EFFICIENT ONE-POT SYNTHESIS OF 7-AZACOUMARINS BY KNOEVENAGEL REACTION USING WATER AS REACTION MEDIUM

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Abstract — 3-Substituted 5-hydroxymethyl-8-methyl-7-azacoumarins were prepared by a Knoevenagel reaction of pyridoxal hydrochloride with acetonitriles in a one-pot procedure in a water-only medium. The reactions occurred in heterogeneous phase with much better yields than those obtained in a homogeneous alcoholic medium.

Coumarins, particularly 3-substituted coumarins, are widely used molecules of great biological interest.[1] Various protocols and experimental conditions have been developed to synthesize them easily.[2]

On the contrary 2*H*-pyranopyridin-2-ones, called "azacoumarins", are difficult to synthesize and their biological and pharmacological activities have been little investigated.[3a]

Very few papers[3] concerning azacoumarins are reported in the literature and the thirty or so known compounds have been prepared by condensation reactions such as the Knoevenagel,[3a,d] the Knoevenagel-Dobner,[3e] the Perkin,[3a] the Pechman, [3a,c] and the Wittig reactions[3f] under severe conditions. The processes have been carried out by multi-step procedures in solvents such as ethanol, acetic anhydride, pyridine and dry benzene with generally unsatisfactory reaction yields.

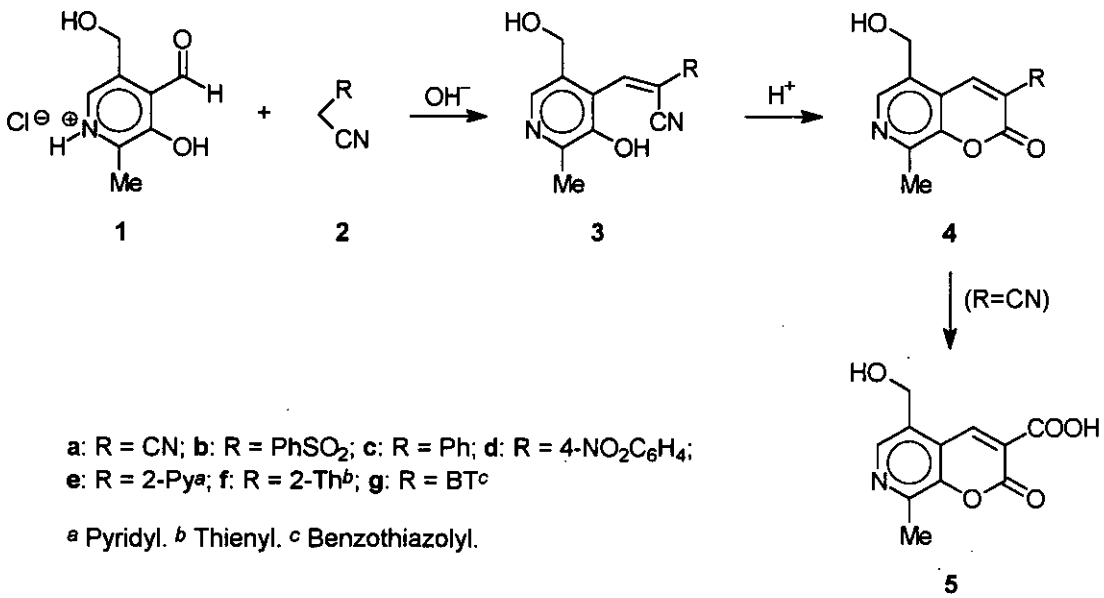
Continuing to use water as the reaction medium in organic synthesis,[2g,4] we recently reported that active methylene compounds gave aldol-type condensation with arylaldehydes in a water-only medium which allowed chalcones, flavonols, acrylonitriles and coumarins to be obtained in high yields using a one-pot procedure.[2g,4e] While the reactions occurred in heterogeneous medium, the unique chemical and physical properties of water[5] and the possibility of accurately controlling the pH of the reaction medium, guaranteed the success of the reactions.[2g,4] At the end of the process, the products were collected in pure form by simple filtration.

In this article we report a simple one-pot synthesis of 3-substituted 5-hydroxymethyl-8-methyl-7-azacoumarins in a water-only medium.

Knoevenagel condensation of pyridoxal hydrochloride (**1**)[6] (Scheme) with a variety of acetonitriles (**2**) in alkaline aqueous medium (pH = 8.3-13.4) at 20 °C or 90 °C, gave pyridylacrylonitriles (**3**). These were not isolated but were quickly converted to 7-azacoumarins (**4**) by acidifying the aqueous medium and continuing the reaction at either room temperature or at 90 °C. The products were obtained in pure form and in excellent yield by simple filtration. The results are summarized in Table 1. If the reaction mixture is not vigorously stirred the reaction time increases and the yield decreases.

