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# (4-Sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulphate: An efficient, eco-friendly and recyclable catalyst for the synthesis of coumarin derivatives *via* Pechmann condensation under solvent-free condition

# Janardhan Banothu and Rajitha Bavantula\*

Department of Chemistry, National Institute of Technology, Warangal-506004, India.

## ABSTRACT

Pechmann condensation of phenols with  $\beta$ -ketoesters in the presence of a novel ionic liquid bearing multi-SO<sub>3</sub>H groups under solvent-free conditions at ambient temperature gave the corresponding coumarin derivatives with excellent yields in shorter reaction times. This methodology is very simple, cost-effective, eco-friendly and the catalyst could be easily recycled.

Keywords: Coumarin derivatives, Ionic liquid, Pechmann condensation, Solvent-free conditions.

## **INTRODUCTION**

In recent year's ionic liquids playing an important role in synthetic organic chemistry due to their use as green alternatives to conventional solvents and catalyst for a wide range of organic transformations. In addition, ionic liquid have high thermal stability, higher selectivity, non volatility, eco-friendly and reusability [1]. Reactions under solvent-free conditions [2,3] are also attracted to the researchers both from academia and industry, due to avoid the expensive hazardous solvents, complexity in reaction workup procedure and to proceed the reaction faster.

It is well known that coumarin derivatives represent an important class of oxygen containing heterocyclic compounds. They are widely used as additives in foods, perfumes, cosmetics, in the preparation optical brighteners [4], dispersed fluorescent and laser dyes [5]. They are also reported to possess various pharmacological activities such as anthelmintic, anticoagulants, hypnotic and insecticidal properties [6-8]. More importantly, polycyclic coumarins such as calanolides [9] isolated from Calophyllum lanigerum trees were found to be highly effective against HIV-1, thereby acting as non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI) [10-12]. Generally, coumarins can be synthesized by Pechmann, Perkin, Knoevenagel and Wittig reactions; among these Pechmann reaction is simple and straight forward which employs the condensation of phenols with  $\beta$ -ketoesters in the presence of variety of acidic condensing agents. Several reagents have been used in Pechmann reaction e.g. sulfuric acid [13-15], chlorosulfonic acid [16], trifluoroacetic acid [17], phosphotungstic acid [18], poly(4-vinylpyridine)-supported sulfuric acid [19], iodine [20], SnCl<sub>2</sub>·2H<sub>2</sub>O [21], TiCl<sub>4</sub> [22], ZrCl<sub>4</sub> [23], FeCl<sub>3</sub> [24], Al-MCM-41 [25], silica triflate [26] and zeolite [27] as catalysts. However, many of these reported methods suffers from one or several drawbacks such as low yield, long reaction time, tedious workup, harsh reaction conditions and use of a large quantity of expensive, poisonous solvents and reagents. Recently, ionic liquid catalysed reactions [28-31] have also reported, but those ionic liquid are expensive. Therefore, still there is a necessity to develop an efficient method for Pechmann reaction. To overcome the above limitations, we have developed an efficient and environment-friendly synthesis of coumarin derivatives under solvent-free conditions using an inexpensive novel ionic liquid.

#### MATERIALS AND METHODS

The melting points of the products were determined by open capillaries on Stuart SMP30 apparatus and are uncorrected. The progress of the reaction was monitored by TLC and visualized with UV light and iodine vapours. IR spectra were recorded on Thermo Nicolet Nexus 670 spectrometer using KBr pellet, values are expressed in cm<sup>-1</sup>. The C, H and N analysis of the compounds were done on a Carlo Erba modal EA1108, NMR spectra were recorded on Bruker 300-MHz spectrometer using TMS as an internal standard and chemical shifts are expressed in ppm. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

#### General Procedure for the synthesis of coumarin derivatives (3):

Phenols (1 mmol),  $\beta$ -ketoesters (1 mmol) and ionic liquid (10 mol%) were mixed without any solvent and stirred at room temperature for an appropriate time (Table-2). After completion of the reaction indicated by TLC, 2 mL of water was added and the mixture was stirred for an additional 5 min. The precipitated product was filtered, washed with water, dried and crystallized from ethanol. The aqueous layer containing ionic liquid was recovered under reduced pressure, washed with acetone, dried and reused for subsequent reactions.

