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Brønsted acidic ionic liquid as the efficient and reusable catalyst for synthesis of coumarins via Pechmann condensation under solvent-free conditions

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ABSTRACT

A mild and efficient method has been developed for the preparation of substituted coumarins from reaction of various phenols with different β-ketoesters via Pechmann condensation in the presence of Brønsted acidic ionic liquid (*N*-(4-sulfonic acid) butyl triethylammonium hydrogen sulfate) as an effective catalyst under solvent-free conditions. Different phenols reacted with ethyl acetoacetate to produce the corresponding substituted coumarins in high to excellent yields and short reaction times. Moreover, [TEBSA][HSO_4] has been used as an effective green catalyst for the synthesis of coumarin derivatives under solvent-free conditions. Using the relatively non-toxic (halogen-free) and reusable Brønsted acidic ionic liquid, high catalytic efficiency, high yields, short reaction times and straightforward work-up are advantages of this protocol.

Keywords*: Coumarins, β-ketoesters, Brønsted acidic ionic liquid, N-(4-sulfonic acid) butyl triethylammonium hydrogen sulfate ([TEBSA][HSO_4]).*

1. Introduction

Coumarins and their derivatives represent an important class of natural products that possess significant biological and pharmaceutical properties. They act as anticancer [1,2], antiviral [3], antibacterial [4], anti-convulsant [5], anti-inflammatory [6], anti-HIV [7], inhibitors for platelet aggregation [8] and steroid 5α-reductase [9]. These heterocyclic compounds are also used in cosmetics, food additives, perfumes [10], optical brightening agents [11], dispersed fluorescent and laser dyes [12].

Various methods such as Pechmann [13], Wittig [14,15] and Knoevenagel [16] reactions have been used for the synthesis of coumarins. Among these, the Pechmann reaction is extensively used for the synthesis of coumarins. This method includes the reaction of phenols with β-ketoesters or malic acid or alkynoates in the presence of acidic catalysts [17-19]. Several acidic catalysts such as H_2SO_4 [20], P_2O_5 [21], $Bi(NO_3)_3$ [22], $Cu(ClO_4)_2$ [23] and etc. [24-28] have been used for this procedure. However these procedures suffer from either long reaction times or using excess amount of catalysts and special apparatus. Because of the importance of coumarins and the great need for environmentally benign chemical productions, the development of suitable green synthetic methods for these compounds can be attractive in this area of research.

Recently, ionic liquids (ILs) have fascinated the attention of chemists due to their particular properties like undetectable vapour pressure, non-inflammability, wide liquid range, reusability and high thermal stability [29,30]. Ionic liquids have been applied for many reactions as useful, clean and green solvents or catalysts [31,32]. In particular, Brønsted acidic ionic liquids containing useful characteristics of solid acids and mineral liquid acids have been designed to replace conventional mineral liquid acids like sulfuric acid and hydrochloric acid in chemical procedures [33,34].

N-(4-sulfonic acid) butyl triethylammonium hydrogen sulfate ([TEBSA][HSO_4]) as a Brønsted acidic ionic liquid has been used as an efficient catalyst for nitration of aromatic compounds [35], selective

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alkylation of *m*-cresol with *tert*-butanol [36] and also synthesis of amidoalkylnaphthol derivatives [37]. In view of the current interest in environmentally benign catalytic processes, a procedure performing under solvent-free conditions would be more appreciable, therefore we wish to report a convenient, mild and efficient procedure for the synthesis of coumarins from various phenols and different β-ketoesters in the presence of [TEBSA][HSO_4] as an effective and reusable catalyst under solvent-free conditions (Scheme 1).

