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SYNTHESIS AND STRUCTURE OF 4-HYDROXY-3-PYRIDYLCOUMARINS

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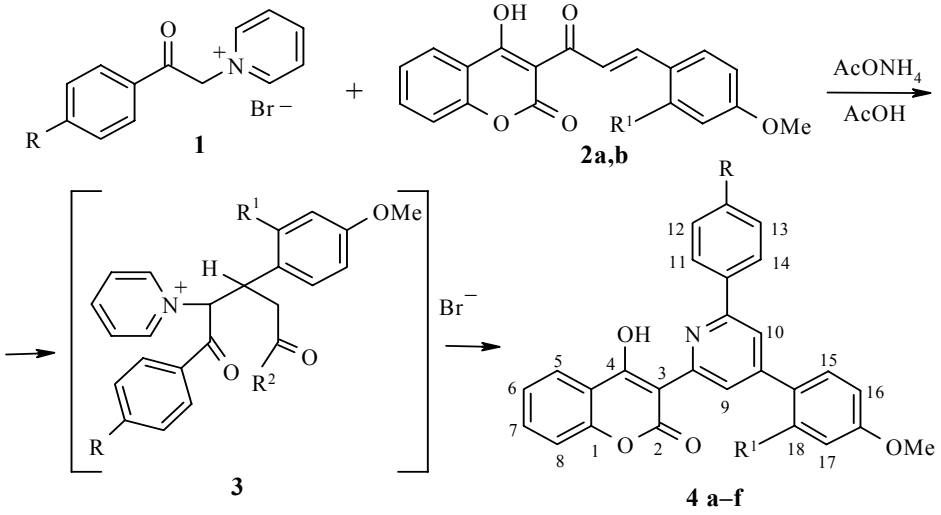
The reaction of substituted 3-cinnamoyl-4-hydroxycoumarins with pyridinium salts of various bromomethyl ketones gives the corresponding 4-hydroxy-3-pyridylcoumarins. The use of microwave radiation decreases the time required and improves the yield of this reaction. The products obtained do not display solvatochromic properties or photochemical activity.

Keywords: 4-hydroxy-3-pyridylcoumarins, 3-cinnamoyl-4-hydroxycoumarins, microwave radiation, Kröhnke reaction, tautomerism.

4-Hydroxycoumarins substituted at C-3 hold special importance among coumarin derivatives, primarily due to the pronounced biological activity of many 3-R-4-hydroxycoumarins [1-4], their tendency to undergo tautomeric transformations, and, as a consequence, their high sensitivity toward the action of solvents and irradiation [5-7].



1 **2a,b** **3** **4 a–f**

4 a R = Cl, R^1 = H, **b** R = Cl, R^1 = OMe, **c** R = F, R^1 = H, **d** R = F, R^1 = OMe, **e** R = NO_2, R^1 = H, **f** R = NO_2, R^1 = OMe; R^2 = 4-hydroxy-3-coumarinyl

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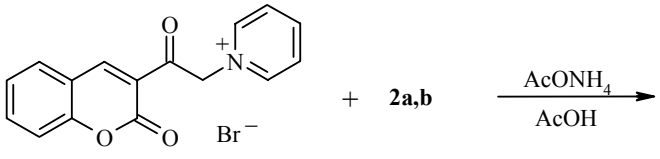
In a continuation of a study of 3-hetaryl-4-hydroxycoumarins [8], we undertook the synthesis of 4-hydroxy-3-pyridylcoumarins. Such compounds hold interest for their potential biological activity as well as their possible use as elements of various sensor systems, including sensors for various metal ions [9-13].

Data have been reported only for 3-pyridylcoumarins [14]. No information is available on 4-hydroxy-3-coumarins. We have synthesized pyridylcoumarins using the Kröhnke method for the synthesis of substituted pyridines [15], which involves the reaction of bromopyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate. Freshly-prepared phenacylpyridinium bromides **1** react with an equimolar amount of 3-cinnamoyl-4-hydroxy-coumarin **2** in the presence of ammonium acetate to give 4-hydroxy-3-pyridylcoumarins **4**. Phenacylpyridinium bromides act in this reaction as C-nucleophiles. According to Zecher and Kröhnke [15], this reaction proceeds through the formation of intermediate diketone **3**.

