

Iodine a Simple, Effective and Inexpensive Catalyst for the Synthesis of Substituted Coumarins

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Abstract Molecular iodine is developed as an efficient catalyst in the von Pechmann condensation of phenols with β -ketoesters which leads to the formation of coumarin derivatives in excellent yields when carried out under microwave irradiation in a Prolabo Synthwave Microwave Reactor. The reaction also proceeds when carried out in the absence of solvent and at room temperature in acetonitrile.

Keywords Coumarins · von Pechmann condensation · Iodine · Microwave irradiations

1 Introduction

Coumarins are of interest because they constitute an important class of compounds, occupying a special place in nature and they form sub-units of many natural products [1a]. They exhibit a broad spectrum of biological activity profiles such as anthelmintic, anticoagulants, hypnotic and insecticidal properties [1]. Because of this significant position of these molecules search for efficient synthesis of this oxygen heterocycle is of considerable interest. The usual methods of preparation of these molecules are Pechmann condensation [2], Knoevenagel condensation [3], Wittig reaction [4], Perkin [5], Reformatsky [6], and by flash vacuum pyrolysis [7]. Recently, a Pd(II)-catalyzed inter- and intramolecular hydroarylation of alkynes by simple arenes at room temperature in a mixed solvent containing trifluoroacetic acid has been reported [8]. Among all these von Pechmann reaction seems to be quite

simple and straight forward which employs the condensation of acetoacetic ester with substituted phenols in the presence of a variety of reagents. In the past, several acid catalysts have been used in the von Pechmann reaction including strong acids like sulfuric acid [2], trifluoroacetic acid [7], phosphorous pentachloride [9], aluminium trichloride [10], zinc iodide [11], and many others of the same type including expensive metal halides of indium [12] and palladium [13] and recently $\text{Bi}_2(\text{NO}_3)_3$ [14]. Moreover, these catalysts have to be used in excess, for example, sulfuric acid in ten to twelve equivalents [2], trifluoroacetic acid in three to four equivalents [7] and phosphorus pentoxide is required in a five-fold excess. All the catalyst used so far are very harsh, hazardous and they are not very efficient in terms of time, yield and formation of other side products [15]. In some cases time needed is several days, yields are very poor even when catalyst is used in excess. These shortcomings certainly demand search for a safer, more convenient and efficient method. In view of current thrust in catalytic processes, there is merit in developing a truly catalytic process for the formation of substituted coumarins.

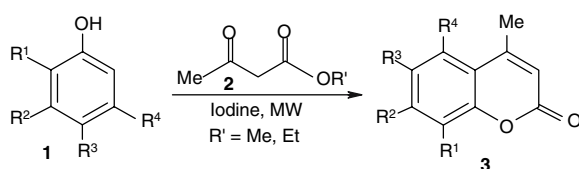
In recent years, iodine has been used as a mild Lewis acid catalyst for various organic transformations [16] because of its unique reactivity in both organic and aqueous media and its stability. It is an electrophilic reagent that adds to alkenes [17] and alkynes [18] to give diiodides; alkenyl carboxylic acids react to give iodolactones [19] and alkenylamides lead to iodolactams [20]; dehydrogenates amines [21] and reacts with ketones in the presence of base, to give α -iodo ketones [22]; carboxylic acids are converted to α -iodo acid derivatives [23] and carbanions react to give the substituted iodides [24], organoboranes can give alkyl iodides [25] and vinyl boranes lead to substituted alkenes [26], and important spotting reagent for

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TLC analysis [27]. The versatility of this reagent encouraged us to study its utility to overcome the drawbacks of the von Pechmann condensation. In continuation to our studies on carbon–carbon bond formation reactions [28] we report herein an efficient and convenient procedure for the synthesis of various coumarin derivatives under microwave irradiations (using Prolabo Synthwave Microwave Reactor 402) in the presence of catalytic amount of iodine (Scheme 1). These reactions also proceed effectively in absence of solvent in excellent yields without the formation of any side products. In a very recent report [29] Chavan et al. have performed the von Pechmann reaction in the presence of zinc (2 equiv) and iodine (0.5 equiv) in refluxing toluene and isolated the coumarin derivatives in 25–78% yields in 5 h time. In contrast we have performed the same reaction using 1 mol% of iodine under microwave irradiations and got the corresponding coumarin derivatives in excellent yields within minutes time.