The 3-cyanoazacoumarin (**4a**) (R = CN) was not isolated because it was hydrolyzed to 3-carboxyazacoumarin (**5**).

Scheme



a: R = CN; **b**: R = $PhSO_2$; **c**: R = Ph; **d**: R = 4-$NO_2C_6H_4$;
e: R = 2-Py[a]; **f**: R = 2-Th[b]; **g**: R = BT[c]

[a] Pyridyl. [b] Thienyl. [c] Benzothiazolyl.

The reaction with hydrophobic nitriles (**2c**, **2d**, **2f** and **2g**) occurred satisfactorily only if a catalytic amount of surfactant cetyltrimethylammonium bromide (CTABr) was present.[8] Tetrabutylammonium bromide was less effective as catalyst than CTABr.

The synthesis of **4g** is of interest because: a) the preparation of **2g** and its reaction with **1** were carried out in the same reaction flask and b) the benzothiazolyl group is a masked formyl group. This could provide a convenient route to 3-formyl-7-azacoumarins.

All the products showed the expected spectral properties. The absorption of C=O group of the lactone

moiety appeared at 1720-1785 cm^{-1}. The chemical shift for methylene protons was found at δ 4.75-4.87 ppm for all compounds, that for methyl group at δ 2.53-2.65 ppm and that for hydrogen at C-6 at δ 8.32-8.43 ppm. The resonance of hydrogen at C-4 depend on the type of substituent at C-3 and appeared at δ 8.23-9.24 ppm. The ^{13}C-NMR spectra had the expected number and type of resonances.

Table 1. One-Pot Synthesis of 7-Azacoumarins by Knoevenagel Condensation in Water

Nitrile	pH[a]	Temp (°C)[b]	Time (h)[b]	Azacoumarin	Yield (%)[c]
2a	8.3	20-90	25-0.5	**5**	80
2b	8.3	20-90	24-0.5	**4b**	90
2c	12.4	90-90	3-0.5	**4c**	70[d]
2d	8.3	90-20	1-1	**4d**	85[d]
2e	8.3	20-20	24-0.5	**4e**	70
2f	12.4	90-90	1.5-0.5	**4f**	85[d]
2g	13.4	20-90	2-0.5	**4g**	95[d,e]

[a] pH value of the reaction medium in the synthesis of the intermediate pyridylacrylonitriles (**3**). The cyclization reaction was carried out under acidic conditions (see Experimental). [b] The first value refers to the reaction time for the preparation of **3** and the second one to that for the cyclizzation reaction. [c] Yield of purified azacoumarins. [d] In the presence of 0.1 mol/equiv of CTABr. [e] The one-pot synthesis also includes the preparation of **2g**.

To evaluate the effect of water and the catalytic effect of CTABr the reactions were carried out also in homogeneous ethanolic solution. The results are summarized in Table 2. The yields were better in heterogeneous aqueous medium than in the homogeneous alcoholic medium and the presence of CTABr was especially important when the hydrophobic acetonitriles were used.

The reasons for the enhanced reactivity and selectivity in some reactions (i.e. aldol condensations, oxidations and Diels-Alder cycloadditions) [10,11,13-15] when carried out in heterogeneous aqueous medium, are still not well understood.

Solvent polarity has been invoked and certainly influences the reaction rate. However, the poor correlations observed between the solvent polarity parameters such as dielectric constant, dipole moment, etc and the reaction rate constants, indicate that polarity alone cannot explain the acceleration in water.[5]

Breslow[10] and Lubineau[11] attribute the "water effect" to hydrophobic interactions,[12] the well-known entropy-driven aggregation of apolar molecules or groups in water, which minimizes their exposure to the water.

Table 2. One-Pot Synthesis of 7-Azacoumarins. Effect of Reaction Medium

		Yield (%)		
Nitrile	Azacoumarin	H_2O/CTABr[a]	H_2O[a]	EtOH[a,b]
2b	**4b**	90	90	43
2c	**4c**	70	traces	traces
2d	**4d**	85	55	43
2e	**4e**	70	70	20
2f	**4f**	85	76	30

[a] Under the experimental conditions described in Table 1. [b] In ethanolic medium the addition step was catalyzed by 0.25N piperidine because of the low solubility of $NaHCO_3$ in ethanol.

It also been suggested that the high cohesive pressure of water.[11,13] could act as an external pressure and, therefore, would greatly favour processes having a negative activation volume. The acceleration in water could also be due to steric compression of the transition state in a cavity within the water structure.[5] Blokzijl and Engberts[14] have explained the "water effect" in terms of "enforced hydrophobic interactions" and hydrogen bonding having shown that the hydrophobic surface of the reactants is reduced during the formation of the activated complex which is highly adaptable and can adapt to an aqueous environment. The role of water is still an open question, but undoubtedly this little explored reaction medium is sometimes the source of unexpected results.