We also obtained pyridylcoumarins **4g** and **4h** by using the pyridinium salt of 3-(α-bromoacetyl)-coumarin **5** as the C-nucleophile.



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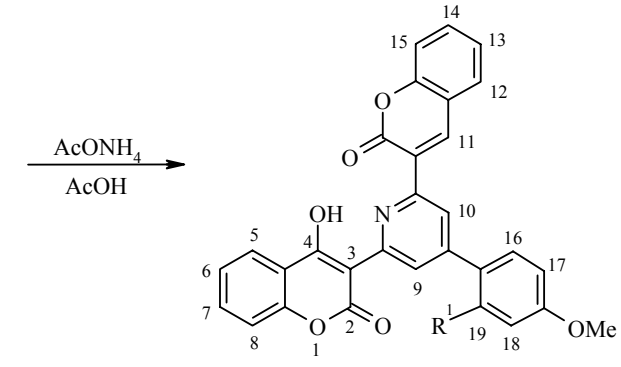


4g,h

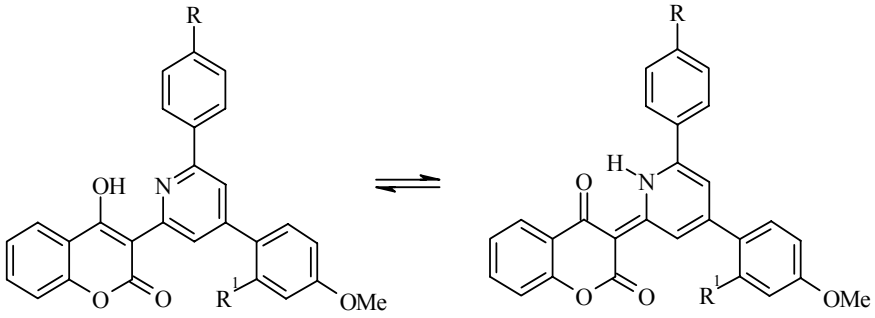
4 g R^1 = H, **h** R^1 = OMe

Zecher and Kröhnke [15] indicated that the reaction time required to obtain arylpyridines using their reaction is 2-3 h, while the yield of the desired products is 70-80%. However, in our first experiments, the reaction time was 30 h, while the yields of the corresponding pyridylcoumarins varied from only 12 to 18%, depending on the 4-hydroxy-3-pyridylcoumarin and starting bromomethyl ketone used. In order to reduce the reaction time required and improve the yields, we attempted to prepare 4-hydroxy-3-pyridylcoumarins using microwave radiation. The experiments carried out at 80°C for 1 h proved unsuccessful. Even when the reaction time was increased to 3 h, the yield of the desired product did not exceed 10% as indicated by GC/MS. Increasing the temperature to 120°C gave the desired pyridylcoumarins **4** after 3 h in good yields (42-53%) with high purity.

The ^{1}H NMR spectra of pyridylcoumarins **4a-d, 4g,** and **4h** in DMSO-d_6 lack signals for protons of the –CH=CH– fragment characteristic for α,β-unsaturated ketones, while signals for the pyridine ring protons are found downfield. The signal for H-9 appears as a singlet with intensity corresponding to one proton at ~9.3 ppm, while the signal for H-10 appears as a singlet at ~8.1 ppm (the assignment of the proton signals was carried out using the NOESY spectral data).

Pyridylcoumarins **4**, similar to previously studied derivatives of 4-hydroxycoumarin [16-18], may exist in theory in several tautomeric forms. The two most likely forms are shown below.

The results of AM1 semiempirical quantum-chemical calculations (Table 1) show that the difference between the enthalpies of formation of forms **A** and **B** for all four compounds **4** is very small (1-3 kcal/mol), which suggests that these forms tend to interconvert.



