Two Methods for the Preparation of 3-Dialkylaminomethyl Derivatives (Mannich Bases) of 4-Aminocoumarin: A New Type of Intramolecular Hydride Transfer

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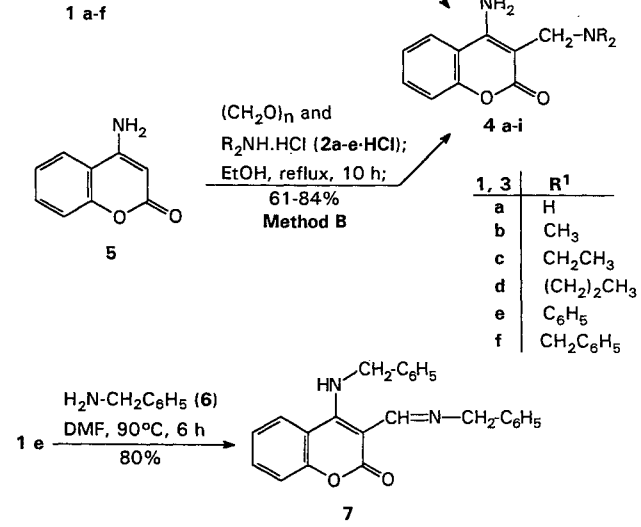
The transformation of 4-alkylaminocoumarin-3-carbaldehydes (**1b–f**) by treatment with secondary amines **2a–i** into 3-dialkylaminomethyl-4-aminocoumarins **4a–i** via intramolecular hydride transfer is reported. The structure of **4** was ascertained by independent Mannich reaction of 4-aminocoumarin (**5**) yielding the 3-dialkylaminomethyl derivatives **4a–e**. By treatment of **1e** with primary amine **6** only the usual Schiff base **7** was obtained.

In our work[1] on the Knoevenagel reaction of *N*-substituted 4-aminocoumarin-3-carbaldehydes we found that in some cases the *N*-monoalkyl derivatives reacted with the piperidine catalyst without the participation of the CH-acidic component. Now we report the results of a more detailed study.

When heated with a secondary amine **2a–i**, the *N*-monoalkyl-4-aminocoumarin-3-carbaldehydes **1b–f** gave the corresponding 3-dialkylaminomethyl derivatives **4a–i** in 24–87% yields (Scheme 1, Table). The products are accompanied by the corresponding aldehyde; thus the *N*-benzyl derivative **1e** gives benzaldehyde, characterised as its 2,4-dinitrophenylhydrazine (DNP) derivative.

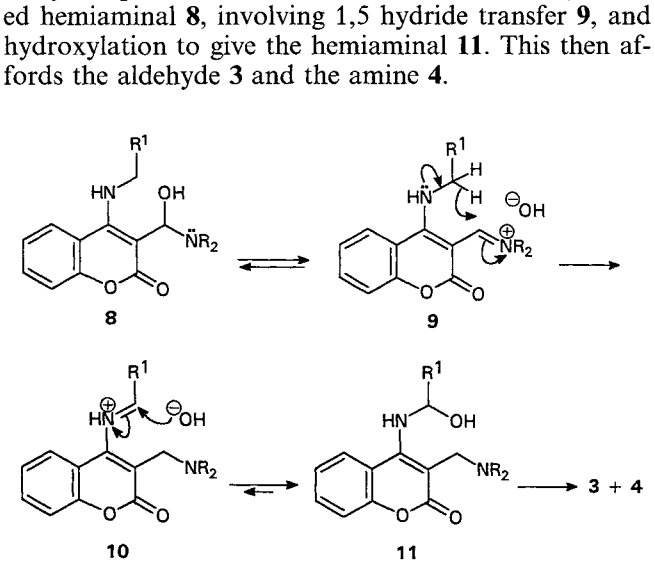


Scheme 1

The intramolecular oxidation–reduction **1** → **4** takes place under a wide range of reaction conditions: molar ratios from 1 : 2 up to 1 : 50, in anhydrous solvents such as DMF, ethanol, heptane, toluene or merely in excess of the amine **2**; at temperatures from 70 up to 120 °C. The greater the excess of the amine **2**, the higher the yield of the reaction and the shorter the reaction time. The yields of the most successful procedure (Method A) are given in the Table. The reaction failed when *N*-methyl-4-aminocoumarin-3-carbaldehyde (**1a**) was employed giving a complex mixture of unidentified yellowish products.

