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New synthetic approach to [1]benzopyrano[4,3-*b*]pyridin-5-one derivatives

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Abstract—A new synthesis of [1]benzopyrano[4,3-*b*]pyridin-5-ones **4** was developed starting from 3-formyl-coumarin N-functionalized amidines **3**. The reaction is based likely on the intramolecular cyclocondensation of the C-α amidinic carbanion in basic medium on the formyl group.

The varied biological activities of the coumarins fused with other heterocycles has encouraged researches with regard to the procedures and substrates, improving the feasibility of broad families of these compounds. Several biological activities have been claimed for compounds comprising both coumarins and coumarins fused to pyridine ring. For instance, coumarin nucleus is present in promising drug candidates as nonpeptidic HIV protease inhibitors,[1] such as topoisomerase II[2] and tyrosine kinase[3] inhibitors.

Coumarins joined to pyridines have been reported to posses antiallergic,[4] anticoagulant,[5] antidiabetic[6] activities, and even analgesic[7] properties, being characterized by a phenantrene-like structure as found in tetrahydrocannabinol.

Previously we reported the synthesis of coumarin imidazole ring[8] obtained from acetamidines substituted with 3-nitrocoumarin group on N-1. As a continuation of our studies and as a part of a program directed toward the synthesis of nitrogen heterocycles from substituted acetamidines[9] we report here the reactivity of acetamidines bearing 3-formyl-coumarin group on N-1 as starting material to synthesize benzopyranopyridin-5-ones.

We proposed to take advantage of nucleophilic character of the α-methylene group of amidines[10] and to exploit the ability of these acetamidines to give intramolecular condensation reaction on 3-formyl group.

An inspection of the literature data related the existing synthetic routes to benzopyranopyridin-5-ones can be divided as a function of the starting materials. One of these synthesis proceeds from 4-oxo-4*H*-1-benzopyran-3-carbonitrile via Michael addition[4] to the malonamide in basic medium, opening of the pyrone ring and subsequent rearrangement. Different syntheses proceed from 4-aminocoumarin reacted with alkylvinylketones,[6] or with keten S,S-acetals[5] or with orthocarboxylic acid amideacetals.[11] The benzopyranopyridin-5-ones have been prepared also from 4-amino-3-formyl-coumarin,[12] which undergoes Knoevenagel condensation with malonic or cyanoacetic esters in the presence of piperidine. A multi-step sequence from 4-chloro-3-formylcoumarin[13] and Wittig phosphorane was also developed to synthesize this tricyclic system.

The novelty of our synthetic scheme is the use of tertiary amidines bearing 3-formyl-coumarin group on N-1 to achieve substituted benzopyranopyridin-5-ones by an intramolecular cyclization reaction.

By reaction of an equimolar amount of 4-azido-3-formylcoumarin[14] **1** and suitable enamines[15] **2a**–**f** in methylene chloride solution at −40 °C the amidines **3a**–**f** were obtained in good yields and in a short reaction time.

The intermediate **A** was never isolated in all cases (Scheme 1). The reaction time, yields and melting points of compounds **3a**–**f** are listed in Table 1.

Keywords: 3-Formylcoumarin amidines; Aldols; [1]Benzopyrano-[4,3-*b*]pyridin-5-ones; Intramolecular cyclization.
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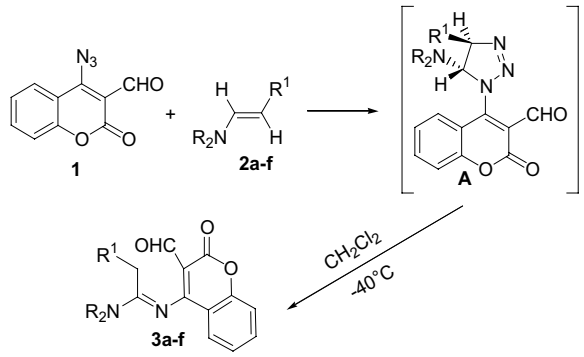
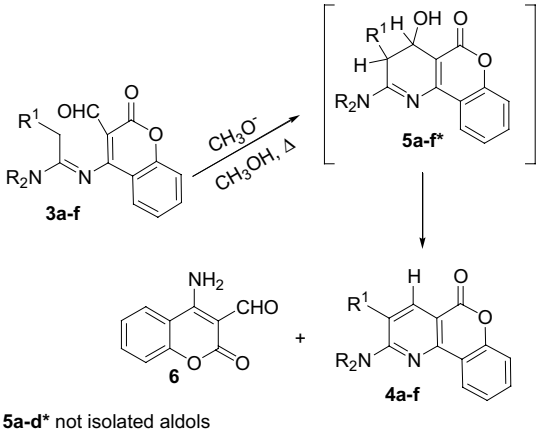


Scheme 1.



