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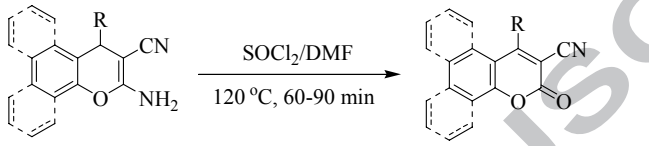

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ABSTRACT

A simple, mild and highly efficient protocol for the synthesis of fused 2-oxo-4-aryl-2*H*-chromene-3-carbonitriles has been developed starting from fused 2-amino-4-aryl-4*H*-chromene-3-carbonitriles utilizing Vilsmeier conditions.

Coumarins are important class of oxygen-containing heterocycles, which are mainly found in plants of the family *Rutaceae* and *Apiaceae*. Coumarins possess a variety of therapeutic and pharmacological properties.[1] Recently, polycyclic coumarins such as (+)-Calanolide-A, which has been isolated from *Calophyllum lanigerum* trees, were found to be highly effective against HIV.[2] Other coumarin derivatives such as Warfarin, Geiparvarin and Novobiocin (Fig 1) are prominent drugs with anticoagulant, antiproliferative and antibiotic activities, respectively. In addition, coumarins are widely used as additives in foods, perfumes, cosmetics, optical brighteners, and dispersed fluorescence and lasers dyes.[3]

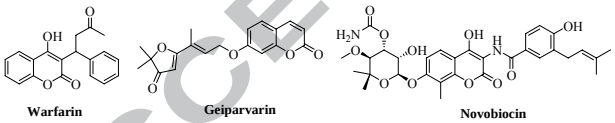


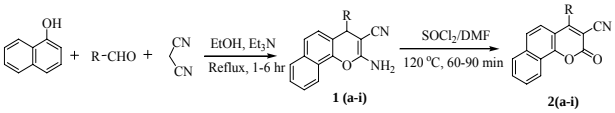
Figure 1. Biologically potent coumarin derivatives

Generally, coumarins can be synthesized utilizing the Pechmann reaction,[4] Knoevenagel condensation reactions,[5] Claisen rearrangement chemistry,[6] Perkin reaction,[7] and Wittig[8] and Reformatsky[9] reactions, as well as other catalytic cyclization reactions.[10] Among these, the Pechmann reaction is often the method of choice because it is simple and straight forward, and involves the condensation of phenols with β-ketoesters in the presence of a variety of acidic condensing agents.

Several methods have been reported for the synthesis of fused 2-oxo-2*H*-chromene-3-carbonitriles which utilize expensive and hazardous catalysts, and which afford only poor yields, even after prolonged reaction times.[11] Recently, Nermien and co-workers[12] reported the formation of substituted 2-oxo-4-aryl-2*H*-chromene-3-carbonitriles by the condensation of phenol with arylidene malononitrile as a by-product under basic conditions in 35% yield, although to-date, there are no direct reports on the efficient synthesis of fused 2-oxo-4-aryl-2*H*-chromene-3-carbonitriles under mild conditions. Thus, there is a need for the development of new and efficient methods for the preparation of such compounds in high yields and under mild reaction conditions.

In continuation of our research towards the synthesis of biologically potent molecules from the readily available substrates,[13] herein we report a new, facile and rapid conversion of fused 2-amino-4-aryl-4*H*-chromene-3-carbonitriles into their corresponding fused 2-oxo-4-aryl-2*H*-chromene-3-carbonitrile counterparts under Vilsmeier conditions.

2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitriles **(1a-i)** and 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitriles **(3a-d)** were synthesized *via* three-component condensation of α/β-naphthol, arylaldehydes and malononitrile in refluxing ethanol under basic conditions.[14] Compound **1a-i** and **3a-d** on reaction with thionyl chloride in dimethylformamide at 120 °C afforded the corresponding 2-oxo-4-aryl-2*H*-benzo[*h*]chromene-3-carbonitriles **(2a-i)** and the 3-oxo-1-aryl-3*H*-benzo[*f*]chromene-2-carbonitriles **(4a-d)** in good yields (Scheme 1 and 2, Table 1).



