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[HSO_3-pmim][CH_3SO_3] Catalyzed One-Pot Protocol for the Synthesis of Coumarins Under Solvent-Free Conditions

S.J. SONG, W.H. LIU, J.J. MA* and J.M. QI

Hebei Key Laboratory of Bioinorganic Chemistry, College of Sciences, Agricultural University of Hebei, Baoding, P.R. China

*Corresponding author: Fax: +86 312 7528292; Tel: +86 312 7528291; E-mail: mjjwjpmartin@sina.com

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A mild and efficient protocol for the synthesis of coumarins from different phenol and ethyl acetoacetate *via* Pechmann reacation using acidic ionic liquids [1-methyl-3-(3-sulfopropyl)-imidazolium methyl sulphate] as catalyst under solvent-free conditions has been developed. The advantages of this protocol are low catalyst loading, better yields, shorter reaction time and environmentally benign.

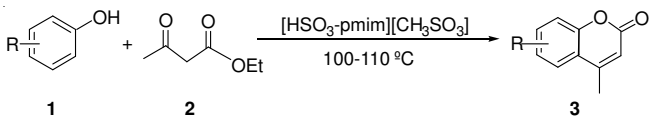
Key Words: Coumarins, Pechmann reaction, Solvent-free, Phenols, Synthesis.

INTRODUCTION

Coumarins and their derivatives are one kind of important compounds because of their extensive applications in synthetic organic and medicinal chemistry, as well as in materials science. They are widely used as additives in food, fragrances, pharmaceuticals and agrochemicals[1] and also used as optical brightening agents[2], dispersed fluorescent and laser dyes[3]. Therefore, many synthetic routes have been reported for the synthesis of coumarins including the Perkin[4], Pechmann[5], Knoevenagel[6], Reformatsky[7] and the Wittig[8] reactions and by flash vacuum pyrolysis[9]. Among these methods, the Pechmann reaction is the most widely applied method for the synthsis of coumarins and their derivatives. The Pechmann reaction involves condensation of phenols and β-ketoesters in the presence of acidic catalyst. A number of acid catalysts have been used in the conventional procedure, such as H_2SO_4[5], P_2O_5[10a], $AlCl_3$[10b], PPA[10c], $TiCl_4$[10d], $InCl_3$[10e], $Sm(NO_3)_3$[10f], $BiCl_3$[10g], $ZrCl_4$[10h], $SnCl_4$ H_2O[10i], $SnCl_2$ $2H_2O$[10j], WO_3-ZrO_2 nanocomposites[10k], *etc*. However, many of these procedures suffer from one or more disadvantages such as long reaction times, tedious work-up procedure, low yields and large amounts of catalysts which would lead to environmental pollution. Thus, a mild, efficient and environmentally friendly method using economical catalyst is desirable.

Room temperature ionic liquids (RTILs) have received increasingly attention as potential "greener" alternatives to volatile organic solvent and they have been investigated extensively as a solvent or catalyst for many important organic reactions because of their special properties such as their negligible vapor pressure, tunable polarity, high thermal stability, good solvating ability, ease of recyclability and their potential to enhance reaction rates and selectivity[11]. They have also been referred as "designer solvents," as their properties can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and alkyl chain attached to the organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent and catalyst, catering for the needs of a particular process[12].

In continuing our endeavor in green synthesis and using ionic liquids as a recyclable reaction medium to enhance rates and selectivity[13], we report herein a mild solvent-free one-pot protocol for the synthesis of coumarins and their derivatives under the Pechmann reaction conditions using acidic ionic liquids 1-methyl-3-(3-sulfopropyl)-imidazolium methyl sulphate ([HSO_3-pmim][CH_3SO_3]) as an efficient catalyst (**Scheme-I**).



1 2 3

Scheme-I

EXPERIMENTAL

Melting points were recorded on an electrothermal apparatus and are uncorrected. ^{1}H NMR (300 MHz) spectra were determined with Brucker AVANCE 300 spectrometer ($CDCl_3$-d_6) using TMS as internal standard. IR spectra (cm^{-1}) were measured with a WQF-510 spectrometer. [HSO_3-pmim][CH_3SO_3] were synthesized according to the literatures[14].

