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Synthesis of new 4-aroyl-pyrano[*c*]chromenes via a one-pot, three-component reaction based on aryl glyoxals

Saeed Khodabakhshi [a,b], Bahador Karami [a,*], Khalil Eskandari [a], Mahnaz Farahi [a]

[a] *Department of Chemistry, Yasouj University, Yasouj 75918-74831, Iran*
[b] *Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica I, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid, Spain*

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ABSTRACT

A new library of pyrano[*c*]chromenes containing an aroyl group has been synthesized by a novel multicomponent process involving the reaction of various aryl glyoxals with 4-hydroxycoumarin and malononitrile. The reactions were catalyzed efficiently by ammonium dihydrogen phosphate to yield the desired products in good to excellent yields.

Demand for the rapid generation of small molecules, particularly heterocyclic compounds, has increased with the advent of high-throughput pharmaceutical screening.[1] Multicomponent reactions (MCRs) represent a very useful tool at the interface of the fields of organic synthesis and chemical biology due to their superior atom economy, convergent nature, and straightforward experimental procedures. In addition, they are valuable in the pharmaceutical industry for the construction of low molecular weight compounds.

Among a number of both biologically active and natural compounds, 2-amino-4*H*-chromenes are important structural motifs.[2] In particular, 4-aryl/alkyl-2-amino-4*H*-chromenes bearing a nitrile or ester group at the 3-position have attracted significant attention because of their pro-apoptotic activity against various tumors,[3–5] as a single agent or in combination with chemo-or radiotherapy. Pyranochromenes have received particular interest because they possess both a coumarin and pyran moiety. A commonly used method for the synthesis of pyranochromenes bearing a nitrile and an amine group is via the three-component reaction of hydroxycoumarins, malononitrile, and carbonyl compounds.[6–8] It should be noted that much attention has also been paid to modify this type of MCR.[9] The use of aryl glyoxals in the synthesis of heterocyclic compounds has been reviewed by Eftekhari-Sis.[10] Despite the fact that, in some cases, aryl glyoxals act similar to aromatic aldehydes, we found that there were no reports on the synthesis of pyrano[*c*]chromenes through a three-component reaction based on aryl glyoxals.

In continuation of our studies on the development of new pyrano-fused coumarins,[11–17] herein, the synthesis of pyrano[*c*]chromenes **4** via the one-pot, multicomponent reaction of 4-hydroxycoumarin (**1**), aryl glyoxals **2**, and malononitrile (**3**) is presented (Scheme 1).

It is noteworthy that the expected products **4** were obtained in excellent yield, and no biscoumarin **5** was observed.[18]

However, a number of our preliminary attempts to carry out this reaction did not furnish the desired product **4**. Initially, we used 4-hydroxycoumarin (**1**), phenyl glyoxal, and malononitrile (**3**) as the model reaction system to investigate systematically the reaction conditions.[19] Using Na_2CO_3 as the base and EtOH as the solvent under reflux, the desired product was not formed and TLC of the reaction mixture showed several spots.

The reaction was also conducted at room temperature in the presence of Na_2CO_3 in both EtOH and an equal mixture of EtOH/H_2O, but the reaction led to undesired and non-isolable products. By changing the catalyst to $NH_4H_2PO_4$ and heating at reflux in EtOH/H_2O (1:1), no observable difference was apparent. After further investigations, it was found that the reaction proceeded efficiently by controlling the temperature. The best conditions were established as room temperature for 30–40 min and then heating under reflux conditions to give the desired products **4** in good to excellent yields.

Using the optimized conditions, a variety of aryl glyoxals **2** were used for the synthesis of new 4-aroyl-pyrano[*c*]chromenes **4** (Table 1).

* Corresponding author. Tel.: +98 7412223048; fax: +98 7412242167.
E-mail address: karami@mail.yu.ac.ir (B. Karami).

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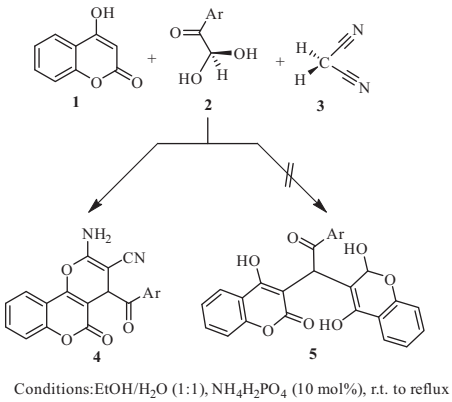


Scheme 1. Synthesis of pyrano[*c*]chromenes.

Aryl glyoxals possessing either electron-withdrawing or electron-donating groups were successfully employed in this reaction (Table 1).

Table 1
Synthesis of 4-aroyl-pyrano[*c*]chromenes using $NH_4H_2PO_4$ (10 mol %) in EtOH/H_2O (1:1)

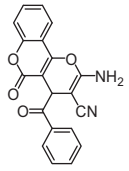
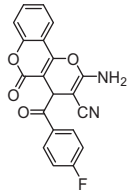
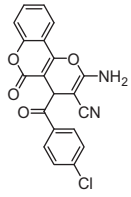
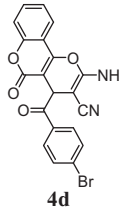
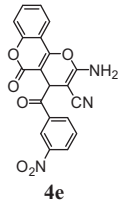
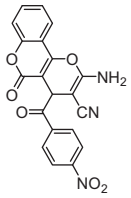
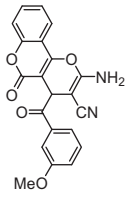
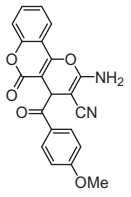
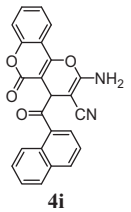
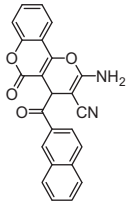
Entry	Ar	Product	Yield[a] (%)	Time (min)	Mp (°C)
1	C_6H_5	 **4a**	85	75	272–274
2	4-F-C_6H_4	 **4b**	80	85	253–255
3	4-Cl-C_6H_4	 **4c**	90	80	263–265
4	4-Br-C_6H_4	 **4d**	88	90	263–265
5	3-O_2N-C_6H_4	 **4e**	85	90	248–250