Form **A** Form **B**

The ^{1}H NMR spectra taken in DMSO-d_6 lack signals for both OH and NH groups. As a consequence of the low solubility of 4-hydroxy-3-pyridylcoumarins **4** in $CDCl_3$, we obtained the ^{1}H NMR spectrum for only **4a**, in which the OH group signal with integral intensity 0.82 is found at 19.72 ppm. The positions of almost all the other signals were virtually the same as in the spectra for samples in DMSO-d_6. An exception is the signal for H-10, which is shifted from 8.16 to 7.71 ppm.

The finding of a strong signal for the OH group proton in the ^{1}H NMR spectrum may be seen as a convincing argument that tautomeric form **A** is characteristic, at least for 4-hydroxy-3-pyridylcoumarins **4**. Table 1 gives also the hydrogen bond energies, which were estimated by comparison of the energies of formation of tautomer **A** calculated in conformations with and without consideration of intramolecular bonding. These values are rather large: 5-6 kcal/mol.

We did not find any indication of tautomeric or isomer transformations of pyridylcoumarins **4** in the electron absorption spectra. Shifting the solvent from 100% DMF to 100% chloroform did not yield an isobestic point, indicating the lack of tautomeric transformations under the conditions for taking these absorption spectra.

We also studied the effect of visible light irradiation on the stability of coumarins **4**. The electronic absorption spectra taken after each irradiation dose indicated the stability of these compounds upon visible light irradiation in 100% DMF, ethanol, and CCl_4.

TABLE 1. Results of AM1 Quantum-Chemical Calculations for Pyridyl-coumarins **4a-h** and Electronic Absorption Spectra Data

Com-pound	ΔH_f°, kcal/mol		$E_{(O\text{-}H\text{-}N)}$, kcal/mol	λ_{max}^{exp}*[2], nm (log ε)	
	Tautomer **A**	Tautomer **B**		in DMF	in $CHCl_3$
4a	-29.88	-31.05	5.42	388 (4.12)	389 (4.03)
4b	-66.09	-67.23	6.01	390 (4.30)	390 (4.18)
4c	-67.77	-69.17	5.18	390 (4.19)	390 (3.92)
4d	-103.59	-105.44	5.14	392 (3.87)	389 (3.60)
4e	-18.91	-15.72	4.93	389 (3.88)	391 (3.74)
4f	-55.48	-54.86	5.22	391 (4.10)	389 (3.82)
4g	-74.01	-73.29	5.30	399 (4.03)	402 (3.94)
4h	-109.58	-109.38	6.47	430 (2.77)	427 (2.49)

*ΔH_f° is the enthalpy of formation, $E_{(O\text{-}H\text{-}N)}$ is the strength of the hydrogen bond.
*[2]λ_{max}^{exp}** is the long-wavelength maximum.

EXPERMENTAL

The ^{1}H NMR spectra were taken on a Bruker WP-400SY spectrometer at 400 MHz in DMSO-d_6 for pyridylcoumarins **4a-d,g,** and **4h** and in CCl_4 for **4a** with TMS as the internal standard. The GC/MS spectra were taken on a PE SCIEX API65 spectrometer (ELSD UV254) using a 20×2.0-mm Synergi 2u Hydro-RP Mercury column. The electronic absorption spectra were taken on an SF-104 spectrometer in DMF, ethanol, chloroform, and carbon tetrachloride. The AM1 semiempirical quantum-chemical calculations were carried out using the MM+ molecular mechanics method.

Phenacylpyridinium bromides 1 were obtained according to Grazia et al. [20].

4-Hydroxy-3-[*E*-3-(R-phenyl)-2-propenoyl]coumarins 2a and 2b were prepared according to our previous procedure [21].