General procedure: A mixture of 10 mmol phenol **1**, 15 mmol ethyl acetoacetate **2** and [HSO_3-pmim][CH_3SO_3] (10 mmol %) was stirred at 100-110 ºC for a certain period of time (Table-1) to complete the reaction (monitored by thin-layer chromatography, TLC). After completion, the reaction mixture was poured into cold water, filtered and the separated solid was washed with cold water. The crude product was re-crystallized from ethanol and dried to yielding the coumarin. All the products were fully characterized by IR and ^{1}H NMR spectroscopy and melting points, which were consistent with literature data.

Spectroscopic data for compounds

3a: ^{1}H NMR (300 MHz, $CDCl_3$-d_6): δ 7.50 (d, *J* = 8.7 Hz, 1H), 6.91 (s, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.15 (s, 1H), 2.41 (s, 3H); IR (KBr, ν_{max}, cm^{-1}): 3448, 3030, 1685, 1590, 1265,1065.

3b: ^{1}H NMR (300 MHz, $CDCl_3$-d_6): δ 6.24 (s, 1H), 6.15 (s, 1H), 5.80 (s, 1H), 2.55 (s, 3H); IR (KBr, ν_{max}, cm^{-1}): 3395, 3020, 1698, 1585, 1232, 1065.

3c: ^{1}H NMR (300 MHz, $CDCl_3$-d_6): δ 6.89-7.22 (m, 2H), 6.10 (s, 1H), 2.40 (s, 3H); OH not observed. IR (KBr, ν_{max}, cm^{-1}): 3415, 3230, 1652, 1956, 1190, 1062.

3d: ^{1}H NMR (300 MHz, $CDCl_3$-d_6): δ 7.10-7.62 (m, 3H), 6.38 (s, 1H) 2.81(s, 3H), 2.60 (s, 3H); IR (KBr, ν_{max}, cm^{-1}): 3054, 1685, 1210, 1065.

3e: ^{1}H NMR (300 MHz, $CDCl_3$-d_6): δ 7.50 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.82 (s, 1H), 6.06 (s, 1H), 3.83 (s, 3H), 2.40 (s, 3H); IR (KBr, ν_{max}, cm^{-1}): 3045, 1680, 1566, 1215, 1078.

3f: ^{1}H NMR (300 MHz, $CDCl_3$-d_6): δ 8.58 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.45-7.70 (m, 4H), 6.40 (s, 1H), 2.54 (s, 3H); IR (KBr, ν_{max}, cm^{-1}): 3020, 1715, 1578, 1245, 1044.

3g: ^{1}H NMR (300 MHz, $CDCl_3$-d_6): δ 7.46 (d, *J* = 6.0 Hz, 1H), 7.12-7.40 (m, 3H), 6.28 (s, 1H), 2.40 (s, 3H); IR (KBr, ν_{max}, cm^{-1}): 3025, 1715, 1533, 1248, 1060.

3h: ^{1}H NMR (300 MHz, $CDCl_3$-d_6): δ 7.40 (d, *J* = 8.7 Hz, 1H), 6.55 (d, *J* = 8.7 Hz, 1H), 6.40 (s, 1H), 5.90 (s, 1H), 2.30 (s, 3H); IR (KBr, ν_{max}, cm^{-1}): 3468, 3312, 3012, 1688, 1570, 1238,1052.

RESULTS AND DISCUSSION

In order to gain the optimal reaction conditions, initially, the loading amount of [HSO_3-pmim][CH_3SO_3] was optimized (Table-2). The results indicated that 10 mmol % [HSO_3-pmim][CH_3SO_3] is sufficient to promote reaction. The optimum yields of the product were obtained when a 1.0:1.5 ratio of hydroxyphenol to ethyl acetoacetate was used. No products were obtained when hydroxyphenol was reacted with ethyl acetoacetate under similar conditions in the absence of the [HSO_3-pmim][CH_3SO_3], thus highlighting the role of the acidic ionic liquids as a promoter. Any excess of acidic ionic liquids beyond this loading did not show any further increase in conversion and yield. Use of less than the required catalyst loading resulted in poor yields. In addition, the reaction was completed in 1 h and solvent-free conditions by heating the reaction mixtures at 100-110 ºC. To generalize the proposed method, a series of monohydric and polyhydric phenols were subjected to react with ethyl acetoacetate to obtain the corresponding substituted coumarins (Table-1). The results indicated that a wide range of structurally varied phenols reacted smoothly to give the coumarins in good yields. It is worth to mention that substrates like phenol, aminophenol and cresols, which failed to react in some of the reported documents, showed better reactivity under the reaction conditions.