Scheme 2.

Amidines **3a**–**d** with a catalytic amount of sodium methoxide in refluxing methanol afforded the expected tricyclic compounds **4a**–**d** (Scheme 2). In these reaction conditions the aldol intermediate resulted likely from nucleophilic attack of the C-α amidinic carbanion on formyl group and the derivatives **4a**–**d** were formed through water elimination favored by aromatization of the pyridine ring. Nevertheless other mechanistic hypotheses cannot be excluded.

In the case of amidines **3e**–**f**, the isolation of the aldol intermediates **5e**–**f** (about 30% yield) validated the proposed mechanism. In these cases the transformation process resulted quite slow (about 2 h compared with 30 min for the compounds **3a**–**d**: see experimental), and besides the expected benzopyranopyridinones **4e**–**f** also the 4-amino-3-formylcoumarin[14] **6** (about 35%) was formed (Scheme 2). The isolation of 4-amino-3-formylcoumarin **6** is not surprising and arose from the known hydrolytic reaction of amidine[16] in basic medium.

It is reasonable to assume that benzopyranopyridinones **4** arise from carbanion intermediacy. In this case the difficult formation of alkyl carbanion could explain the low yields of benzopyranopyridinones **4e**–**f** such as the isolation of the aldols **5e**–**f** and the hydrolysis derivative **6**.

In conclusion, a new approach to benzopyranopyridin-5-ones **4** is reported, by way of an intramolecular cyclization starting from easily accessible substituted acetamidines of 3-formyl coumarin. This method can be applied with good yields and short reaction time to get benzopyranopyridin-5-one derivatives substituted on C-3 with aromatic chain. It is in progress a different synthetic strategy directed to implementation the yields of compounds like **4e**–**f**, bearing an alkyl chain on C-3.

General procedure for the synthesis of amidine derivatives **3a**–**f**: The suitable enamine **2a**–**f** (10 mmol) was dissolved in CH_2Cl_2 (20 mL). Checking strictly the inner temperature (−40 °C, acetone–CO_2 bath) an equimolar amount of azide **1**, dissolved in CH_2Cl_2 (30 mL), was slowly dropped in, under stirring. The mixture was kept at −30 °C for the time indicated in Table 1, until disappearance of the starting azide. The mixture came back to room temperature, the solvent was then evaporated and the crude product purified by crystallization from iPr_2O to give pure **3a**–**f**. Yields are reported in Table 1. All new compounds gave satisfactory analytical and spectroscopic data.

Selected spectroscopic data: **3a**, yellow crystals; IR (Nujol) 1698 (C=O), 1656 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$): 3.60–4.13 (10H, m, morpholine and CH_2), 7.10–7.36 (5H+2H, m, ArH and H-6 and H-8 coum.), 7.56 (1H, td, $J = 8.4$ and 1.8 Hz, H-7 coum.), 8.01 (1H, dd, $J = 8.0$ and 1.8 Hz, H-5 coum.), 10.14 (1H, s; CHO); ^{13}C NMR ($CDCl_3$): 37.5 (CH_2), 46.8 (CH_2NCH_2), 66.0 (CH_2OCH_2), 100.9 (C-3 coum.), 117.1, 123.8, 126.7, 133.4 (CH coum.), 119.7 (C-4a coum.), 127.4, 128.3, 129.1 (ArCH), 134.2 (ArCqu), 154.2 (C-4 coum.), 158.0 (C-8a coum.), 164.6 (N=C—N), 164.9 (C=O), 189.1 (CHO).

