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Efficient synthesis of benzopyrano[2,3-*b*]pyridines by sequential reactions of 1,3-bis-silyl enol ethers with 3-cyanobenzopyrylium triflates

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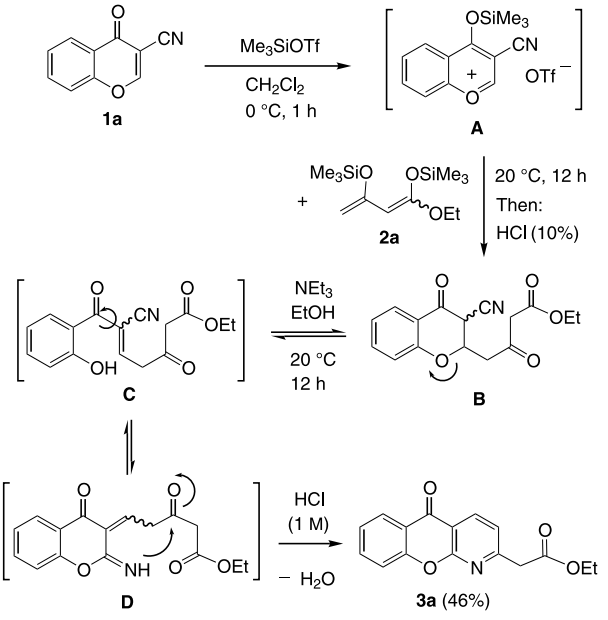
Abstract—Benzopyrano[2,3-*b*]pyridines were efficiently prepared by condensation of 1,3-bis-silyl enol ethers with 3-cyanobenzopyrylium triflates and subsequent domino 'retro-Michael–lactonization–aldol' reactions. © 2003 Elsevier Science Ltd. All rights reserved.

Domino reactions allow the rapid assembly of complex products in a one-pot process.[1] 5-Oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridines are of considerable pharmacological relevance and represent chromone natural product analogues.[2,3] For example, these molecules suppress rat adjuvant arthritis and are candidates for the development of antiinflammatory drugs for rheumatoid diseases. In addition, they represent potent inhibitors of the passive cutaneous anaphylaxis. A number of synthetic approaches to benzopyrano[2,3-*b*]pyridines are known.[2,3] Herein, we wish to report an efficient method for the synthesis of functionalized 5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridines. Our methodology relies on the condensation of 1,3-bis-silyl enol ethers, unsymmetrical acetoacetone d^4 synthons, with 3-cyanobenzopyrylium triflates to give open-chained products.[4,5] Treatment of the latter with NEt_3 resulted in formation of 5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridines by a domino 'retro-Michael–lactonization–aldol' reaction. Closely related base-mediated domino cyclizations of electroneutral 3-cyanochromones with active hydrogen compounds have been reported.[3] However, the substitution pattern present in our products is, to the best of our knowledge, not available by these transformations. All reactions reported herein proceeded with very good regio- and chemoselectivity and were carried out under mild conditions.

The direct reaction of 3-cyano-4-benzopyranone (**1a**) with the dianion of ethyl acetoacetate resulted in the formation of a complex mixture. The problem could be solved by the use of 1,3-bis(trimethylsilyloxy)-1,3-butadiene **2a** which can be regarded as an electroneutral dianion equivalent.[6–8] Benzopyran-4-one **1a** was used in the form of the benzopyrylium triflate **A** which was generated by treatment of a CH_2Cl_2 solution of **1a** with Me_3SiOTf (Scheme 1). The product, 3-cyano-2,3-dihy-



Scheme 1. Synthesis of benzopyrano[2,3-*b*]pyridine **3a**.

Keywords: cyclizations; domino reactions; pyrylium salts; pyridines; silyl enol ethers.