Table 1 (*continued*)

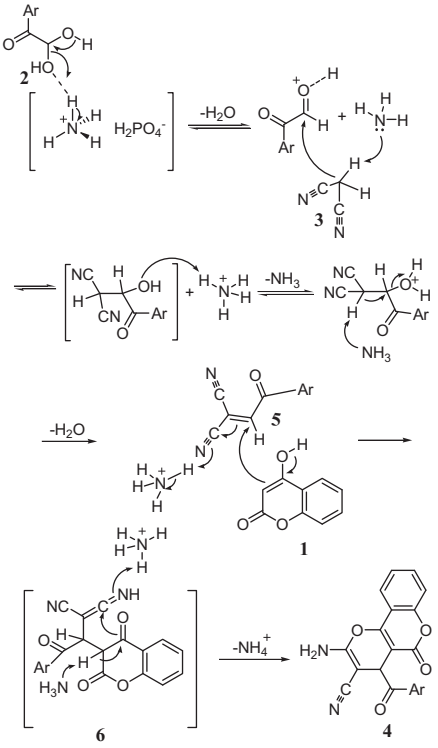
Entry	Ar	Product	Yield[a] (%)	Time (min)	Mp (°C)
6	4-O_2N-C_6H_4	 **4f**	90	75	273–275
7	3-MeO-C_6H_4	 **4g**	85	80	268–270
8	4-MeO-C_6H_4	 **4h**	90	75	266–268
9	1-Naphthyl	 **4i**	85	80	271–273
10	2-Naphthyl	 **4j**	93	70	278–280

[a] The isolated yield.

All the products were characterized from their elemental and spectral data including NMR and FT-IR spectroscopy. As a representative example, the ^1H NMR spectrum of compound **4g** showed signals for the aromatic protons at 7.91–7.31 ppm. The singlet at 7.69 ppm corresponded to the amine protons. Two sharp singlets at 5.40 ppm and 3.87 ppm were due to the methine and methyl protons, respectively. The ^{13}C NMR spectrum of compound **4g** also confirmed the suggested structure showing the expected 21 signals. The IR spectrum of compound **4g** contained a characteristic absorption band due to the conjugated cyano-group in the region of 2196 cm^{-1}.

Mechanistically, a reasonable pathway for the synthesis of pyrano[*c*]chromenes **4** is described in Scheme 2. The process involves a typical cascade reaction in which the aryl glyoxal **2** first condenses with malononitrile (**3**) to produce the corresponding aryloylidene malononitrile **5** catalyzed by $NH_4H_2PO_4$. Next, intermediate **5** is attacked via a Michael-type addition of **1** to give the intermediate **6**, followed by intramolecular heterocyclization to form the product **4**.

In conclusion, this Letter describes the first report on the one-pot, three-component, $NH_4H_2PO_4$-catalyzed synthesis of new pyrano[*c*]chromenes by employing 4-hydroxycoumarin, malononitrile,



Scheme 2. Suggested mechanism for the synthesis of 4-aroyl-pyrano[*c*]chromenes using $NH_4H_2PO_4$ as the catalyst.

and aryl glyoxals. The reactions were selective for pyrano[*c*]chromenes instead of biscoumarins. Additionally, high product yields, simple operation, and avoidance of toxic organic solvents are important advantages of this method. Due to the presence of functional groups such as primary amine, cyano, and ketone in the products, more synthetic studies and developments are possible. This method should allow the synthesis of other pyrano[*c*]chromenes for studies on their potential biological activities.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.072.

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19. *Typical procedure for the synthesis of pyrano[c]chromene* **4a**.
To a 25 mL round-bottomed flask, 4-hydroxycoumarin (**1**) (1.0 mmol), phenyl glyoxal (1 mmol), malononitrile (**3**) (1.2 mmol), EtOH/H_2O (1:1, 10 mL), and $NH_4H_2PO_4$ (0.1 mmol) were added. The mixture was stirred at room temperature for 30 min, then stirred vigorously under reflux conditions for 45 min. The progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature and the resulting precipitate filtered. The product **4a** was obtained after recrystallization from EtOH/THF (3:1).
2-Amino-4-(benzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (**4a**) IR (KBr): 3402, 3292, 2201, 1708, 1678, 1606, 1373, 1064 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ = 8.16 (s, 2H, J = 7.2 Hz), 7.90 (dd, 1H, J_1 = 8.2, J_2 = 1.6 Hz), 7.81–7.73 (m, 2H), 7.69 (s, 2H), 7.62 (t, 2H, J = 8.2 Hz), 7.57–7.53 (m, 2H), 5.42 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 198.12, 160.08, 159.55, 154.72, 152.11, 135.34, 134.13, 133.35, 129.13, 128.89, 125.03, 122.15, 118.54, 116.83, 112.58, 101.91, 51.91, 37.14; Anal. Calcd for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51; N, 8.14. Found: C, 69.55; H, 3.41; N, 8.09.