Scheme 1. Synthesis of 2-oxo-4-aryl-2*H*-benzo[*h*]chromene-3-carbonitriles

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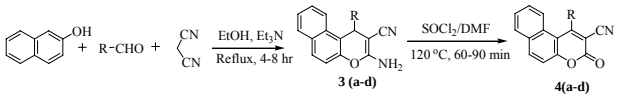


Scheme 2. Synthesis of 3-oxo-1-aryl-3*H*-benzo[*f*]chromene-2-carbonitriles

Table 1. Synthesis of fused 2-oxo-4-aryl-2*H*-chromene-3-carbonitriles.

Entry[a]	R	Product	Time (min)	Yield[b] (%)
1	C_6H_5	**2a**	60	94
2	2-ClC_6H_4	**2b**	75	92
3	4-ClC_6H_4	**2c**	60	96
4	4-$OCH_3C_6H_4$	**2d**	60	92
5	3,4-$(OCH_3)_2C_6H_3$	**2e**	60	93
6	4-$CH_3C_6H_4$	**2f**	75	90
7	4-OHC_6H_4	**2g**	90	88
8	3-$NO_2C_6H_4$	**2h**	90	90
9	4-OH-3-$OCH_3C_6H_3$	**2i**	60	90
10	C_6H_5	**4a**	75	88
11	4-OHC_6H_4	**4b**	75	88
12	3-$NO_2C_6H_4$	**4c**	90	86
13	4-OH-3-$OCH_3C_6H_3$	**4d**	75	90

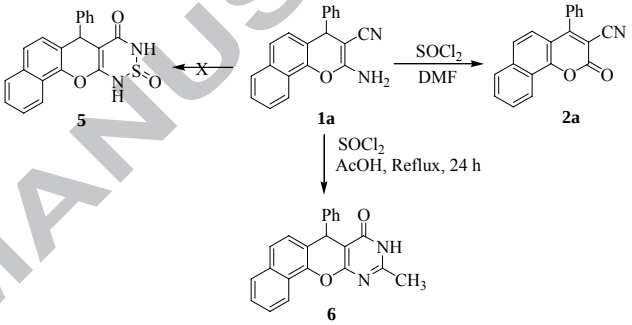
[a]**Reaction conditions:** Fused 2-amino-4-aryl-4*H*-chromene-3-carbonitrile (1 mmol), thionylchloride (3 mmol), DMF (5mL), 120 °C.
[b]Isolated yields.

Ghorab and co-workers[15] have reported the synthesis of sulfoxido derivatives by the reaction of 3-amino-6,7,8,9-tetrahydro-6-oxo-5-aryl-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxamides with thionyl chloride. The interesting feature of these molecules prompted us to investigate similar reaction conditions on fused 2-amino-4-aryl-4*H*-chromene-3-carbonitriles without conversion of the nitrile moiety into amide functionality. Thus, we carried out this reaction utilizing 1 mmole of 2-amino-4-phenyl-4*H*-benzo[*h*]chromene-3-carbonitrile **(1a)** and 5mL of neat thionyl chloride and observed several unidentified products. We subsequently carried out the same reaction (1:1 ratio of **1a** and $SOCl_2$) in a variety of different solvents such as ethanol, acetic acid, acetonitrile, benzene, water and dimethylformamide at the solvent reflux temperature. Unexpectedly, utilizing DMF we obtained the desired product **2a** in good yield (88%) after a short reaction time (1 h); we also observed that none of the remaining solvents produced even a trace amount of **2a**, even after 24 h at reflux. Interestingly, in acetic acid, we obtained a product in 32% yield, which we later confirmed to be the chromeno pyrimidinone **6 (Scheme 3)**.