2. Experimental

2.1. General

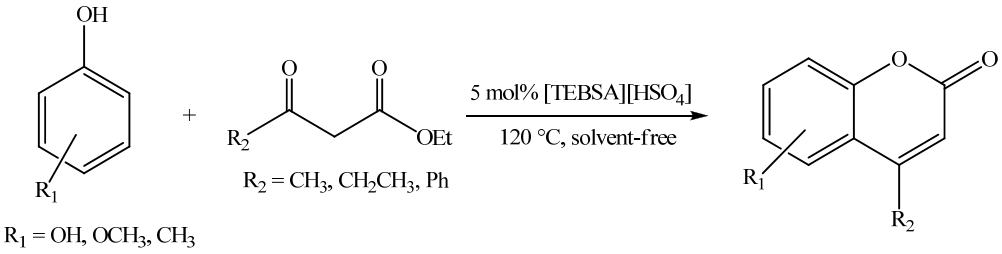
All reagents were purchased from Merck and Aldrich and used without further purification. All yields referred to isolated products after purification. [TEBSA][HSO_4] was synthesized according to previous reported procedure [37]. Products were characterized by spectroscopy data (IR, ^{1}HNMR and ^{13}CNMR spectra), melting points and elemental analysis. ^{1}HNMR (400 MHz) and ^{13}CNMR (100 MHz) spectra were run in DMSO-d_6 and $CDCl_3$ relative to TMS (0.00 ppm)**.** IR spectra were recorded on a Shimadzu 435 IR spectrophotometer and performed using KBr pellets. All melting points were taken on a Gallenkamp melting apparatus and were uncorrected.

2.2. General procedure for the preparation of coumarin derivatives

A mixture of a phenol (1 mmol), β-ketoester (1.2 mmol) and [TEBSA][HSO_4] (0.05 mmol) were stirred at 120°C in oil bath. The reaction was monitored with TLC (ethyl acetate/cyclohexane, 1/3). After completion, the reaction mixture was cooled to room temperature, then water was added to the reaction mixture and stirred for 5–10 min. The crystalline product was collected by filtration, washed with ice-cold water (10 ml) and recrystallized from ethanol to afford pure product.

3. Results and discussion

To optimize the reaction conditions, the reaction of resorcinole (1 mmol) and ethyl acetoacetate (1.2 mmol) was examined in the presence of different amounts of [TEBSA][HSO_4] at different temperatures (Table 1). It was found that the best result was obtained when the reaction carried out at 120°C by using 0.05 mmol of [TEBSA][HSO_4] under solvent-free conditions (Table 1, entry 4). An increase of the amount of the catalyst from 0.05 to 0.30 mmol did not improve the results. Therefore, only 5 mol% of [TEBSA][HSO_4] was suitable for this reaction. It emonstrated high catalytic efficiency of [TEBSA][HSO_4] due to having two acidic group (Table 1).



Scheme 1. The synthesis of coumarins from various phenols and different β-ketoesters in the presence of [TEBSA][HSO_4] under solvent-free conditions.

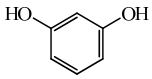
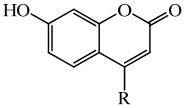
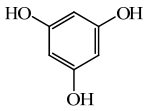
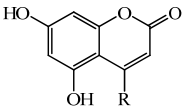
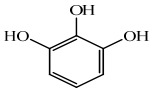
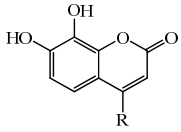
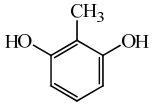
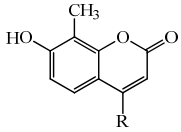
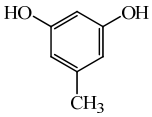
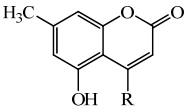
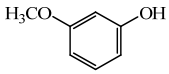
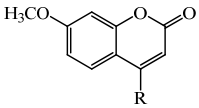
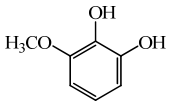
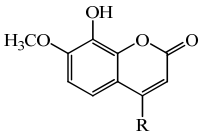
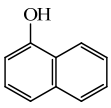
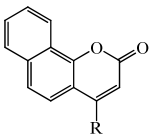
Table 1. Synthesis of coumarins from resorcinol and ethyl acetoacetate under different conditions.

Entry	[TEBSA][HSO_4] (mmol)	Temp. (°C)	Time (min)	Yield of **1a** (%)[a]
1	0.05	r.t.	90	30
2	0.05	100	10	75
3	0.025	120	4	85
4	0.05	120	4	94
5	0.1	120	20	80
6	0.15	120	120	50
7	0.30	120	120	40
8	0.05	130	5	80

[a]Isolated yields.

Using these optimized conditions, various substituted coumarins were prepared by reaction of the different phenols with various β-ketoesters such as ethyl acetoacetate, ethyl-3-oxovalerate and ethylbenzoyl acetate under solvent-free conditions at 120°C (Table 2, entries 1-8). As demonstrated in Table 2, different phenols reacted with ethyl acetoacetate to produce the corresponding substituted coumarins in high to excellent yields and short reaction times. When the 3-oxovalerate and ethylbenzoylacetate were used, the yields of the related products were approximately high but the reaction times were longer than the others because of their steric effects (Table 2, all **b** and **c** products).

