One-pot synthesis of 2-alkyl/arylamino-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde from 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde

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Zn/NH_4Cl–mediated reactions of aldehyde **1** with nitro compounds **2** afford 2-(*N*-alkyl/arylamino)-3-formylchromones **4**, which on heating with 70% H_2SO_4 produces **9a-d** and **11e-h** from **4a-d** and **4e-h**, respectively.

Keywords: 1-benzopyran, nitrone, Zn-reduction, 3-formylchromone, quinoline

The synthesis of the aminochromone class of compounds has received considerable attention because of the wide range of biological activities. 5, 4'-Diaminoflavone and some of its congeners exhibited a remarkable antiproliferative effect against the human breast cancer cell line MCF – 7 irrespective of the presence or absence of estrogen.[1] Increasing interest in the 2-aminochromone class of compounds is mainly due to the antiplatelet activity.[2]

2-(*N*,*N*-Dialkylamino)chromone has been synthesised (i) by reacting salicylic esters with ynamines,[2a] (ii) by Vilsmeier condensation of β–aminoester with phenol,[3] (iii) by replacement of sulfoxide group in 2-ethylsulfinyl-5, 8-dimethoxychromone by $NHRR_1$[4] (iv) by reaction of phosgeniminium salt with the BF_3-complex of *o*-hydroxyacetophenone, followed by hydrolysis,[5] and (v) by cyclisation of *o*-hydroxybenzoyl–*N*,*N*-dimethylacetamide by PPA or Tf_2O.[6] 2-Anilino-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **4a** has been obtained by the intramolecular rearrangement of nitrone **3a**, which was synthesised from 3-formylchromone **1** and phenylhydroxyl amine.[7] Compound **4a** has been utilised for the synthesis of different 2-(*N*-alkyl/arylamino)-3-formylchromones.[7c] Recently, nitrones have been synthesised by treating aldehydes, nitroalkanes or nitroarenes with Zn in presence of HOAc[8] or in presence of aqueous solution of NH_4Cl in THF.[9]

In this paper we report a one-pot synthesis of 2-alkyl/arylamino-4-oxo-4*H*-1-benzopyran-3-carboxaldehydes **4** from 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **1** and also the deformylation of 2-alkylamino-3-formylchromones **4e-h** to form 2-monoalkylaminochromones **11e-h**.

A mixture of 3-formylchromone **1** (1 eq), nitroarene (1 eq) or nitroalkane (1.1 eq) and Zn-powder (4 eq) in THF was stirred at room temperature for 2 h. No change was noticed when checked by TLC. But on addition of saturated aqueous solution of NH_4Cl, the reaction started immediately and a yellowish green colour developed within 1 min. The reactions involving nitroalkanes were much more exothermic than the reactions where nitroarenes were used. On stirring for 7 h under these conditions, the reaction mixtures containing nitroalkanes produced 2-alkylamino-3-formylchromones **4e–h**. A very small amount (8–10%) of **7** was also isolated when nitromethane was used. On reduction of the reaction time from 7 h to 4 h, nitrone **3** was also isolated along with **4**. Under similar reaction condition (stirring for 7 h at room temperature), reaction mixtures containing nitroarenes produced nitrones **3** as the major products along with small amounts of 2-arylamino-3-formylchromones **4**. On stirring the reaction mixtures containing nitroarenes at 60 °C for 4 h, moderate to good yields of **4a–d** were obtained.

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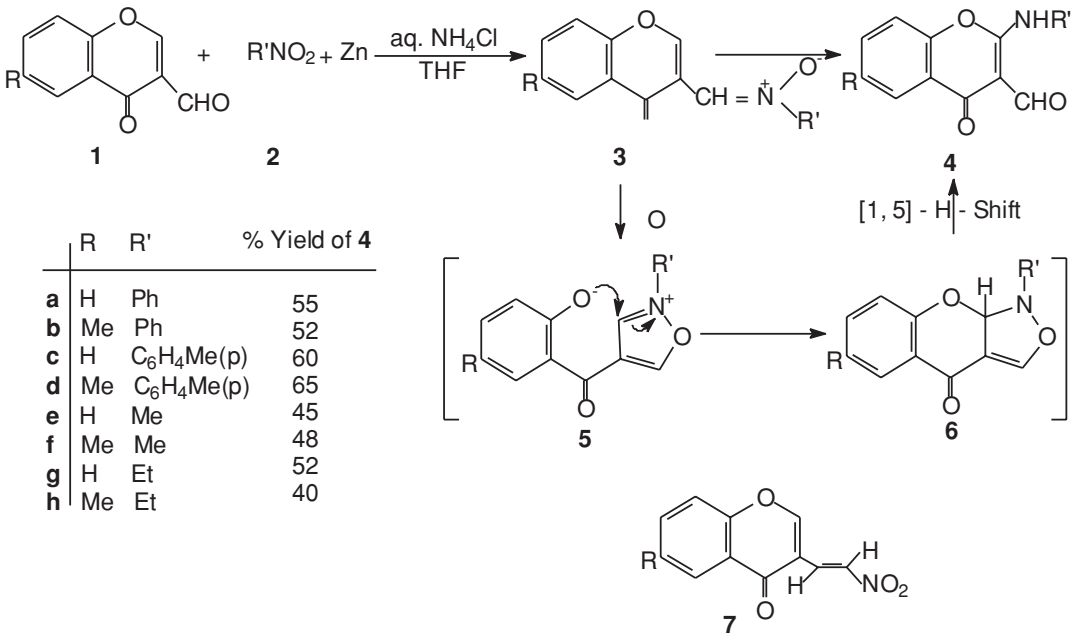
This one-pot reaction includes reduction of a nitro compound to the hydroxylamine derivative, condensation with 3-formylchromone to form nitrone **3** and rearrangement of **3** to **4**. This rearrangement step involves 1,5-electrocyclisation followed by the opening of the pyran ring to form **5**. Compound **4** is obtained by a [1, 5]-H shift from **6** (Scheme 1).[7] This one-pot reaction provides a direct synthesis of 2-alkyl/arylamino-3-formylchromones **4** from 3-formylchromones **1,** whereas, an earlier report[7c] describes the same synthesis in four steps.