TABLE-1
SYNTHESIS OF COUMARINS CATALYZED BY [HSO_3-pmim][CH_3SO_3] IN SOLVENT-FREE CONDITION

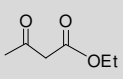
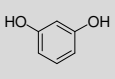
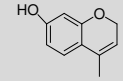
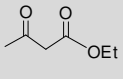
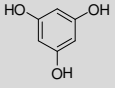
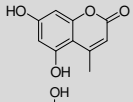
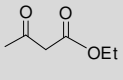
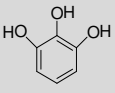
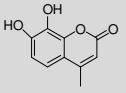
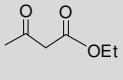
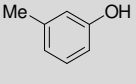
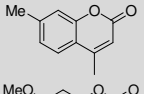
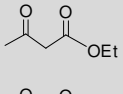
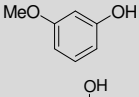
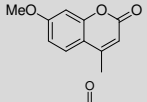
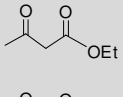
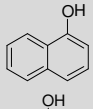
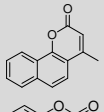
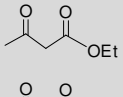
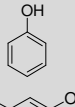
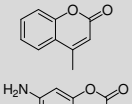
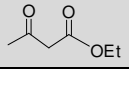
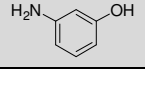
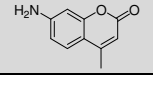
Entry	β-Keto ester	Substituents (Phenols 1)	Product	Time (min)	Yield (%)	m.p. (ºC)	m.p.^{lit} (ºC)
a				15	94	183-185	185[15]
b				15	96	280-282	280-285[15]
c				20	82	242-244	241- 243[10h]
d				25	85	130-131	131-132[10d]
e				20	87	160-162	161 – 162[16]
f				25	78	154-155	155-156[15]
g				25	70	79-81	82[16]
h				25	78	221-223	220-224[17]

TABLE-2
YIELD OF REACTIONS ON DIFFERENT QUANTITIES OF CATALYST

Catalyst (mmol %)	0	1	2	5	10	15
Yield (%)	–	17	42	85	94	94

Since the recovery and reuse of catalyst and solvent are highly preferable for a green process, so we investigated the reusability and recycling of the ionic liquid. After completion of the reaction, water was added into the reaction mixture and the solid was collected by filtration to give the product. The filtrate containing [HSO_3-pmim][CH_3SO_3] was concentrated under reduced pressure to recover the ionic liquid. The recycled [HSO_3-pmim][CH_3SO_3]was reused in the model reaction of 1a and 2a. The catalytic activity of [HSO_3-pmim][CH_3SO_3] did not show any significant decrease even after 5 runs. The results were shown in Table-3. The results also indicated that the ionic liquid employed was stable under the reaction temperature.

TABLE-3
STUDIES ON THE REUSE OF THE [HSO_3-pmim][CH_3SO_3] FOR THE PREPARATION OF **3a**

Round	1	2	3	4	5
Yield (%)	94	92	92	90	88

Conclusion

We have described a simple, rapid and environmentally benign method for synthesis of coumarins under solvent-free conditions using [HSO_3-pmim][CH_3SO_3] as catalyst. The advantages of this protocol are good yields, short reaction times, greenness of procedure and can avoid the use of the hazardous organic solvents and toxic catalysts. We believe that this method can be a useful contribution to the present methodologies for the synthesis of coumarins. The application studies of the task-specific ionic liquids for other reactions are in progress.

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