4-Hydroxy-3-pyridylcoumarins 4a-h (**General Method**). A. 3-Cinnamoyl-4-hydroxycoumarin **2** (1 mmol) was dissolved in acetic acid (20 ml) upon heating at reflux. Then, corresponding bromide **1** (1 mmol) and ammonium acetate (0.1 g, 0.13 mmol) were added and the reaction mixture was heated at reflux for 20-30 h with monitoring by thin-layer chromatography. The reaction product was recrystallized from ethanol and dried.

B. Cinnamoylcoumarin **2** (0.3 mmol) was dissolved in acetic acid (6 ml) at reflux in a heat-resistant glass microwave test tube equipped with a magnetic stirrer and an equimolar amount of bromomethyl ketone pyridinium salt and ammonium acetate (0.3 g, 0.39 mmol) were added to the solution obtained. The reaction mixture was maintained in the microwave oven for 3 h at 120°C. The precipitate was filtered off, washed with ethanol, and dried.

3-[6-(4-Clorophenyl)-4-(4-methoxyphenyl)pyridin-2-yl]-4-hydroxycoumarin (4a) was obtained in 17% yield by method A and 53% yield by method B; mp-227-229°C. ^{1}H NMR spectrum in DMSO-d_6, δ, ppm (*J*, Hz): 3.84 (3H, s, OCH_3); 7.13 (2H, d, *J* = 7.9, H-16, H-17); 7.31 (2H, m, H-6, H-8); 7.62 (1H, m, H-7); 7.75 (2H, d, *J* = 7.9, H-15, H-18); 7.92 (2H, d, *J* = 8.1, H-11, H-14); 8.03 (1H, d, *J* = 7.7, H-5); 8.15 (2H, d, *J* = 8.1, H-12, H-13); 8.17 (1H, s, H-10); 9.12 (1H, s, H-9). ^{1}H NMR spectrum in $CDCl_3$, δ, ppm (*J* Hz): 3.81 (3H, s, OCH_3); 7.28 (2H, d, *J* = 8.4, H-16, H-17); 7.33 (2H, m, H-6, H-8); 7.62 (3H, m, H-7, H-15, H-18); 7.71 (1H, s, H-10); 7.28 (2H, d, *J* = 8.8, H-11, H-14); 7.97 (2H, d, *J* = 8.8, H-12, H-13); 8.18 (1H, d, *J* = 8.1, H-5); 9.39 (1H, s, H-9); 19.72 (0.82H, s, OH). Mass spectrum, *m/z* (I_{rel}, %): 455.5 (70). Found, %: C 71.32; H 3.88; N 3.15. $C_{27}H_{18}ClNO_4$. Calculated, %: C 71.13; H 3.95; N 3.07.

3-[6-[4-Chlorophenyl)-4-(2,4-dimethoxyphenyl)pyridin-2-yl]-4-hydroxycoumarin (4b) was obtained in 12% yield by method A and 49% yield by method B; mp 284-286°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.89 (6H, s, $2OCH_3$); 6.76 (2H, m, H-16, H-17); 7.35 (2H, m, H-6, H-8); 7.61 (1H, d, *J* = 7.8, H-15); 7.66 (1H, m, H-7); 7.78 (2H, d, *J* = 8.3, H-11, H-14); 8.08 (2H, m, H-5, H-10); 8.15 (2H, d, *J* = 8.3, H-12, H-13); 9.15 (1H, s, H-9). Mass spectrum, *m/z* (I_{rel}, %): 485.5 (85). Found, %: C 69.33; H 4.17; N 2.79. $C_{28}H_{20}ClNO_5$. Calculated, %: C 69.21; H 4.12; N 2.88.

3-[6-(4-Fluorophenyl)-4-(4-methoxyphenyl)pyridin-2-yl]-4-hydroxycoumarin (4c) was obtained in 15% yield by method A and 51% yield by method B; mp 269-271°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, OCH_3); 7.11-7.30 (4H, m, H-15, H-16, H-17, H-18); 7.48 (2H, m, H-6, H-8); 7.64 (1H, m, H-7); 7.95 (2H, d, *J* = 8.4, H-11, H14); 8.06 (1H, d, *J* = 7.8, H-5); 8.14 (1H, s, H-10); 8.23 (2H, d, *J* = 8.4. H-12, H-13); 9.21 (1H, s, H-9). Mass spectrum, *m/z* (I_{rel}, %): 439 (65). Found, %: C 73.69; H 4.15; N 3.13. $C_{27}H_{18}FNO_4$. Calculated, %: C 73.80; H 4.10; N 3.18.