When **1e** was treated with primary amine, e.g. benzylamine (**6**) under the same conditions as above, the expected Schiff base **7** was isolated as the main product, and no byproducts were detected by TLC. We failed in our attempts to perform the Mannich reaction of **5** under the conditions described by Möhrle et al.[2,3] for some other enaminocarbonyl compounds (40% aq. formaldehyde, secondary amine as base). In contrast, we achieved good results using classic Mannich conditions, i.e. by refluxing **5** with paraformaldehyde and the corresponding amine hydrochloride **2** · HCl in ethanol (Method B). In a similar way, the products **4a–e** were prepared in 61–84% yields, and shown to be identical with the corresponding compounds obtained by Method A.

The self-reductive amination (Method A) can be explained by a sequence of transformations of the initially formed hemiaminal **8**, involving 1,5 hydride transfer **9**, and hydroxylation to give the hemiaminal **11**. This then affords the aldehyde **3** and the amine **4**.



Scheme 2

It must be underlined that benzaldehyde and **4c** (from **1e** + **2c**) were detected by TLC during the course of the reaction, hence, the products were not formed after hydrolysis.

Starting compounds such as **1** and **5** are readily obtainable from 4-hydroxycoumarin,[1,4,5] so that both methods A and B can be employed for the preparation of **4**. While the Mannich reaction is simpler and gives purer products in good yields, the intramolecular self-reductive amination of **1** is a hitherto unknown reaction.

Table. Preparation of 4-Amino-3-dialkylaminomethyl-[1]benzopyran-2-ones **4a–i**[a]

Product	$-NR_2$	Yield (%)		mp (°C) (solvent)	FT-IR (Nujol) ν (cm^{-1})
		Method A[b,c]	Method B		
4a	diethylamino	51 (**1e**)	61	132–133 (50% EtOH)	1660, 3208, 3308, 3382
4b	1-pyrrolidinyl	24 (**1e**)	68	196–198 (EtOAc)	1667, 3218, 3389
4c[d]	piperidino	80 (**1d**)	82	189–190 (EtOH)	1669, 3220, 3312, 3401
4d	1-perhydroazepinyl	39 (**1b**)	81	152–153 (MeCN)	1664, 3185, 3403
4e	morpholino	63 (**1d**)	84	191–192 (EtOH)	1670, 3221, 3310, 3400
4f	2-methylpiperidino	51 (**1b**)	–	181–184 (EtOH)	1653, 3189, 3372
4g	3-methylpiperidino	60 (**1d**)	–	166–167 (EtOH)	1665, 3181, 3399
4h	4-methylpiperidino	87 (**1d**)	–	198–200 (85% EtOH)	1671, 3227, 3386, 3430
4i	4-methyl-1-piperazinyl	75 (**1c**)	–	209–210 (MeCN)	1671, 3222, 3323, 3427

[a] Satisfactory microanalyses obtained: C, H, N ± 0.25%. Molecular mass confirmed by EI-MS (70 eV).
[b] Starting compound **1** shown in brackets.
[c] Products **4a, b** prepared by Typical Procedure I; products **4c–i** prepared by Typical Procedure II.
[d] ^{1}H NMR (250 MHz; $CDCl_3$): δ = 1.35–1.60 (m, 6H, $3CH_2$), 2.43 (s, 4H, CH_2NCH_2), 3.65 (s, 2H, 3-$CH_2N<$), 6.1–7.9 (br, 2H, NH_2), 7.2–7.7 (m, $4H_{arom}$).
^{13}C NMR (62.9 MHz; $CDCl_3$): δ = 24.3 (C-4'), 26.2 (C-3'), 53.7 (C-2'), 55.2 (3-CH_2N), 92.9 (C-3), 114.7 (C-4a), 117.3 (C-8), 120.8 (C-6), 123.4 (C-5), 131.4 (C-7), 153.1 (C-4 or C-8a), 153.4 (C-8a or C-4), 163.1 (C-2).