Initially a systematic study was carried out for catalytic evaluation of iodine in the von Pechmann condensation. A model reaction of resorcinol and ethyl acetoacetate was carried out in the presence of 1 mol% of molecular iodine under microwave irradiations. It was found that the reaction could go smoothly and the corresponding coumarin derivative **3a** was obtained in 95% yield when the mixture was irradiated at 110 °C in a Prolabo Synthwave Microwave Reactor 402 for 1.5 min. Rate enhancement of the reaction was observed when 5 or 10 mol% of iodine was used but relatively lower yield (80 or 75%) was obtained due to decomposition of the starting material. Moreover, use of lesser amount 0.5 mol% of iodine led to weaker results (50–60%) in longer reaction time. In view of the current interest in environmentally benign catalytic processes, a protocol involving a lower amount of iodine would be more appreciable, so we decided to extend the scope of the reaction using only 1 mol% of the catalyst. The reaction is found to be also effective when carried out

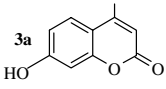
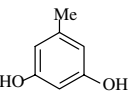
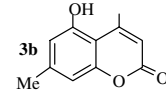
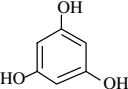
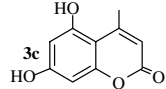
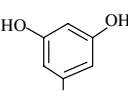
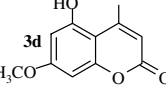
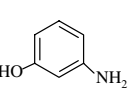
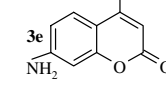
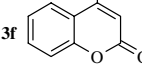
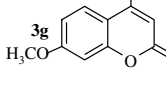
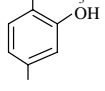
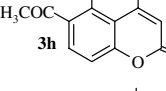
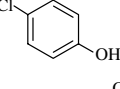
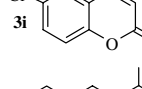
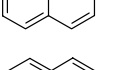
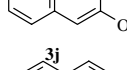
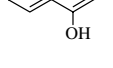
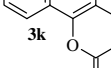
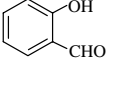
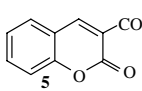
without using any solvent at 80 °C, and the corresponding coumarin derivatives were obtained in almost comparable yields (Table 1). The use of this solvent free approach is better, because when the reaction is carried out in solvent like acetonitrile at room temperature, it took longer reaction time (4–7) h and in comparatively lesser yields. Further increase in the reaction time gave no significant improvement. It is also to be noted that in the present procedure there was no evidence for the formation of any side products. All the compounds obtained were characterized by spectroscopic analysis (IR, ^1H NMR, MS) and finally by comparison with authentic samples [30]. A wide range of structurally varied phenols reacted smoothly to give the corresponding coumarins in good yields. Phenols having electron donating group at *meta* position gave generally high yield in shorter time period as shown in Table 1. This is due to the fact that electron donating group enhance the electron density at *para* position to it which in turn become more susceptible for electrophilic attack. Phenol (entry 6) gave lesser yields and need higher temperature as well as longer time as no electron donating group is present. The present method tolerates a variety of functional groups such as ether, hydroxyl, amino, acetyl, halo etc. For most of the substrates, the reaction time is reduced dramatically under microwave irradiations, in contrast to earlier methods [31]. From literature, it revealed that resacetophenone failed to give a coumarin derivative in the presence of sulfuric acid as the catalyst [31a]. However, the reaction proceeded under aluminum chloride catalysts [10], but required a temperature of 130 °C in nitrobenzene. In contrast, molecular iodine furnished high yields of the products under microwave irradiations. The use of methyl acetoacetate in lieu of ethyl acetoacetate gave similar results but acetoacetic acid does not perform well. The use of scandium triflate also gave satisfactory results but does not seem to be attractive as it is relatively very expensive. Interestingly, the Knoevenagel condensation of *o*-hydroxybenzaldehyde with ethyl acetoacetate was also found to proceed effectively in the presence of iodine under microwave irradiations in the molten state and the corresponding coumarin derivative was obtained in 80% yield (Scheme 2). In an earlier report we employed LiBr efficiently in the Knoevenagel condensation of salicylaldehyde with active methylene compounds for the synthesis of coumarin derivatives [32]. However, the von Pechmann condensation using LiBr under microwave irradiation without using any solvent did not proceed as efficiently as it proceeds with molecular iodine, and the corresponding coumarin derivatives were obtained in 30–50% yields. Recently, montmorillonite KSF was employed in the Knoevenagel condensation of salicylaldehyde with diethyl malonate in the absence of solvent at 160 °C to give the corresponding coumarin in 44% yield [33].