3-[6-(4-Fluorphenyl)-4-(2,4-dimethoxyphenylpyridin-2-yl]-4-hydroxycoumarin (4d) was obtained in 14% yield by method A and 47% yield by method B; mp 221-223°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.89 (6H, s, $2OCH_3$); 6.77 (2H, m, H-16, H-17); 7.33 (3H, m, H-6, H-8, H-15); 7.57 (2H, d, *J* = 8.3, H-11, H-14); 7.66 (1H, m, H-7); 8.02 (1H, m, H-10); 8.07 (1H, d, *J* = 7.6, H-5); 8.17 (2H, d, *J* = 8.3, H-12, H-13); 9.16 (1H, s, H-9). Mass spectrum, *m/z* (I_{rel}, %): 469 (85). Found, %: C 71.75; H 4.19; N 2.91. $C_{28}H_{20}FNO_5$. Calculated, %: C 71.64; H 4.26; N 2.99.

4-Hydroxy-3-[4-(4-Methoxyphenyl)-6-(4-nitrophenyl)pyridin-2-yl]coumarin (4e) was obtained in 16% yield by method A and 50% yield by method B; mp 267-269°C. The ^{1}H NMR spectrum could not be recorded due to low solubility of this compound. Found, %: C 69.41; H 3.77; N 6.09. $C_{27}H_{18}N_2O_6$. Calculated, %: C 69.53; H 3.86; N 6.01.

3-[4-(2,4-Dimethoxyphenyl)-6-(4-nitrophenyl)pyridin-2-yl]-4-hydroxycoumarin (4f) was obtained in 15% yield by method A and 52% yield by method B; mp 258-260°C. The ^{1}H NMR spectrum could not be recorded due to low solubility of this compound. Found, %: C 66.82; H 4.04; N 5.63. $C_{27}H_{20}N_2O_7$. Calculated, %: C 66.94; H 4.13; N 5.79.

3-[6-(3-Coumarinyl)-4-(4-methoxyphenyl)pyridin-2-yl]-4-hydroxycoumarin (4g) was obtained in 18% yield by method A and 45% yield by method B; mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.79 (3H, s, OCH_3); 7.19 (2H, d, *J* = 8.0, H-17, H-18); 7.33 (2H, d, *J* = 8.0, H-16, H-19); 7.48-8.07 (7H, m, H-6, H-7, H-8, H-12, H-13, H-14, H-15); 8.05 (1H, s, H-5); 8.24 (1H, s, H-10); 8.91 (1H, s, H-11); 9.38 (1H, s, H-9). Mass spectrum, *m/z* (I_{rel}, %): 489 (75). Found, %: C 73.71; H 3.83; N 2.91. $C_{30}H_{19}NO_6$. Calculated, %: C 73.62; H 3.89; N 2.86.

3-[6-(3-Coumarinyl)-4-(2,2-dimethoxyphenyl)pyridin-2-yl]-4-hydroxycoumarin (4h) was obtained in 17% yield by method A and 42% yield by method B; mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.75 (6H, s, $2OCH_3$); 6.76 (3H, m, H-16, H-17, H-18); 7.26-8.18 (10H, m, H-5, H-6, H-7, H-8, H-10, H-11, H-12, H-13, H-14, H-15); 9.17 (1H, s, H-9). Mass spectrum, *m/z* (I_{rel}, %): 519 (90). Found, %: C 71.54; H 4.16; N 2.79. $C_{31}H_{21}NO_7$. Calculated, %: C 71.68; N 4.05; N 2.70.

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