### Spectral data:

**7-Methoxy-4-methyl-2***H***-chromen-2-one (Table-2, Entry-3):** IR (KBr, cm<sup>-1</sup>)  $\upsilon_{max}$ : 1704 (C=O stretching of ester), 1595 (C-C=C stretching) 1189 (C-O-C stretching); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  2.32 (s, 3H), 4.15 (s, 3H), 6.39 (s, 1H), 6.97 (s, 1H), 7.18 (d, 1H), 7.64 (d, 1H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  162.4, 156.9, 153.6, 151.7, 146.3, 126.5, 119.7, 118.1, 110.2, 108.9, 20.6; EIMS (*m*/*z*): 190 (M<sup>+</sup>); Anal. Calcd. For C<sub>11</sub>H<sub>10</sub>O<sub>3</sub>: C, 69.46; H, 5.30; Found: C, 69.78; H, 5.13.

**4-(Chloromethyl)-7-Hydroxy-2***H***-chromen-2-one (Table-2, Entry-6):** IR (KBr, cm<sup>-1</sup>)  $\upsilon_{max}$ : 3390 (OH stretching), 1711 (C=O stretching of ester), 1583 (C-C=C stretching), 715 (C-Cl stretching); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  3.73 (s, 2H), 6.12 (s, 1H), 6.49 (s, 1H), 6.81 (d, 1H), 7.44 (d, 1H), 10.11 (s, 1H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  160.7, 156.9, 151.2, 129.1, 126.3, 125.5, 121.8, 115.7, 110.3, 52.8; EIMS (*m*/*z*): 210 (M<sup>+</sup>); Anal. Calcd. For C<sub>10</sub>H<sub>7</sub>ClO<sub>3</sub>: C, 57.03; H, 3.35; Found: C, 57.38; H, 3.12.

**7-Hydroxy-4,8-methyl-2***H***-chromen-2-one (Table-2, Entry-8):** IR (KBr, cm<sup>-1</sup>)  $\upsilon_{max}$ : 3223 (OH stretching), 1693 (C=O stretching of ester), 1608 (C-C=C stretching); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  2.15 (s, 3H), 2.36 (s, 3H), 6.10 (s, 1H), 6.85 (d, 1H), 7.42 (d, 1H), 10.41 (s, 1H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  161.3, 159.7, 154.6, 153.6, 123.9, 112.8, 112.5, 111.5, 110.7, 19.0, 8.9; EIMS (*m*/*z*): 190 (M<sup>+</sup>); Anal. Calcd. For C<sub>11</sub>H<sub>10</sub>O<sub>3</sub>: C, 69.46; H, 5.30; Found: C, 69.75; H, 5.12.

**7,8-Dihydroxy-4-methyl-2***H***-chromen-2-one (Table-2, Entry-11):** IR (KBr, cm<sup>-1</sup>)  $v_{max}$ : 3392 (OH stretching), 1721 (C=O stretching of ester), 1610 (C-C=C stretching); <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  2.21 (s, 3H), 6.14 (s, 1H), 6.85 (d, 1H), 7.37 (d, 1H), 9.54 (s, 1H), 10.16 (s, 1H); <sup>13</sup>C NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  161.8, 155.6, 153.9, 149.4, 145.2, 122.5, 114.2, 112.5, 110.7, 24.2; EIMS (m/z): 192 (M<sup>+</sup>); Anal. Calcd. For C<sub>10</sub>H<sub>8</sub>O<sub>4</sub>: C, 62.50; H, 4.20; Found: C, 62.81; H, 4.03.