Table 2. Synthesis of coumarins from phenols and different β-ketoesters using [TEBSA][HSO_4] at 120°C under solvent-free conditions.[a]

Entry	Phenol	Product	Time (min)	Yield (%)[b]	m.p. (°C)
1		 **1a** R = CH_3	4	94	184-185
		1b R = CH_2CH_3	10	87	165-168
		1c R = Ph	60	81	243-245
2		 **2a** R = CH_3	2	93	281-283
		2b R = CH_2CH_3	5	88	261-264
		2c R = Ph	60	83	232-234
3		 **3a** R = CH_3	7	90	232-234
		3b R = CH_2CH_3	20	83	226-229
4		 **4a** R = CH_3	2	92	260-262
		4b R = CH_2CH_3	20	88	210-212
		4c R = Ph	30	85	272-274
5		 **5a** R = CH_3	5	85	254-256
		5b R = CH_2CH_3	25	81	192-194
6		 **6a** R = CH_3	60	83	153-155
		6b R = CH_2CH_3	75	70	93-95
7		 **7a** R = CH_3	90	72	156-158
		7b R = CH_2CH_3	120	61	162-164
8		 **8a** R = CH_3	50	70	168-170
		8b R = CH_2CH_3	90	60	169-172

[a]Reaction conditions: phenol (1.0 mmol), β-ketoester (1.2 mmol), and ionic liquid (0.05 mmol).

[b]Yields referred to isolated pure products and all synthesized coumarins were characterized by spectral data (IR, ^1H and ^{13}CNMR), melting points and comparison with authentic samples.

As shown in Table 2, electronic effects were observed on these reactions. The kind of groups on the phenols affected the yield and reaction time. We found that electron-donating group *para* to the site of electrophilic substitution on the phenols increased both the reaction rate and the yield of the product (Table 2, entries 1-5). In the cases of 3-methoxy phenol (entry 6) and *3-methoxy catechol* (entry 7) longer reaction time was required but they showed no detectable demethylation under the reaction conditions. 1-Naphthol (entry 8) required longer reaction time due to the presence of another phenyl ring [38]. As expected, the reaction of other phenols having no electron-donating group or electron with-drawing group such as phenol and 4-nitro phenol with ethyl acetoacetate failed to give corresponding coumarins after 120 minutes.

As a result, this procedure was suitable for the synthesis of coumarins from different phenols having electron-donating group. It was noteworthy that hydroxycoumarins were synthesized in high to excellent yields and short times in this procedure because they are useful intermediates with potential biological activity. It was remarkable that the work-up of products was very convenient. All of the products were isolated by adding water to the reaction mixture and filtrated off the solid compounds as pure products. Furthermore, this procedure was environmental benign because of using halogen-free and reusable acidic ionic liquid with high catalytic efficiency under solvent-free conditions without using any organic solvent (Table 2).

A suggested mechanism for the Pechmann condensation by using [TEBSA][HSO_4] as a catalyst was given in Scheme 2.

In comparison with other catalysts employed for the synthesis of coumarin (1a) from resorcinole and ethyl acetoacetate under different conditions, [TEBSA][HSO_4] showed more catalytic reactivity than the others in terms of low amount of catalyst, short reaction time and simplified conditions (Table 3).

To investigate the reusability of the [TEBSA][HSO_4] catalyst, after each run, the catalyst was extracted from the reaction mixture according to the previous reported method [37] and reused for the reaction of resorcinol with ethyl acetoacetate under solvent-free conditions at 120°C (Figure1). It was considerable that the catalyst could be employed four times, although the efficiency of the catalyst was gradually decreased. These observations demonstrated that the acidic ionic liquid ([TEBSA][HSO_4]) could be used as an effective and reusable catalyst for the synthesis of substituted coumarins (Fig. 1).

4. Conclusions

In conclusion, *N*-(4-sulfonic acid) butyl triethylammonium hydrogen sulfate has been used as an effective green catalyst for the synthesis of coumarin derivatives in high yields under solvent-free conditions. Using the relatively non-toxic (halogen-free) and reusable Brønsted acidic ionic liquid, high catalytic efficiency, high yields, short reaction times and convenient work-up are advantages of this protocol.

