

# An Efficient and Simple Procedure for the Synthesis of 4-Substituted Coumarins by *von*-Pechmann Reaction using Mixture of $\text{FeCl}_3$ and Tetrabutylammoniumbromide as Catalyst

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**Abstract:** *Von-Pechmann reaction is modified by using a cheap, easily available and a very effective Lewis acid catalyst -  $\text{FeCl}_3$ . A series of 4-substituted coumarin derivatives have been prepared from a mixture of a phenol derivatives and ethyl acetoacetate using catalytic amount of  $\text{FeCl}_3$  in nitrobenzene in presence of phase transfer catalyst tetrabutylammoniumbromide.*

**Keywords:** von-Pechmann reaction, coumarin, phenol, ethyl acetoacetate and  $\text{FeCl}_3$  catalyst.

## 1. Introduction

Coumarins are an important class of organic compounds belonging to the oxygen heterocyclic that occur naturally in fruits, vegetables, nuts, seeds, flowers, and barks. They are an integral part of the human diet and have been reported to exhibit a wide range of biological activity profiles such as anthelmintic, anticoagulants, hypnotic properties.<sup>1a,b</sup> Coumarins are also used as food additives, in cosmetics,<sup>1b</sup> as optical brightening agents<sup>1c</sup> and dispersed fluorescent and in laser dyes.<sup>1d</sup> In addition, some coumarins are of interest because of their toxicity and carcinogenicity<sup>1e</sup> and photodynamic effects.<sup>1f</sup> For example, dicoumarol derivatives are used as rat poison, which are commonly known as Warfarin.<sup>1e</sup> Coumarins also act as intermediates for the synthesis of fluorocoumarins, chromones, coumarones and 2-acylsorcinols.<sup>1g</sup>

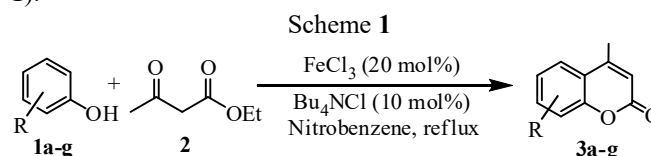
Thus, in the synthetic point of view, these compounds have been both extensively studied and widely used but still generate much interest.<sup>1a-b</sup> In the class of coumarins, derivatives of 4-methylcoumarins have enjoyed a special status as they form the core of industrially important coumarins like 7-hydroxy-4-methylcoumarin (coumarin 47 or coumarin 460)<sup>2</sup> and 7-diethylamino-4-methylcoumarin (umbelliferon-47).<sup>2</sup>

There are a number of methods available in the literature for the synthesis of these biologically active coumarin compounds. These include Perkin,<sup>3a</sup> Pechmann,<sup>3b</sup> Knoevenagel,<sup>3c</sup> Reformatsky<sup>3d</sup> and Wittig<sup>3e</sup> reactions. Among these, the Pechmann reaction has been the most widely used method since it proceeds from very simple starting materials and gives good yields of variously substituted coumarins. Classically, the process consists of the condensation of phenols with  $\beta$ -keto esters in the presence of a variety of catalysts and gives good yields of our desired 4-substituted coumarins.<sup>3f</sup> The commonly used catalysts reported in the literature are sulphuric acid,<sup>3b</sup> aluminium chloride,<sup>4</sup> trifluoroacetic acid,<sup>5</sup> phosphorous pentoxide<sup>6a-b</sup> and many

more.<sup>7a-d</sup> However, most of them require using excess acid or expensive acid catalyst; for example sulphuric acid in ten to twelve fold excess, phosphorous pentoxide in five to six fold excess and trifluoroacetic acid is needed to be added in three to four fold excess. Moreover, in some cases, mixtures of substituted phenols,  $\beta$ -ketoesters and the acidic catalyst were allowed to stand overnight or for a number of days (depending on their reactivity) or were heated above  $150^\circ\text{C}$ , and undesired side-products such as chromones, in addition to coumarins were isolated.<sup>7d</sup> As a result, the disposal of excess acid waste leads to environmental pollution. Consequently, there is a scope for further development of milder reaction conditions, increased variation of the substituents in both components and better yields.

## 2. Results and Discussion

In view of the current thrust in catalytic processes, we set out to develop an easy preparation of 4-substituted coumarins (**3a-g**) using an inexpensive and non-polluting catalyst. In this context, ferric chloride ( $\text{FeCl}_3$ ) is a good Lewis acid catalyst, easily available, inexpensive and easy to use. In this project for the first time, we developed a method for the preparation of 4-methylcoumarins (**3a-g**) using  $\text{FeCl}_3$  (20 mol %) as the catalyst in the *von*-Pechmann reaction of a mixture of a phenol (**1a-g**) and a  $\beta$ -keto ester (**2**) in nitrobenzene in presence of a phase transfer catalyst tetrabutylammoniumbromide ( $\text{Bu}_4\text{NCl}$ , 10 mol%) (Scheme 1).



A wide variety of the derivatives of phenol (**1a-g**) and ethyl acetoacetate (**2**) were subjected to the above conditions and the results obtained are tabulated in Table 1.