**4-Methyl-2***H***-benzo[***h***]chromen-2-one (Table-2, Entry-13): IR (KBr, cm<sup>-1</sup>) \upsilon\_{max}: 1722 (C=O stretching of ester), 1603 (C-C=C stretching); <sup>1</sup>H NMR (300 MHz, DMSO-***d***<sub>6</sub>): \delta 2.17 (s, 3H), 6.12 (s, 1H), 7.25-7.51 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-***d***<sub>6</sub>): \delta 160.9, 156.6, 154.7, 143.6, 129.0, 127.9, 126.4, 126.2, 124.5, 122.9, 122.4, 121.5, 112.2, 22.7; EIMS (***m***/***z***): 210 (M<sup>+</sup>); Anal. Calcd. For C<sub>14</sub>H<sub>10</sub>O<sub>2</sub>: C, 79.98; H, 4.79; Found: C, 79.70; H, 4.91.** 

#### **RESULTS AND DISCUSSION**

In continuation of our interest in the development of new synthetic methods for pechmann reaction [32-36], herein we report a simple, efficient and eco-friendly procedure for the synthesis of coumarin derivatives via Pechmann condensation of phenols with  $\beta$ -ketoesters under solvent-free conditions at room temperature using Brønsted acidic ionic liquid, (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulphate as catalyst with excellent yields (Scheme-1). This ionic liquid is inexpensive and can be easily prepared in the laboratory from the readily available starting materials as shown in Scheme-2 [37].



Scheme-2. Synthesis of (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulphate

Initially, the reaction between resorcinol and ethyl acetoacetate was performed as a modal reaction to known the optimistic conditions at room temperature without and with variant amount of catalyst (5, 10, 15mol%) in different solvents (methanol, acetic acid, acetonitrile and water) as well as under solvent-free conditions. The experimental results are as follows; without catalyst only trace amount of compound (3e) has observed in all the above solvents but under solvent-free conditions 10% of product was formed, when we used 5 mol% of ionic liquid the yield of the product has enormously increased and observed maximum yield (68%) under solvent-free conditions, as the amount of catalyst increased to 10 mol% the yield of the product has increased from 68% to 97% within shorter reaction time. Further increment in amount of catalyst has not shown any affect on product yield and reaction time. In aqueous medium also observed good yields, but it requires longer reaction times. To know the effect of temperature on product yield and reaction time (Table-1). From these results we deduce that 10 mol% of ionic liquid under solvent-free conditions at room temperature is the optimistic condition for getting the excellent yield.

Entry	Ionic liquid (mol%)	Solvent	Temp.	Time (min)	Yield <sup>a</sup> (%)
1	-	CH <sub>3</sub> OH	RT	180	Trace
2	-	CH <sub>3</sub> COOH	RT	180	Trace
3	-	CH <sub>3</sub> CN	RT	180	Trace
4	-	$H_2O$	RT	180	Trace
5	-	Solvent-free	RT	180	10
6	5	CH <sub>3</sub> OH	RT	120	51
7	5	CH <sub>3</sub> COOH	RT	120	39
8	5	CH <sub>3</sub> CN	RT	120	46
9	5	$H_2O$	RT	120	61
10	5	Solvent-free	RT	120	68
11	10	CH <sub>3</sub> OH	RT	60	83
12	10	CH <sub>3</sub> COOH	RT	60	60
13	10	CH <sub>3</sub> CN	RT	60	76
14	10	$H_2O$	RT	60	92
15	10	Solvent-free	RT	20	97
16	15	CH <sub>3</sub> OH	RT	60	83
17	15	CH <sub>3</sub> COOH	RT	60	60
18	15	CH <sub>3</sub> CN	RT	60	76
19	15	$H_2O$	RT	60	92
20	15	Solvent-free	RT	20	97
21	10	Solvent-free	40 °C	20	97

Table-1:	Optimisation	of the	reaction	conditions	١.

<sup>a</sup> Reaction conditions: Resorcinol (1 mmol), Ethyl acetoacetate (1 mmol), Stirring. <sup>a</sup>Yields refer to pure isolated product (3e).

