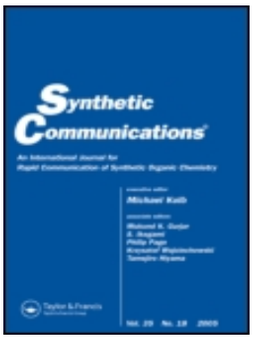

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EXPEDITIOUS PECHMANN CONDENSATION BY USING BIODEGRADABLE CELLULOSE SULFURIC ACID AS A SOLID ACID CATALYST

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A facile synthesis of coumarins was performed in excellent yields via Pechmann condensation by using different type of phenols and ethylacetoacetates under solvent–free media using both conventional method and microwave irradiation in short reaction times is described. The reaction workup is very simple, and the catalyst can be easily separated from the reaction mixture and reused several times in subsequent reactions.

Keywords: Cellulose sulfuric acid; coumarins; Pechmann condensation; solvent-free conditions

INTRODUCTION

In recent years, there has been extensive effort to synthesize coumarins and their derivatives. The coumarin molecule has had a wide variety of applications in organic and medicinal chemistry for many years as a large number of natural products contain this heterocyclic nucleus and they are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals,[1] and in the preparations of insecticides, optical brightening agents, and dispersed fluorescent and laser dyes.[2] They have various bioactivities, such as inhibition of platelet aggregation,[3] antibacterial[4] and anticancer activities[5] inhibition of steroid 5α-reductase,[6] and inhibition of HIV-1 protease.[7] Coumarins can be synthesized by various methods such as Pechmann,[8] Perkin,[9] Knoevenagel,[10] and Witting,[11] reactions. However, because of its simplicity and relatively inexpensive starting materials, the Pechmann reaction was widely used for the synthesis of coumarins and its derivatives. This method involves the reaction between phenol with β-keto ester in the presence of acidic catalysts such as polyphosphoric acid (PPA),[12] $InCl_3$,[13] $ZrCl_4$,[14] $Yb(OTf)_3$,[15–18] *p*-TsOH,[19] $BiCl_3$,[20] I_2 or AgOTf,[21] and $Sm(NO_3)_3$,[22] as well as chloroaluminate

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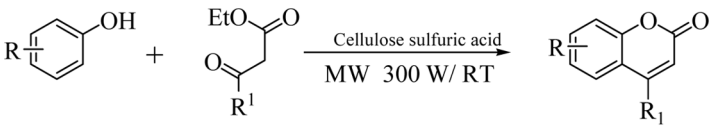
ionic liquids.[23,24] The main disadvantages of the processes using these catalysts are longer reaction time, large amount of the catalyst, and tedious purification process after completion of the reaction. Some of the catalysts are highly expensive; some of the existing methods destroy the catalysts in the workup procedure and they cannot be recovered or reused. These shortcomings surely indicate demand for a safe, ecofriendly, and efficient method. Hence, it is essential to develop biodegradable, ecofriendly, green synthesis of coumarins.

Cellulose is one of the most abundant natural biopolymers and has been studied during the past several decades because it is a biodegradable material and a renewable resource. Its unique properties make it an attractive alternative to conventional organic or inorganic supports in catalytic applications. Recently, the approach has been shifting more toward ecofriendly and reusable catalysts. Recently, cellulose sulfuric acid has emerged as a solid acid-catalyst for acid catalyzed reactions, such as synthesis of α-aminonitriles,[25] imidazoazines,[26] quinolines,[27] aryl-14H-dibenzo[*a.j*]xanthenes,[28] and 3,4-dihydropyrimidine-2(1H)-ones.[29] Cellulose sulfuric acid can be easily prepared by the reaction of inexpensive cellulose with chlorosulfonic acid.

RESULTS AND DISCUSSION

It is an established fact in the literature that the Pechmann reaction proceeds through *trans* esterification and intramolecular hydroxyalkylation, followed by dehydration. These three steps are all typical acid-catalyzed reactions. Therefore, the outcome of the Pechmann reaction depends on an acid catalyst. We now report a new and efficient method for the synthesis of coumarin. Recently, cellulose sulfuric acid has emerged as attractive alternative catalyst in terms of acidic strength and environmentally benign character for various reactions. Presently, thermally driven organic transformations take place by one of two ways: conventional heating and microwave (MW) irradiation. Comparatively, MW irradiation is more advantageous than the conventional method because in the conventional heating method reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel to reach the solvent and reactants. This is a slow and inefficient method for transferring energy into the reacting system. In the MW irradiation method, MWs couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in temperature. Because the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole reaction or ionic conduction—the two fundamental mechanisms for transferring energy from microwaves to the substance(s) being heated. When the reaction was carried out in MW irradiation (method A), phenol and β-ketoester were irradiated in the presence of cellulose sulfuric acid (catalytic amount) without using any solvent at 300-W power levels affords the corresponding coumarin in 1–3 min. In the conventional method (method B), phenol and β-ketoester were stirred at r.t. in the presence of cellulose sulfuric acid (catalytic amount) under solvent-free conditions, which afforded the corresponding coumarin in 15–35 min (Scheme 1).

To illustrate the need of the cellulose sulfuric acid for these reactions, an experiment was conducted in the absence of cellulose sulfuric acid. The yields



1 2 3

Scheme 1. Synthesis of coumarins by using cellulose sulfuric acid as a solid acid catalyst.