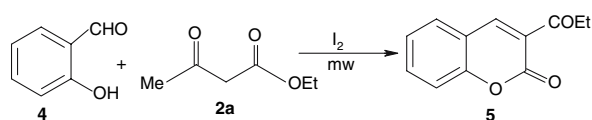
- a: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{OH}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{H}$.
 b: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{OH}$.
 c: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{OH}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{OH}$.
 d: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{CH}_3\text{O}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{OH}$.
 e: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{NH}_2$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{H}$.
 f: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{H}$.
 g: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{CH}_3\text{O}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{H}$.
 h: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{CH}_3\text{CO}$; $\text{R}^4 = \text{OH}$.
 i: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{Cl}$; $\text{R}^4 = \text{H}$.

Scheme 1

Table 1 Synthesis of coumarins derivatives via von Pechmann condensation of phenols **1** and ketoester **2**

Entry	Phenols 1	Coumarins	MW	Yield ^a (%)	Thermal heating		Room temperature		Mp (°C)
					Reaction ^b time, (h)	Yield (%)	Reaction ^c time, (h)	Yield (%)	
1			1.5	95	1.0	90	4.0	75	183–84 ^{30c}
2			2.5	96	1.5	91	5.0	70	244–46 ^{31a}
3			2.0	93	1.0	88	3.5	73	284–86 ^{30c}
4			3.0	90	1.8	80	5.5	68	118–20 ^{35a}
5			4.5	80	2.0	70	7.0	0	221–24 ^{30b}
6			5.0	80	3.0	76	7.0	60	83–84 ^{35b}
7			4.0	85	2.0	80	5.0	75	170–71 ^{35b}
8			5.0	80	3.0	75	8.0	70	164–65 ^{31a}
9			4.5	90	3.0	80	7.5	75	184–85 ^{35b}
10			5.0	90	2.1	83	8.0	75	183–84 ^{35c}
11			5.0	88	2.2	80	8.0	70	154–55 ^{30a}
12			5.0	88	3.0	80	–	–	95–96 ^{35d}

^a Refers to pure isolated^b The reaction was carried out at 80 °C^c The reaction was performed in acetonitrile



Scheme 2

The main feature of the present method [34] is that it provides an efficient, economical and environment-friendly route, with the use of safer catalyst under microwave irradiation and thermal condition. Thus, several pharmacologically relevant coumarin derivatives viz dicoumarol, warfarin, phenpro coumarin etc could be introduced with efficiency following the environmentally benign procedure.

2 Experimental

Mps were determined by using a Buchi melting point apparatus and are uncorrected. IR spectra were recorded for KBr discs on Perkin-Elmer 240 °C analyzer. ¹H NMR spectra were recorded on 90 MHz spectrometers and chemical shift values are recorded in δ units (ppm) relative to Me₄Si as internal standard. Mass spectra were recorded on an AEIMS-30 spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyzer. All solvents were distilled before use. The materials were obtained from commercial suppliers and were used without further purification.

General procedure for the synthesis of coumarin derivatives under microwave irradiations:

A mixture of resorcinol (1.1 g, 10 mmol), ethyl acetoacetate (1.3 g, 10 mmol) and iodine (0.025 g) was placed in a quartz reaction vessel of Prolabo Synthwave Microwave Reactor 402 and allowed to react under microwave irradiations at a temperature of 110 °C for 1.5 min. During the reaction the temperature was not allowed to rise above 110 °C (by setting the programmer). After completion (monitored by TLC), the reaction mixture was cooled to room temperature and added 6% cold sodium thiosulphate solution and stirred for 10–15 min. The precipitated products were then separated, washed with ice-cold water and recrystallized from hot ethanol to afford 7-hydroxy-4-methyl coumarin **3a** in 95% yield, mp 184–185 °C (lit [30c] mp. 186–187 °C). Similarly other phenols and β -ketoesters were reacted in the presence of molecular iodine under microwave irradiations and the reaction times and yields are recorded in Table 1.

General procedure for the synthesis of coumarin derivatives under thermolytic conditions:

A mixture of resorcinol (1.1 g, 10 mmol), ethyl acetoacetate (1.3 g, 10 mmol) and iodine (0.025 g) was taken in a R. B. flask (50 mL) and dipped in pre-heated oil bath

at 85 °C (bath temperature) for 1 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and added 6% cold sodium thiosulphate solution and stirred for 10–15 min. The precipitated products were then separated, washed with ice-cold water and recrystallized from hot ethanol to afford 7-hydroxy-4-methyl coumarin **3a** in 90% yield, mp 184–185 °C. Similarly other substituted phenols and β -ketoester were reacted together in the presence of 1 mol% of molecular iodine to produce the corresponding coumarin derivatives in high yields. The results are summarized in the Table 1.

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