



# The indium(III) chloride-catalyzed von Pechmann reaction: a simple and effective procedure for the synthesis of 4-substituted coumarins

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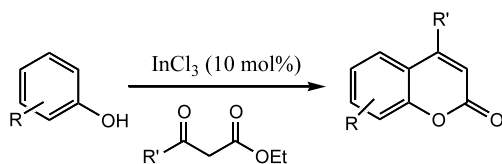
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**Abstract**—Indium(III) chloride is used as an efficient catalyst in the von Pechmann condensation of phenols with  $\beta$ -ketoesters leading to the formation of coumarin derivatives in excellent yields with good purity. © 2002 Published by Elsevier Science Ltd.

The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, cosmetics, pharmaceuticals<sup>1</sup> and in the preparation of insecticides, optical brighteners<sup>2</sup> and dispersed fluorescent and laser dyes.<sup>3</sup> Thus, the synthesis of this heterocyclic nucleus is of much current interest. Coumarins have been synthesized by several routes including von Pechman,<sup>4a</sup> Perkin,<sup>4b</sup> Knoevenagel,<sup>4c,d</sup> Reformatsky<sup>4e</sup> and Wittig reactions.<sup>5</sup> In the course of our recent work on the design and synthesis of new analogues of coumarins with potent pharmacological value, we planned to prepare 7-amino-4-trifluorocoumarins, which can be employed as intermediates in the synthesis of useful bioactive compounds.<sup>6</sup>

The von Pechmann reaction is a venerable reaction and it is one of the most simple and straightforward methods used to produce coumarins. Classically, the process



## Scheme 1.

**Keywords:** coumarins; von Pechmann reaction;  $\beta$ -ketoesters; cosmetics; phenols; indium(III) chloride.

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consists of the condensation of phenols with  $\beta$ -ketoesters in the presence of a variety of reagents and gives good yields of 4-substituted coumarins.<sup>7</sup> Several acid catalysts have been used in the von Pechmann reaction including sulfuric acid,<sup>4a</sup> aluminium chloride,<sup>8</sup> phosphorus pentoxide,<sup>9</sup> trifluoroacetic acid<sup>10</sup> and many more.<sup>11</sup> However, these catalysts have to be used in excess; for example, sulfuric acid in ten to twelve equivalents,<sup>4a</sup> trifluoroacetic acid in three to four equivalents<sup>10</sup> and phosphorous pentoxide is required in a five-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°C, and undesired side-products such as chromones, in addition to coumarins were isolated. As a result, the disposal of excess acid waste leads to environmental pollution. Consequently, there is scope for further development of milder reaction conditions, increased variation of the substituents in both components and better yields.

In view of the current thrust in catalytic processes, there is merit in developing a truly catalytic method for the formation of 4-substituted coumarins. Recently, InCl<sub>3</sub> has emerged as a powerful Lewis acid catalyst imparting high chemo- and regioselectivity in various chemical transformations<sup>12</sup> such as the aldol, Diels–Alder, and Friedel–Crafts reactions because of its unique reactivity in both organic solvents and aqueous media and its stability. The versatility of indium(III) chloride encouraged us to carry out the von Pechmann reaction under benign reaction conditions. In this communication, we report herein for the first time, the catalytic activity of InCl<sub>3</sub> for the synthesis of coumarins

(Scheme 1). In a typical general experimental procedure, which involves the condensation of phenol with  $\beta$ -ketoesters (e.g. ethyl acetoacetate, ethyl 4,4,4-trifluoroacetoacetate, ethyl 4-chloroacetoacetate). The reactants were heated together in the presence of a catalytic amount of indium(III) chloride (10 mol%) at 65°C for a short period of time as required to complete the reaction (TLC).<sup>13</sup> The reaction mixture was then poured into crushed ice and the solid product which separated was filtered and recrystallized. In order to study substituent effects on the reactivity of the phenol, the reactions were performed on a wide range of structurally diverse phenols and  $\beta$ -ketoesters. The reaction proceeds and the results are summarized in Table 1.