Table 1. Effect of catalysts on yield

Entry	Catalyst	Yield[a] (%)
1	Cellulose sulfuric acid	97
2	Silica sulfuric acid	92
3	*p*-Toluene sulfonic acid	85
4	Sulfuric acid in acetic acid	55
5	No catalyst	15

[a]Yields refer to the pure isolated recovered catalyst.

obtained are very poor, side products are formed, and reactants are not involved completely in this reaction. Obviously, cellulose sulfuric acid is an important component of the reaction.

The efficiency of the cellulose sulfuric acid compared to various sulfur-analog acidic catalysts was also examined (Table 1). In this study, it was found that cellulose sulfuric acid is a more efficient and superior catalyst over other acidic catalysts with respect to reaction time and yield. It was also observed that the yield was only 15% in the absence of the cellulose sulfuric acid catalyst.

EXPERIMENTAL

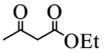
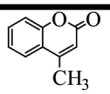
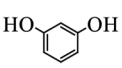
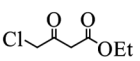
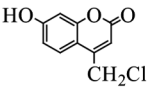
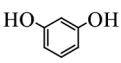
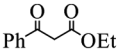
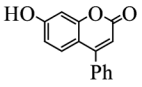
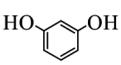
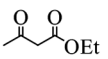
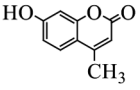
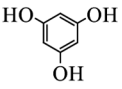
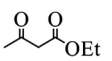
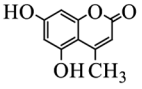
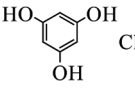
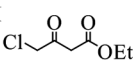
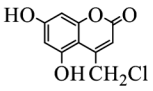
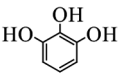
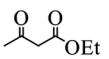
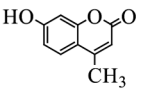
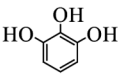
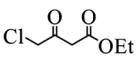
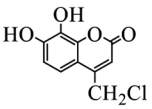
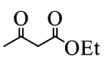
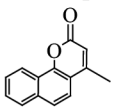
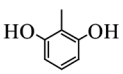
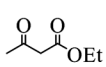
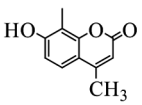
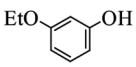
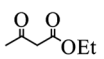
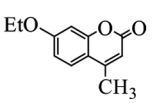
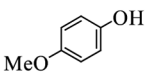
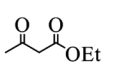
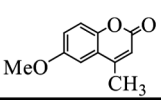
General Procedure: Method A (Microwave Irradiation)

A mixture of the phenol **1** (1 mmol), β-ketoester **2** (1 mmol), and cellulose sulfuric acid (0.1 g) was inserted in a microwave oven (BPL, 800 T model) on a silica-gel solid support and irradiated at 300 W for the appropriate time (Table 2). Progress of the reaction was checked by thin-layer chromatography (TLC). The reaction mass was cooled to room temperature, water (5 ml) was added, and it was stirred for 1–2 min, filtered, and recrystallized from ethanol to afford expected products **3** in excellent yields.

Method B (Conventional Method)

A mixture of the phenol **1** (1 mmol), β-ketoester **2** (1 mmol), and cellulose sulfuric acid (0.1 g) was stirred at room temperature for the appropriate time according to Table 2. Completion of the reaction was confirmed by (TLC). After completion of the reaction, water (5 ml) was added to the reaction mixture, and it was stirred for 2 min, filtered, and recrystallized from ethanol to afford

Table 2. Cellulose sulfuric acid–catalyzed synthesis of coumarins

Entry	Phenol	Ester	Coumarin	Method A		Method B	
				Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]
1				2	88	35	85
2				1.5	94	20	93
3				2	97	20	96
4				1.5	96	25	94
5				1.5	94	20	93
6				3	92	30	91
7				2.5	95	25	94
8				1	95	15	94
9				2.5	94	25	93
10				2.5	97	25	97
11				2	92	30	90
12				2	90	30	89

[a]Yields refer to pure products and all products were characterized by comparison of their physical data and ^{1}H NMR, IR, and mass spectral data with those authentic samples.

Table 3. The effect of reusability of catalyst on yield

Run	Cycle	Yield[a] (%)
1	0	97
2	1	96
3	2	92
4	3	86

Note. Reaction conditions: Phenol **1** (1 mmol), β-ketoester **2** (1 mmol), and cellulose sulfuric acid (0.1 g) were stirred at room temperature.

[a]Yields refer to the pure isolated recovered catalyst.

corresponding products in good yields. After filtration, the filtrate (water) containing the catalyst could be evaporated under reduced pressure to give a white solid. The recovered catalyst was washed with CH_2Cl_2, dried in an oven at 60 °C for 5 h under high pressure prior to use in the other reaction. The recovered catalyst can be reused at least three additional times in subsequent reactions without significant loss in product yield (Table 3).

CONCLUSION

In summary, we have successfully developed a facile economic and green method for construction of coumarins by employing phenols and β-ketoester under solvent-free conditions in the presence of cellulose sulfuric acid. The notable factors of this reaction are (a) reasonably good yields, (b) fast reaction, and (c) easy recovery of catalyst, cellulose sulfuric acid. Thus we believe our procedure will find important application in the synthesis of coumarin.

ACKNOWLEDGMENT

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