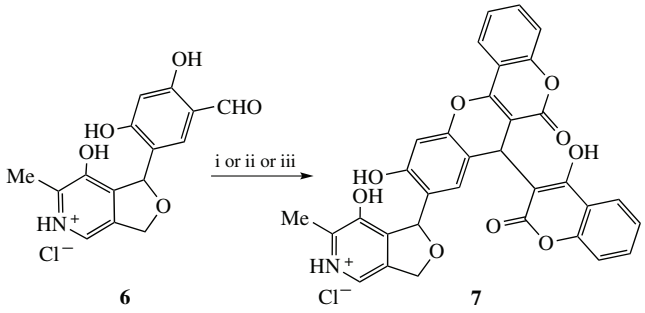


Figure 1 Molecular structure of compound **5**.



Scheme 3 *Reagents and conditions*: i, **2** (2 equiv.), EtOH (abs.), TsOH (cat.), 78 °C, 3 h, 98%; ii, **2** (2 equiv.), EtOH (abs.), without catalyst, 78 °C, 3 h, 90%; iii, **2** (2 equiv.), EtOH (abs.), piperidine (cat.), 78 °C, 3 h, 86%.

structure was assigned on the basis of MALDI mass spectrometry and ^{1}H NMR spectroscopy data.

To conclude, a preparative synthesis of novel hybrid hetarylfuropyridines and chromenes containing furopyridine, coumarin and phenol fragments in the molecule has been accomplished.

The authors are grateful to the Collective Spectral-Analytical Center of Physicochemical Studies of Structure, Properties, and Composition of Substances and Materials of the Federal Research Center Kazan Scientific Center of RAS for technical support of the studies. X-ray studies were performed using the equipment of the Federal Research Center Kazan Scientific Center of RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.025.

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† *Crystal data for* **5**. $2(C_{26}H_{17}NO_7)\cdot 2(C_2H_6OS)\cdot Cl$ (M = 1102.52), monoclinic, space group *C*2/*c* at 294 K: a = 25.553(4), b = 13.0547(19) and c = 16.853(2) Å, β = 101.570(7)°, V = 5507.7(14) Å^3, Z = 4, d_{calc} = 1.330 g cm^{-3}; μ(MoKα) = 0.216 mm^{-1}; F(000) = 2292. Total of 36001 reflections were collected (5409 independent reflections with θ < 26°, R_{int} = 0.110) and used in the refinement, which converged to wR_2 0.3743, GOOF 1.21 for all independent reflections [R_1 = 0.1048 was calculated for 2780 reflections with $I \geqslant 2\sigma(I)$]. X-ray diffraction analysis was performed at room temperature on a Bruker Kappa Apex II CCD automatic diffractometer using graphite monochromated MoKα (0.71073 Å) radiation and ω-scan rotation. Data collection: images were indexed, integrated, and scaled using the APEX2[23] data reduction package and corrected for absorption using SADABS.[24] The structure of **5** was solved by the direct methods and refined using SHELX.[25] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were calculated on idealized positions and refined as riding atoms. All calculations were performed using WinGX.[26] Intermolecular interactions were analyzed using the program PLATON.[27] All the figures were produced by the MERCURY program.[28] Bad experimental data from crystal of compound **6** are due to a weakly reflecting crystal.

CCDC 2018191 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Detailed synthesis procedures and characteristics of compounds **4**, **5**, **7** are presented in Online Supplementary Materials.

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Received: 20th July 2020; Com. 20/6266