General procedure for the synthesis of [1]benzopyrano[4,3-b]pyridin-5-one derivatives **4a**–**f**: A catalytic amount of sodium methoxide (0.5 mL, 30% solution) was added to a stirred suspension of the appropriate 3-formylamidine **3a**–**f** (4 mmol) in methanol (100 mL). The mixture was refluxed until the starting amidine disappeared (reaction times indicated in Table 2). The

Table 1. Reaction time, yields and melting points of amidines **3**

Entry	NR_2	R^1	Reaction time (h)	Yield (%)	Mp (°C)
a	Morpholine	Phenyl	1.5	76	170
b	Diethylamine	Phenyl	1.5	65	127
c	Morpholine	4-Bromophenyl	1	78	153
d	Morpholine	4-Methoxyphenyl	3	63	138
e	Morpholine	*iso*Propyl	2	70	134
f	Morpholine	Benzyl	2	69	108

Table 2. Reaction time, yields and melting points of benzopyranopyridin-5-ones **4a–f**

Entry	NR_2	R^1	Reaction time (h)	Yield (%)	Mp (°C)
a	Morpholine	Phenyl	1	46	182
b	Diethylamine	Phenyl	1	58	123
c	Morpholine	4-Bromophenyl	0.5	94	141
d	Morpholine	4-Methoxyphenyl	0.5	85	165
e	Morpholine	*iso*Propyl	7	36[a]	175
f	Morpholine	Benzyl	7	38[a]	174

[a] Total yield: see experimental.

solvent was evaporated under reduced pressure and the crude residue was crystallized from *i*Pr_2O to afford compounds **4a–d**. The crude reaction mixture of amidines **3e–f** was chromatographed on a silica gel column (EtOAc/cyclohexane, 1:4) affording a first fraction containing **4e–f**, a second fraction of 4-amino-3-formylcoumarin[14] **6** and finally the aldols **5e–f**, respectively. A catalytic amount of sodium methoxide (0.3 mL, 30% solution) was added to the previously obtained aldols **5e–f**. The mixture was refluxed for an additional time (5 h) yielding a second batch of benzopyranopyridin-5-one **4e–f** then crystallized from *i*Pr_2O. Yields are reported in Table 2. All new compounds gave satisfactory analytical and spectroscopic data.

Selected spectroscopic data: **4a**, cream crystals; IR (Nujol) 1715 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): 3.42–3.58 (4H, m, CH_2NCH_2), 3.63–3.78 (4H, m, CH_2OCH_2), 7.23–7.60 (5H+3H, m, ArH and H-7,8,9 coum.), 8.28 (1H, s, H-4), 8.46 (1H, dd, $J = 8.0$ and 1.8 Hz, H-10 coum.); ^{13}C NMR ($CDCl_3$): 30.1 (CH_2), 49.1 (CH_2NCH_2), 66.8 (CH_2OCH_2), 110.2 (C-4a), 117.4, 124.7, 124.9, 132.0 (CH coum.), 119.8 (C-10a), 126.7 (C-3), 127.8, 128.5, 129.5 (ArCH), 139.3 (ArCqu), 141.4 (CH-4), 150.3 (C-6a), 153.5 (C-10b), 161.8 (C-2), 162.3 (C=O).

Selected spectroscopic data: **5e**, cream crystals, mp 146–148 °C (from *i*Pr_2O); IR (Nujol) 3450 (OH), 1663 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): 0.95 (3H, d, $J = 6.7$ Hz, CH_3), 1.03 (3H, d, $J = 6.7$ Hz, CH_3), 1.58–1.65 (1H, m, CH_3–C*H*–CH_3), 2.20 (1H, br s, exchangeable, OH), 2.89 (1H, d, $J = 7.7$ Hz, CH-3), 3.60–3.75, 4.00–4.08 and 4.40–4.48 (3H, 3 m, C*H*NCH_2), 3.75–3.85 (4H+1H, m, CH_2OCH_2 and C*H*NCH_2), 5.02 (1H, s, CH-4), 7.23–7.35 (2H, m, H-6 and H-8 coum.), 7.47–7.59 (1H, m, H-7 coum.), 8.19 (1H, dd, $J = 7.4$ and 1.3 Hz, H-5 coum.); ^{13}C NMR ($CDCl_3$): 20.6 (CH_3), 21.7 (CH_3), 29.7 (CH), 46.2 (CH-3), 45.2 and 47.8 (CH_2NCH_2), 63.7 (CH-4), 67.3 (CH_2OCH_2), 100.5 (C-4a), 117.0, 123.8, 125.7, 131.9 (CH coum.), 119.8 (C-10a), 154.5 (C-6a), 155.0 (C-10b), 164.0 (C-2), 169.0 (C=O).

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