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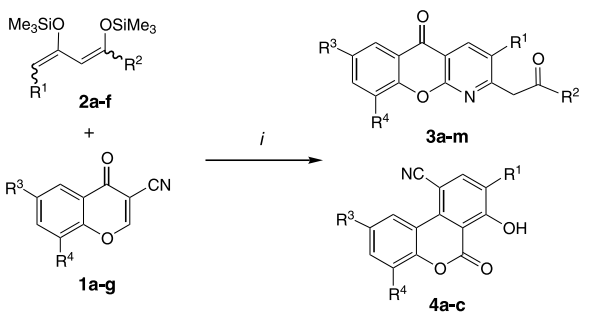
dropyran-4-one **B**, was formed with very good regioselectivity. During the optimization, best results were obtained when the reaction was carried out at 0→20°C (reaction time: 12 h). The presence of a base was not required. To completely hydrolyze the silyl groups, an aqueous solution of hydrochloric acid (10%) was used for the work-up. Treatment of an EtOH solution of crude **B** with NEt_3 directly afforded the 5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridine **3a**.[9]

The formation of **3a** can be explained by a domino retro-Michael–lactonization–aldol reaction. The open-chained intermediate **C** was formed by a base-mediated retro-Michael reaction. Attack of the hydroxy group onto the nitrile resulted in formation of intermediate **D**. The carbonyl group was subsequently attacked by the imino nitrogen to give **3a** after elimination of water and aromatization (Scheme 1). In the overall transformation **1**+**2a**→**3a**, two carbon atoms of the pyridine moiety of **3a** are derived from carbons C-3 and C-4 of the bis-silyl enol ether. The bridgehead carbon located between the oxygen and the nitrogen atom stems from the nitrile group.

The preparative scope of our methodology was next studied. The reaction of 3-cyano-4-benzopyranone (**1a**) with bis-silyl enol ethers **2a**–**c** afforded benzopyrano[2,3-*b*]pyridines **3a**–**c** (Scheme 2, Table 1). The cyclization of **2a**,**c** with alkyl substituted benzopyrans **1b**–**d** afforded the methyl, ethyl and *iso*propyl substituted products **3d**–**f**, respectively. Benzopyrano[2,3-*b*]pyridines **3g**–**j** were prepared from halogenated benzopyrans **1e**–**g** and 1,3-bis-silyl enol ethers **2a** and **2c**. The reaction of **1a** with bis-silyl enol ethers **2d**–**f**, prepared from methyl 3-oxopentanoate, ethyl 3-oxohexanoate and methyl 4-methoxyacetoacetate, afforded the methyl, ethyl and methoxy substituted benzopyrano[2,3-*b*]pyridines **3k**–**m**. In these reactions, significant amounts of the biaryl lactones **4a**–**c** were formed by a domino retro-Michael–aldol–lactonization mechanism.[8] However, the azaxanthones **3l**–**m** could be separated and isolated in pure form. All products **3a**–**m** were prepared in two steps by sequential reactions.

The sequential reaction of **1a** with 1,3-bis-silyl enol ether **2g**, prepared from ethyl cyclohexanone-2-carboxylate, afforded the tetracyclic azaxanthone **3n** (Scheme 3).

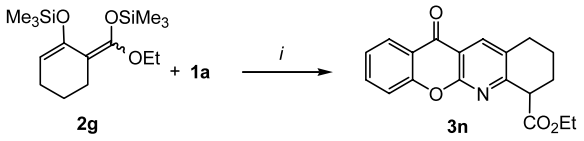


Scheme 2. Synthesis of azaxanthones **3a**–**m**. (i) (1) TMSOTf, CH_2Cl_2, 20°C, 12 h, then HCl (10%); (2) NEt_3, EtOH or MeOH (for **3b**,**k**,**m**), 20°C, 12 h, then HCl (1 M).