The use of just 10 mol% of  $\text{InCl}_3$  is sufficient to push the reaction forward. Higher amounts of  $\text{InCl}_3$  did not improve the result to any extent. The yields are, in general, very high regardless of the structural variations in  $\beta$ -ketoesters or phenol. The crude products obtained are of high purity (>95% by  $^1\text{H NMR}$ ). Another important aspect of this procedure is survival of a variety of functional groups such as Cl, OH,  $\text{OCH}_3$  under the reaction conditions.

For most of the substrates, the reaction time is reduced drastically even at ambient conditions in contrast to reported methods,<sup>6,7</sup> with an excellent yield of the coumarins. Substrates (entries 1–4) having electron-donat-

**Table 1.** Synthesis of coumarins via von Pechmann condensation of phenols with  $\beta$ -ketoesters induced by  $\text{In(III)Cl}_3$

Entry	Substrate <b>1</b>	Time (min.)	Temperature ( $^\circ\text{C}$ )	Product <b>2</b> <sup>a</sup>	Yield (%) <sup>b</sup>
1.		30	65	 a: R = CH <sub>3</sub> b: R = CF <sub>3</sub> c: R = CH <sub>2</sub> Cl	98
		30	65		96
		30	65		93
2.		30	65		95
3.		30	65		90
4.		30	65		92
5.		240	130		65
6.		30	65		85, 10
7.		90	95		88
8.		120	65		55

<sup>a</sup> All products were characterized by comparison of their mp, IR and  $^1\text{H NMR}$  spectra with those of authentic samples.<sup>14</sup>

<sup>b</sup> Isolated yields.

ing groups in the *para* position to the site of electrophilic substitution gave maximum yields under mild reaction conditions in a short period of time. Phenol (entry 5) required a higher reaction temperature and longer reaction duration, as no electron-donating group is present. *m*-Methoxyphenol (entry 2) showed no detectable demethylation under the reaction conditions. Similarly, 1-naphthol (entry 7) requires a slightly higher temperature and longer reaction time. When the condensation of *m*-aminophenol (entry 6) with ethyl 4,4,4-trifluoroacetoacetate is carried out, the major product is the coumarin **2h** and 10% yield of quinoline **2i** was obtained.<sup>14</sup> A literature survey revealed that, resacetophenone (entry 8) failed to react to give a coumarin derivative in the presence of sulfuric acid as the catalyst.<sup>6</sup> However, the reaction was observed under aluminium chloride catalysts,<sup>8</sup> but required a temperature of 130°C in nitrobenzene as the solvent. In contrast, the indium(III) chloride furnished moderate yields of the product at 65°C.

In conclusion, the present procedure of the synthesis of coumarins by the indium(III) chloride catalyzed condensation of phenol and  $\beta$ -ketoesters provides an efficient and much improved modification of the von Pechmann reaction. In addition to its simplicity and mild reaction conditions, this method has the ability to tolerate a wide variety of substitutions in both components. Thus, this method will offer easy access to substituted coumarins with varied substitution patterns in high yields. We believe, our procedure will find important applications in the synthesis of coumarins.

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- Typical experimental procedure*: A mixture of resorcinol (1.1 g, 10 mmol) and ethyl acetoacetate (1.3 g, 10 mmol) was heated under reflux (65°C) in the presence of indium(III) chloride (222 mg, 10 mol%) for 1 h (TLC) under nitrogen. The reaction mixture, after being cooled to room temperature was poured onto crushed ice (40 g) and stirred for 5–10 min. The crystalline products were collected by filtration under suction (water aspirator), washed with ice-cold water (40 ml) and then recrystallized from hot ethanol to afford pure 7-hydroxy-4-methylcoumarin **2a** as colorless prisms (1.73 g, 98%), mp 185–187°C (lit.<sup>6</sup> mp 186–187°C).  
This procedure was followed for the preparation of all the 4-substituted coumarins listed in Table 1. All the compounds were identified by comparison of analytical data (IR, <sup>1</sup>H NMR, and mass spectra) and mp with those reported.