Acknowledgment

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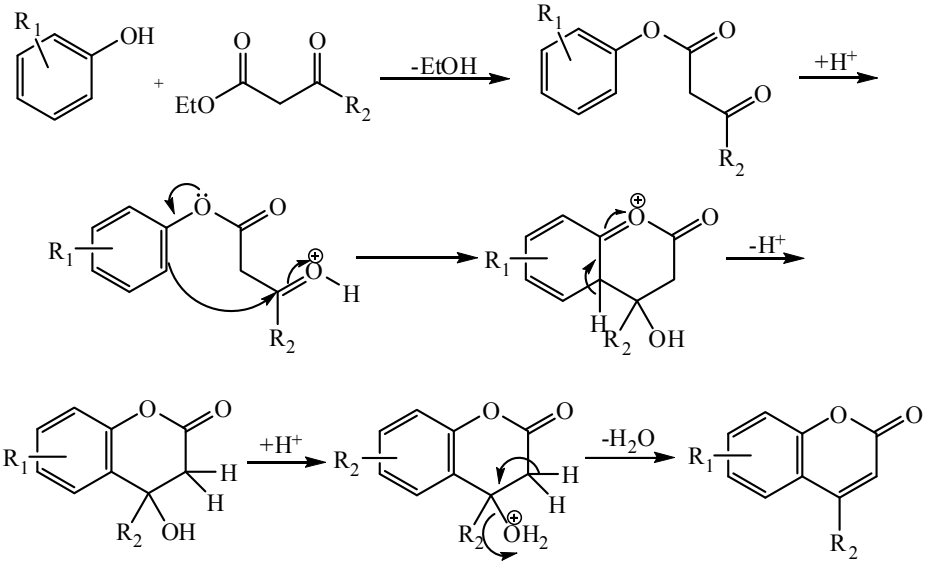

Scheme 2. A suggested mechanism for the Pechmann condensation by using [TEBSA][HSO_4] as a catalyst.

Table 3. The synthesis of **1a** coumarin from resorcinole and ethyl acetoacetate under different conditions.

Entry	Catalyst (mol %)	Solvent	Conditions	Time (min)	Yield (%)	Ref.
1	$TiCl_4$ (100)	-	r.t.	1	97	[20]
2	$Bi(NO_3)_3.5H_2O$ (5)	-	80°C	15	94	[22]
3	$Cu(ClO_4)_2$ (20)	-	Ultrasonic irradiation	30	95	[23]
4	$SnCl_2.2H_2O$ (10)	Ethyl alcohol	Reflux 80°C	150	52	[24]
5	PMSCl (7)	-	130°C	60	94	[25]
6	PEG-SO_3H (10)	-	80°C	10	91	[26]
7	Cellulose sulfuric acid (0.1 g)	-	Microwave	1.5	94	[27]
8	[TEBSA][HSO_4] (5)	-	120°C	4	94	-

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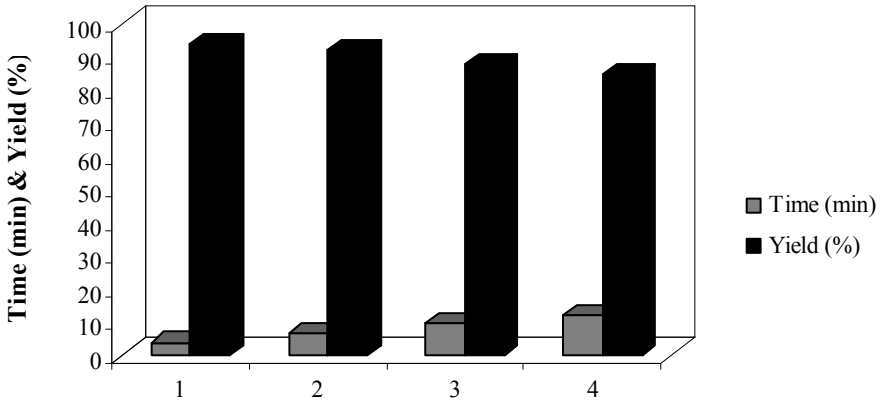

Fig. 1. Recycling of the Brønsted acidic ionic liquid catalyst.

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