The structures of all new compounds are consistent with their spectroscopic data (IR, NMR, MS) and give satisfactory elemental analyses. FT-IR spectra were taken in Nujol on a Shimadzu FTIR-8101M spectrophotometer. NMR spectra were determined in $CDCl_3$ on a Bruker AM 250 or Bruker WP 100 spectrometer, with TMS as internal standard. Elemental analyses were performed at the Microanalytical Laboratory, University of Stuttgart (Germany). TLC was carried out on Merck Kieselgel F_{254} pre-coated aluminium sheets, using chloroform/hexane/acetone/aq. NH_3 (3:5:2:0.1, vol. parts) as the elution system.

All starting *N*-alkylaminoaldehydes **1a–f** were obtained according to literature[1,5] methods with the corresponding constants except **1f**: mp 153–154°C (EtOH) (Lit.,[5] mp 139–140°C).

4-Amino-3-dialkylaminomethyl-[1]benzopyran-2-ones (4a–i) by Method A (see Table); Typical Procedures:

4-Amino-3-piperidinomethyl-[1]benzopyran-2-one (**4c**);
Typical Procedure I:

A solution of **1e** (558 mg, 2.0 mmol) and piperidine (**2c**; 0.4 mL, 4.0 mmol) in dry DMF (4 mL) was heated at 90°C for 20 h (TLC monitoring). After cooling, the separated crystals (100 mg) of **4c** were filtered off and the filtrate poured int 20 mL of water. A second portion (282 mg) of crude **4c** precipitated and was filtered. Recrystallization from EtOH gave 230 mg (45%) total yield of **4c**. The aqueous filtrate (an emulsion) was made acidic with H_2SO_4 and extracted with $CHCl_3$ to afford, on evaporation of the solvent under reduced pressure, almost pure benzaldehyde (TLC; mp and R_f of its DNP derivative).

Typical Procedure II:

A solution of **1d** (245 mg, 1.0 mmol) and piperidine (**2c**; 4.9 mL, 50 mmol) in dry heptane (10 mL) was refluxed for 8 h (TLC monitoring). After cooling, the product **4c** crystallized, and was filtered and washed with heptane and Et_2O to afford 207 mg (80%) of pure **4c**.

Preparation of 4a–e by Mannich Reaction of 5 (Method B); General Procedure:

A mixture of 4-aminocoumarin[4] (**5**; 161 mg, 1.0 mmol), paraformaldehyde (60 mg, 2.0 mmol) and the corresponding amine hydrochloride (**2a–e** · HCl; 2.0 mmol) was refluxed in dry EtOH (10 mL) for 10 h (TLC monitoring). The precipitate formed was filtered off and dissolved in water (20 mL), the solution was clarified by filtration and made alkaline with 25% NH_4OH. The separated crystals of colourless **4a–e** were then filtered, washed with water (5–10 mL) and dried at 100–105°C. The products were satisfactorily pure and did not need recrystallization. For further details see Table.

4-Benzylamino-3-(benzylimino)methyl-[1]benzopyran-2-one (7):

Prepared according to Typical Procedure I from **1e** and benzylamine (**6**) in molar ratio 1:5; yield 80% of colourless **7**, mp 165–166°C (EtOH).

FT-IR: ν = 1694 (lactone C=O), 1636, 1607 cm^{-1}.

^{1}H NMR ($CDCl_3$; 100 MHz): δ = 4.62 (s, 2H, $CH_2N=$), 5.01 (d, 2H, J = 4.4 Hz, CH_2NH), 6.9–7.7 (m, $13H_{arom}$), 8.01 (d, 1H, J = 8.3 Hz, 5-H_{arom}), 8.94 (s, 1H, 3-CH=N), 13.19 (br, 1H, NH).

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(1) Ivanov, I.C.; Karagiosov, S.K.; Simeonov, M.F. *Liebigs Ann. Chem.* **1992**, 203.
(2) Möhrle, H.; Reinhardt, H.W. *Arch. Pharm. (Weinheim, Ger.)* **1981**, *314*, 767.
(3) Möhrle, H.; Reinhardt, H.W. *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 1017.
(4) Ivanov, I.C.; Karagiosov, S.K.; Manolov, I. *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 61.
(5) Tabakovic, K.; Tabakovic, I.; Ajdini, N.; Leci, O. *Synthesis* **1987**, 308.