At these optimistic conditions (10 mol% of ionic liquid, solvent-free conditions, R.T), we synthesized different coumarin derivatives with the average of 94% yield and the results are postulated in Table-2. After completion of the reaction shown by TLC, the catalyst was recovered by evaporating the aqueous layer under reduced pressure, washed with acetone, dried and reused at least five additional times in subsequent reactions without significant loss in its activity (Table-3). All the compounds were characterized by their analytical and spectroscopic data and compared with those of authentic samples.

<b>.</b>		<b>D</b> (		<b>T</b> : ( )	X7: 1 16 (0/)	Meltin	g Point (°C)
Entry	Phenol	Ester	Coumarin	Time (min)	Yield <sup>c</sup> (%)	Found	Lit. [Ref]
1	OH	H <sub>3</sub> C OEt	CH <sub>3</sub>	15	94	84	81 [32]
2	H <sub>3</sub> C OH	H <sub>3</sub> C OEt	H <sub>3</sub> C C C H <sub>3</sub> C	15	93	131-132	130-131 [31]
3	MeO	H <sub>3</sub> C OEt	MeO O O CH <sub>3</sub>	20	94	160	160-161 [31]
4	O <sub>2</sub> N OH	H <sub>3</sub> C OEt	O <sub>2</sub> N CH <sub>3</sub>	20	93	175-176	176-178 [31]
5	НОСОН	H <sub>3</sub> C OEt	HO O O CH <sub>3</sub>	20	97	183-185	182-184 <sup>21d</sup>
6	НОСОН	ClOEt	HO O O CH <sub>2</sub> Cl	20	91	181-182	180 [36]
7	HOUTOH	O O Ph OEt	HO O O Ph	20	92	255-256	257 [32]
8	HO CH <sub>3</sub> OH	H <sub>3</sub> C OEt	HO HO CH <sub>2</sub>	15	92	138	137-138 [31]
9	HO OH OH	H <sub>3</sub> C OEt	HO O O OH CH <sub>3</sub>	10	96	282-284	280-283 [31]
10	HO OH OH	ClOEt	HO O O OH CH <sub>2</sub> Cl	15	94	185	187 [32]
11	HO OH OH	H <sub>3</sub> C OEt	HO CH <sub>3</sub>	10	97	238-240	234-237 [31]
12	HO OH OH	ClOEt	OH HO CH <sub>2</sub> Cl	20	94	135-136	134 [36]
13	OH	H <sub>3</sub> C OEt		20	92	156	154-155 [31]
14	ОН	H <sub>3</sub> C OEt	CH <sub>3</sub>	20	93	181-182	183-184 [20]

<sup>*a*</sup> *Reaction condition*: phenols (1 mmol),  $\beta$ -ketoesters (1 mmol) and ionic liquid (10 mol%), Neat, R.T.

<sup>b</sup>All the products were characterized by comparison of their physical data, IR, NMR and Mass with those of authentic samples. <sup>c</sup> Isolated yields.

Table-3: Effect of rec	vclability of the ionic	liquid on 7-hydrox	xy-4-methyl-2 <i>H</i> -chrom	en-2-one viled <sup>a</sup> .
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Run	Cycle	Yield <sup>b</sup> (%)
1	0	97
2	1	97
3	2	96
4	3	95
5	4	93
6	5	90

<sup>a</sup> Reaction conditions: resorcinol (1 mmol), ethyl acetoacetate (1 mmol) and ionic liquid (10 mol%) stirring at R.T for 20 min under solvent-free conditions.

<sup>b</sup> Isolated yields.

#### CONCLUSION

In conclusion, we have developed a simple, efficient and environmentally friendly method for the synthesis of coumarin derivatives via Pechmann condensation of phenols with  $\beta$ -ketoesters under solvent-free conditions at ambient temperature using inexpensive novel ionic liquid, (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulphate as catalyst. This method is very effective and superior to earlier reported methods in terms of product yield, reaction time, reusability of the catalyst and isolation of the product.

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