Table 1. Products and yields

1	2	3	R^1	R^2	R^3	R^4	3 (%)[a]	Mp (°C)
a	**a**	**a**	H	OEt	H	H	46	127
a	**b**	**b**	H	OMe	H	H	41	138
a	**c**	**c**	H	O*i*Pr	H	H	42	148
b	**a**	**d**	H	OEt	Me	H	40	128
c	**c**	**e**	H	O*i*Pr	Et	H	31	127
d	**a**	**f**	H	OEt	*i*Pr	H	41	140
e	**a**	**g**	H	OEt	Cl	H	37	118
f	**a**	**h**	H	OEt	Cl	Cl	48	155
g	**a**	**i**	H	OEt	Br	H	34	127
g	**c**	**j**	H	O*i*Pr	Br	H	32	128
a	**d**	**k**	Me	OMe	H	H	52	–
a	**e**	**l**	Et	OEt	H	H	54 (13)	108
a	**f**	**m**	OMe	OMe	H	H	47 (11)	134

[a] For **3a**–**j**: Yields of isolated product over two steps (based on **1**). For **3k**–**m**: combined yield of **3** and **4** (in brackets: yield of pure **3**).



Scheme 3. Synthesis of azaxanthone **3n** (mp 172°C); (i) (1) TMSOTf, CH_2Cl_2, 20°C, 12 h, then HCl (10%); (2) NEt_3, EtOH, 20°C, 12 h, then HCl (1 M).

Acknowledgements

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9. *Typical procedure*: Synthesis of 10-oxo-10*H*-9-oxa-1-azaanthracen-2-yl)acetic acid ethyl ester (**3a**): To 3-cyanochromone **1a** (300 mg, 1.75 mmol) was added Me_3SiOTf (0.41 ml, 2.28 mmol) and CH_2Cl_2 (2 ml) at 20°C. After stirring for 1 h, CH_2Cl_2 (13 ml) and **2a** (624 mg, 2.28 mmol) were added at 0°C. The mixture was stirred for 12 h at 20°C and subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (4×80 ml). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was filtered through a pad of silica gel (EtOAc/hexane = 5:1) to give **B**. For a number of products **3** the open chained intermediates were purified by chromatography. To an ethanol solution (20 ml) of crude **B** was added NEt_3 (1.22 ml, 8.77 mmol) and the solution was stirred for 12 h at 20°C. To the solution were subsequently added an aqueous solution of hydrochloric acid (1 M) and ether (50 ml). The organic and the aqueous layer were separated and the latter was extracted with ether (4×80 ml). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc/hexane = 1:5) to give **3a** as a colourless solid (229 mg, 46%), mp 127°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.99 (s, 2H, CH_2), 4.23 (q, ^3J = 7.0 Hz, 2H, OCH_2CH_3), 7.44 (m, 2H, 3-H, 6-H), 7.62 (d, ^3J = 8.3 Hz, 1H, 8-H), 7.79 (ddd, ^3J = 8.3 Hz, ^3J = 7.2 Hz, ^4J = 1.7 Hz, 1H, 7-H), 8.31 (dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1H, 5-H), 8.69 (d, ^3J = 7.9 Hz, 1H, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.16 (CH_3), 44.15 (C-1′), 61.50 (C-3′), 115.3 (C), 118.52, 121.54 (CH), 121.67 (C), 124.74, 126.71, 135.63, 137.96 (CH), 155.70, 159.91, 160.17 (C), 169.35, 177.34 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3200 (w), 2985 (m), 2928 (m), 1728 (s), 1669 (s), 1614 (s), 1602 (m), 1472 (s), 1372 (m), 1342 (m), 1322 (m), 1281 (m), 1207 (s), 1191 (s). UV–vis (CH_3CN, nm): λ_{max} (log ε): 236.0 (4.36), 285.2 (4.20), 331.4 (3.92). MS (EI, 70 eV): m/z = 283 (M^+, 85), 238 (16), 212 (12), 211 [M^+, 100], 182 (10), 127 (5); the exact molecular mass for $C_{16}H_{13}O_4N$ m/z = 283.0845±2 mD (M^+) was confirmed by HRMS (EI, 70 eV). For **3b**,**k**,**m**, methanol was used as the solvent. All new compounds gave satisfactory spectroscopic and analytical and/or high-resolution mass data.