From the above observations, we determined that the reaction proceeds through the formation of Vilsmeier's reagent. In order to determine optimal conditions, the above reaction was carried out at different temperatures and we were able to observe a maximal yield of 94% at 120 °C. Furthermore, in an effort to improve the yield, we increased the amount of thionyl chloride and observed no change in the product yield but saw a significant decrease in the reaction time. Thus, maximal yield at 120 °C for 60 min was observed with 3 mmol of thionylchloride. We also observed a decrease in yield when the reaction temperature was >120 °C and the amount of thionylchloride was >3 mmol, coupled with the formation of unidentified impurities. We also carried out the reaction with phosphorus oxychloride (3 mmol) in place of thionyl chloride, but this reaction required longer reaction times (3-4 h) for complete conversion.

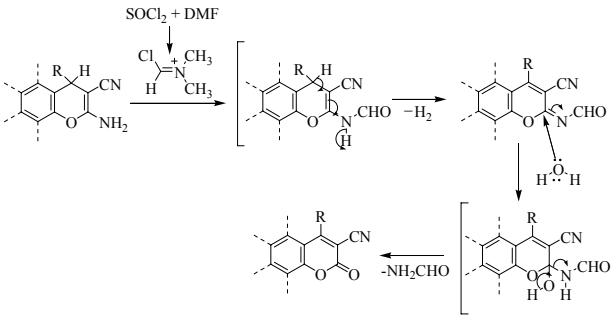
From the IR spectrum of the product, the disappearance of two absorption bands at 3323 and 3171 cm^{-1} for the NH_2 in the starting material, and at the same time, the appearance of a strong band at 1724 cm^{-1} for C=O of lactone moiety, and a medium band at 2228 cm^{-1} for the C≡N group was indicative of product formation. From the ^{1}H NMR spectrum, the absence of one singlet at 4.85 ppm (proton attached to 14th carbon) and 7.15 ppm (two amine protons) in the starting material, and the disappearance of signals at 40.4 ppm (14th carbon) and 56.3 ppm (13rd carbon) and the presence of signals at 164.1 ppm (14th carbon) and 157.1 ppm (12nd carbon) in the ^{13}C NMR spectra also confirm the formation of compound **2a**, and rule out the sulfoxido analog **5** as the product. In addition, the molecular ion peak from the mass spectral and the elemental analysis data are consist with the formation of product **2a.**

Utilizing these optimal conditions (i.e. 3 mmol of $SOCl_2$ in DMF at 120 °C), we have synthesized a variety of fused 2-oxo-4-aryl-2*H*-chromene-3-carbonitriles **(2a-i** and **4a-d**) in good yields and short reaction times (Table 1). The structures of all these newly synthesized compounds were confirmed by their spectral and analytical properties.



Scheme 3. Reaction of 2-amino-4-phenyl-4*H*-benzo[*h*]chromene-3-carbonitrile under different solvent conditions.

The proposed reaction pathway for the formation of fused 2-oxo-4-aryl-2*H*-chromene-3-carbonitriles is shown in Scheme 4. Initially, Vilsmeier formylation likely occurs on the free amine of the starting material, followed by hydration and subsequent elimination of formamide, to afford the final product in good yield.



Scheme 4. Proposed mechanism for the formation of fused 2-oxo-4-aryl-2*H*-chromene-3-carbonitriles

In conclusion, we have developed a simple, efficient and fast method for the synthesis of fused 2-oxo-4-aryl-2*H*-chromene-3-carbonitriles in good yield under Vilsmeier conditions. Further expansion of this reaction and biological applications of these molecules are currently in progress in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at.....

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16. General experimental procedure: Thionyl chloride (3 mmol) was added drop-wise to 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitrile/3-amino-1-aryl-1*H*- benzo[*f*]chromene-2-carbonitrile (1 mmol) dissolved in 5 mL of DMF. After complete addition the mixture turned yellow in colour, and was heated at 120 ^{o}C for an appropriate time, as shown in Table 1. After completion of the reaction (monitered by TLC), the mixture turned to a green color. The mixture was cooled to ambient temperature and poured into ice cold water. The solid that separated out was filtered, washed with water and purified over coloumn chromatography using 5% ethyl acetate/hexane as eluent to afford the pure product.

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