EXPERIMENTAL

The azacoumarin (**4d**) is known[3a] but only its mp is reported. The azacoumarins (**4b**, **4c**, **4e**, **4f**, **4g** and **5**) are new compounds. IR spectra were recorded in KBr pellets and ^{1}H- and ^{13}C-NMR spectra were run at 200 MHz in $(CD_3)_2SO$ solution. All starting materials were purchased from the Aldrich Chemical Co. and used without further purification, except 2-benzothiazoylacetonitrile.[15]

General Procedure

Pyridoxal hydrochloride (**1**) (20.36 g, 100 mmol), nitrile (**2**) (100 mmol) and CTABr (3.64 g, 10 mmol) when necessary (see Table 1) were added to an aqueous solution of $NaHCO_3$ (500 mL, 0.25M) or to an aqueous solution of NaOH (500 mL, 0.225 M). The mixture was vigorously stirred at 20 °C or 90 °C for the time reported in Table 1. The heterogeneous mixture was then acidified with conc HCl (12.5 mL) at rt

and stirred at 20 °C or 90 °C for the time reported in Table 1. After cooling at 1-3 °C for 2 h, the mixture was filtered under reduced pressure to give the solid which was washed with cold water and dried. The isolated azacoumarin had a purity higher than 98% (determined by ^{1}H-NMR analyses) and was further purified by recrystallization. The yields of purified specimens are listed in Table 1.

5-Hydroxymethyl-8-methyl-3-phenylsulfonyl-2*H*-pyrano[2,3-*c*]pyridin-2-one (4b): mp 212-214°C from MeCN/H_2O; IR cm^{-1}: 3280 (OH), 1765 (C=O), 1330, 1165 (SO_2); ^{1}H-NMR δ: 2.53 (s, 3H, Me), 4.24 (br s, 1H, OH), 4.87 (s, 2H, CH_2), 7.60-7.84 (m, 3H, H-3',H-4', H-5') 8.04 (m, 2H, H-2',H-6'), 8.43 (s, 1H, H-6), 9.12 (s, 1H, H-4); ^{13}C-NMR δ: 18.3, 58.0, 120.7, 128.7, 129.2, 130.7, 132.5, 134.4, 137.8, 142.6, 144.6, 146.7, 148.0, 153.4. Anal. Calcd for $C_{16}H_{13}NO_5S$: C, 58.00; H, 3.96; N, 4.23. Found: C, 58.19; H, 4.04; N, 4.23.

5-Hydroxymethyl-8-methyl-3-phenyl-2*H*-pyrano[2,3-*c*]pyridin-2-one (4c): mp 209-210°C from EtOH/Me_2CO; IR cm^{-1}: 3180 (OH), 1725 (C=O); ^{1}H-NMR δ: 2.58 (s, 3H, Me), 4.79 (d, 2H, CH_2, J = 4.2 Hz), 5.50 (t, 1H, OH, J = 4.2 Hz), 7.48 (m, 3H, H-3', H-4', H-5') 7.75 (m, 2H, H-2', H-6'), 8.23 (s, 1H, H-4), 8.32 (s, 1H, H-6); ^{13}C-NMR δ: 18.4, 58.0, 122.3, 128.3, 128.7, 129.2, 131.0, 131.3, 134.2, 135.8, 142.5, 145.7, 146.5, 158.5. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.89; H, 4.91; N, 5.24. Found: C, 71.91; H, 4.87; N, 5.24.

5-Hydroxymethyl-8-methyl-3-(4'-nitrophenyl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (4d): mp 232-234°C from PhMe/EtOH; IR cm^{-1}: 3300 (OH), 1730 (C=O), 1520, 1350 (NO_2); ^{1}H-NMR δ: 2.55 (s, 3H, Me), 4.80 (d, 2H, CH_2, J = 5.4 Hz), 5.55 (t, 1H, OH, J = 5.4 Hz), 7.99 (d, 2H, H-2', H-6', J = 8.8 Hz), 8.28 (d, 2H, H-3', H-5', J = 8.8 Hz), 8.32 (s, 1H, H-6), 8.35 (s, 1H, H-4); ^{13}C-NMR δ: 18.4, 57.9, 121.9, 123.2, 129.3, 130.1, 131.3, 137.7, 140.5, 142.6, 145.9, 146.6, 147.4, 158.0. Anal. Calcd for $C_{16}H_{12}N_2O_5$: C, 61.52; H, 3.88; N, 8.97. Found: C, 61.45; H, 3.91; N, 8.91.