Since most of the modified procedure of the Von Pechmann reaction involved the use of inorganic acids or inorganic lewis acids as a catalyst, so, we have also attempted to modify the procedure by using organic acids. For this we used some cheap and commercially available organic acids such as oxalic acid and stearic acid in different conditions. However all of the procedures failed to produce the desired coumarin derivatives (Scheme 2).

Scheme 2

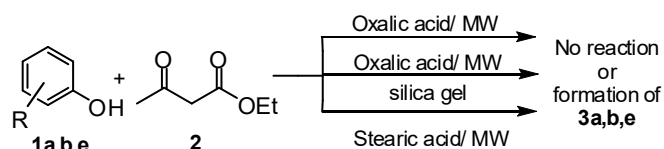


Table 1

Sl no	Starting material		Product (3) <sup>a</sup>	Yield(%) (isolated)
	Phenol (1)	$\beta$ -Ketoester (2)		
a				78%
b				76%
c				83%
d				80%
e				48%
f				59%
g				65%

<sup>a</sup>. All products were characterized by comparison of their melting point, IR and <sup>1</sup>H NMR spectra with those of authentic samples.<sup>8</sup>

### 3. Conclusion

In conclusion, we have developed an efficient and simple alternative for the preparation of substituted coumarins via the FeCl<sub>3</sub>-catalysed Pechmann reaction. Prominent among the advantages of this new method are operational simplicity, good yields, short reaction times and an easy work-up.

### 4. Experimental

All melting points were measured in sulphuric acid bath and were uncorrected. The IR spectra were recorded on an FTIR-8300 Shimadzu spectrometer. The NMR spectra were recorded in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> solution at 300 MHz for <sup>1</sup>H on a Bruker AC-300 spectrometer using tetramethylsilane as an internal standard unless mentioned otherwise. Ordinary

column chromatography was performed using silica gel (60–120 mesh). Petroleum ether used was of the boiling range 60–80°. Ether refers to diethyl ether. Solvents were purified and dried using reported procedure.

### Synthesis of Coumarins (3a-g):

In a typical procedure, the phenol derivatives (**1a-g**) (20 mmol) and ethyl acetoacetate (**2**) (30 mmol) were mixed thoroughly in nitrobenzene and ferric chloride (20 mol%) and tetrabutyl ammonium bromide (10 mol%) were added to the mixture with stirring at argon atmosphere. The reaction mixture was refluxed for 5 h and monitored by TLC. The reaction was worked up using saturated aqueous NH<sub>4</sub>Cl. The compound was extracted with ethyl acetate. The solvent was then concentrated under reduced pressure and the residue thus obtained was precipitated using pet. ether and recrystallized with suitable solvent. The compound was then filtered and dried to furnish the corresponding coumarin (**3a-g**). Selected spectroscopic data of **3a**, **3c**, **3e**, **3f** along with the melting points are given below:

**Compound 3a** (4-methyl-7-hydroxy-2H-chromen-2-one): Mp 184–185°C (lit.<sup>8</sup> mp 184–186°C); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.65 (s, 3H, Me), 6.41 (s, 1H, C=CH), 6.91–7.72 (m, 3H, ArH), OH not observed; IR (KBr)  $\nu_{\max}$ : 3260–3080, 1690 cm<sup>-1</sup>.

**Compound 3c** (4,7-dimethyl-2H-chromen-2-one): Mp 129–131 °C (lit.<sup>8</sup> mp 131–132°C); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.62 (s, 3H, Me), 2.80 (s, 3H, Me), 6.41 (s, 1H, C=CH), 7.10–7.60 (m, 3H, ArH), IR (KBr)  $\nu_{\max}$ : 1685 cm<sup>-1</sup>.

**Compound 3e** (4-methyl-2H-chromen-2-one): Mp 83–84°C (lit.<sup>8</sup> mp 83–84°C); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.62 (s, 3H, Me), 6.48 (s, 1H, C=CH), 7.30–7.65 (m, 4H, ArH), IR (KBr)  $\nu_{\max}$ : 1665, 1610, 1450, 1400 cm<sup>-1</sup>.

**Compound 3f** : Mp 150–152°C (lit.<sup>8</sup> mp 155–157°C); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.71 (s, 3H, Me), 6.51 (s, 1H, C=CH), 7.50–8.91 (m, 6H, ArH), IR (KBr)  $\nu_{\max}$ : 1675 cm<sup>-1</sup>.

### 5. Acknowledgements

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**Dr. Asitanga Ghosh** received the B.Sc. and M.Sc. degrees in Chemistry from Calcutta University, Calcutta, India in 1998 and 2000 respectively. He completed his Doctoral degree under the supervision of Prof. S. Lahiri of Indian Association for the Cultivation of Science (IACS), Jadavpur, India on 2011. He joined at the Department of Chemistry, Jalpaiguri Govt. Engg. College, Jalpaiguri, WB as Assistant Professor on 2007. He is now at the Department of Chemistry, Hooghly Mohsin College, Chinsurah, Hooghly, WB since 2013, holding the same post. His research interest is mainly focused on synthetic organic chemistry and organic photochemistry.