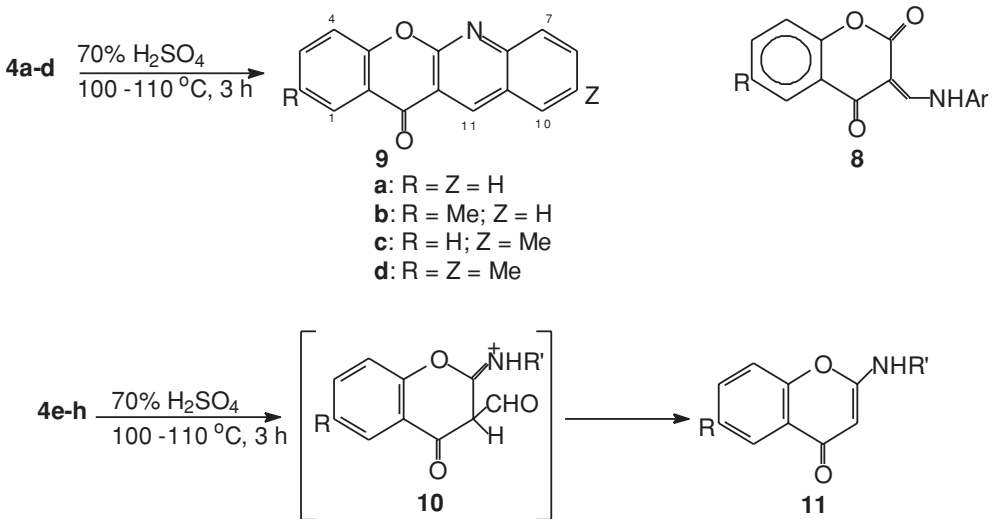
It should be mentioned that nitrones **3**(R' = Aryl), on heating under reflux in toluene for 6 h produce enaminoketone **8**[7a, 10] as the major product (70%) along with **4** (R' = Aryl) as minor product. Although enaminoketone **8** underwent a rearrangement to 4-arylamino-3-formylcoumarin when heated with $POCl_3$ at 60–70 °C,[10] isomeric compound **4**(R' = Aryl) does not undergo any change under these reaction conditions. Again on further heating at higher temperature compound **4** decomposes. In an endeavour to synthesise 4-hydroxy-3-formylcoumarin, a very good precursor for different types of heterocycles,[11] compound **4** was heated with 70% H_2SO_4 on an oil bath at 110-115 °C for 3 h. Surprisingly, 2-arylamino-3-formylchromone **4a–d** produced the same cyclised product 1-benzopyrano[2, 3-*b*]quinoline **9a–d** in high yields as was also reported by Ishar under slightly different conditions,[7] but 2-alkylamino-3-formylchromones **4e–h** produced white solids which were identified as 2-alkylaminochromones **11e–h**. Hence it is clear that depending on the presence of the 2-alkylamino or arylamino group, compound **4** behaves differently towards aqueous acid. This observation may be rationalised as follows. The presence of the aryl group facilitates the electrophilic ring closure with the formyl group at the C_3-position of the pyran ring to form **9**, whereas, the 2-alkylaminochromone moiety behaves as an enamine leading to the deformylated product **11**. The ^{1}H NMR spectrum of **11** deserves special mention. The peak around δ 10.2 corresponding to the aldehydic proton of **4e–h** has disappeared in **11e–h** and a new peak around δ 5.4 due to C_3–H has appeared. Again the peak around δ 10.5 corresponding to H-bonded N-H proton in **4e–h** appears as an up-field proton around δ 5.0 in **11e–h** due to the absence of a CHO group at the C_3 – position. Formation of **11e–h** from **4e–h** may be envisaged as involving the deformylation of **10**, which was obtained by the protonation of the enamine moiety of **4e–h** (Scheme 2).

In conclusion, we have reported a one-pot reduction, condensation and rearrangement reaction, which constitutes a direct method for the synthesis of 2-monosubstitutedamino-3-formylchromones **4** from 3-formylchromones **1**. The synthesis of 2-monosubstitutedaminochromones **11e–h** from 2-alkylamino-3-formylchromones **4e–h** has also been achieved.



	R	R'	% Yield of **4**
a	H	Ph	55
b	Me	Ph	52
c	H	$C_6H_4Me(p)$	60
d	Me	$C_6H_4Me(p)$	65
e	H	Me	45
f	Me	Me	48
g	H	Et	52
h	Me	Et	40

Scheme 1



Scheme 2

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Techniques used: 1H NMR, IR, chromatography, elemental analysis

References: 12

Scheme: 2

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