5-Hydroxymethyl-8-methyl-3-(2'-pyridyl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (4e): mp 228-230°C from EtOH/H_2O; IR cm^{-1}: 3340 (OH), 1730 (C=O); ^{1}H-NMR δ: 2.58 (s, 3H, Me), 4.77 (d, 2H, CH_2, J = 5.2 Hz), 5.55 (t, 1H, OH, J = 5.2 Hz), 7.46 (dd, 1H, H-5', J = 7.1, 4.9 Hz), 7.92 (dd, 1H, H-4', J = 8.0, 7.1 Hz), 8.25 (d, 1H, H-3', J = 8.0 Hz), 8.32 (s, 1H, H-6), 8.72 (d, 1H, H-6', J = 4.9 Hz), 8.91 (s, 1H, H-4); ^{13}C-NMR δ: 18.5, 58.2, 122.2, 123.9, 124.3, 128.9, 131.2, 136.8, 137.6, 142.6, 146.1, 146.8, 149.6, 150.3, 158.2. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.14; H, 4.51; N, 10.45. Found: C, 67.18; H, 4.55; N, 10.38.

5-Hydroxymethyl-8-methyl-3-(2'-thienyl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (4f): mp 250-251°C from DMSO/H_2O; IR cm^{-1}: 3190 (OH), 1720 (C=O); ^{1}H-NMR δ: 2.58 (s, 3H, Me), 4.83 (d, 2H, CH_2, J = 5.5 Hz), 5.52 (t, 1H, OH, J = 5.5 Hz), 7.23 (dd, 1H, H-4', J = 5.1, 4.0 Hz), 7.79 (d, 1H, H-3', J = 5.1 Hz), 8.01 (d, 1H, H-5', J = 4.0 Hz), 8.33 (s, 1H, H-6), 8.51 (s, 1H, H-4); ^{13}C-NMR δ: 18.4, 57.9, 122.2, 124.7, 127.5, 128.3, 130.4, 130.7, 130.8, 134.6, 142.6, 145.6, 147.2, 157.9. Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.53; H, 4.06; N, 5.13. Found: C, 61.36; H, 4.01; N, 5.09.

5-Hydroxymethyl-8-methyl-3-(2'-benzothiazolyl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (4g): A mixture of 2-aminothiophenol (12.5 g, 100 mmol), malononitrile (**2a**) (6.6 g, 100 mmol), acetic acid (5.7 mL, 100 mmol) and CTABr (3.64 g, 10 mmol) in water (150 mL) was vigorously stirred at rt for 12 h. Water (350 mL), pyridoxal hydrochloride (**1**) (20.36 g, 100 mmol) and NaOH (13 g, 32.6 mmol) were added and the resulting mixture stirred at 20 °C for 2 h. The mixture was then acidified with conc HCl (28 mL) and heated at 90 °C for 0.5 h. After cooling in an ice-bath for 2 h, the azacoumarin precipitate (**4g**) was collected, washed with cold water and dried; 30.8 g (yield 95%). mp 284-286°C from DMSO/EtOH; IR cm^{-1}: 3200 (OH), 1715 (C=O); ^{1}H-NMR δ: 2.63 (s, 3H, Me), 4.86 (d, 2H, CH_2, J = 5.2 Hz), 5.66 (t, 1H, OH, J = 5.2 Hz), 7.53 (m, 2H, H-4', H-7'), 8.17 (t, 2H, H-6', H-5', J = 8.2 Hz), 8.40 (s, 1H, H-6), 9.24 (s, 1H, H-4); ^{13}C-NMR δ: 18.5, 58.2, 121.9, 122.3, 122.9, 123.4, 125.9, 126.9, 131.6, 136.2, 136.9, 143.0, 146.5, 146.7, 151.8, 158.0, 158.9. Anal. Calcd for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.77; H, 3.75; N, 8.72.

5-Hydroxymethyl-8-methyl-3-carboxy-2*H*-pyrano[2,3-*c*]pyridin-2-one (5): mp 228-229°C from DMF; IR cm^{-1}: 3460 (OH), 1785 (C=O); ^{1}H-NMR δ: 2.55 (s, 3H, Me), 4.75 (s, 2H, CH_2), 8.33 (s, 1H, H-6) 8.70 (s, 1H, H-4); ^{13}C-NMR δ: 18.5, 58.0, 121.0, 123.3, 131.7, 142.6, 142.9, 146.4, 147.6, 155.3, 163.7. Anal. Calcd for $C_{11}H_9NO_5$: C, 56.16; H, 3.86; N, 5.96. Found: C, 56.29; H, 3.89; N, 5.91.

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