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Coumarin synthesis *via* Pechmann condensation utilizing starch sulfuric acid as a green and efficient catalyst under solvent-free conditions

Ramin Rezaei*, Mohammad Hossein Farjam, Maryam Farasat

Department of Chemistry, Firoozabad Branch, Islamic Azad University, P.O. Box 74715-117 Firoozabad, Fars, (IRAN)

E-mail: rezaier4@gmail.com

ABSTRACT

Starch sulfuric acid (SSA) was used as an efficient catalyst in the von Pechmann condensation of phenols with β-ketoesters leading to the formation of coumarin derivatives in excellent yields with good purity.Compared with conventional methods, the main advantages of the present procedure are milder conditions, shorter reaction time and green chemistry procedure.

KEYWORDS

Coumarins;
Starch sulfuric acid;
Pechmann condensation;
Solvent-free;
Biodegradable catalysts.

INTRODUCTION

The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, cosmetics, pharmaceuticals[1] and in the preparation of insecticides, optical brighteners[2] and dispersed fluorescent and laser dyes[3]. Thus, the synthesis of this heterocyclic nucleus is of much current interest. Coumarins have been synthesized by several routes including von Pechman[4], Perkin[5], Knoevenagel[6], Reformatsky[7] and Wittig reactions[8]. The von Pechmann reaction is a venerable reaction and it is one of the most simple and straightforward methods used to produce coumarins. Classically, the process consists of the condensation of phenols with β-ketoesters in the presence of a variety of reagents and gives good yields of 4-substituted coumarins[9]. Several acid catalysts have been used in this reaction including H_2SO_4,[4] $HClO_4$,[10] P_2O_5,[11] CF_3COOH.[12] Other methods have utilized ionic liquids[13] and microwave irradiation[14], but these methods also generate strongly acidic by-products and/or they utilize highly expensive and non recyclable reagents. Recently, a number of heterogeneous catalysts such as Nafion-H[15], zeolite H-BETA, Amberlyst 15,[16] montmorillonite clay[17], silica sulfuric acid[18], alumina[19], water-tolerant sulfonic acid nanoreactor[20], scandium (III) triflate[21], oxalic acid[22], Silica-bonded S-sulfonic acid[23], silica triflate[24], $ZrCl_4$[25], samarium(III)[26], zeolite[27], LiBr[28], dipyridine copper chloride[29], tetrakis(acetonitrile)copper(I) hexafluorophosphate[30], Pentafluorophenylammonium triflate[31], PEG-SO_3H[32], Polyvinylpolypyrrolidone-supported boron trifluoride[33], and ultrasound irradiation[34] have been employed in the Pechmann condensation.

In recent years, the direction of science and technology have been shifting more towards eco-friendly, natural product resources and reusable catalysts. Thus, natural biopolymers are attractive candidates in the search for such solid support catalysts[35]. Biopolymers, especially starch and its derivatives have some unique properties[36], which make them attractive alternatives for conventional organic or inorganic supports for catalytic applications[37].

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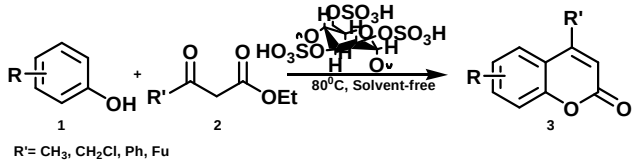
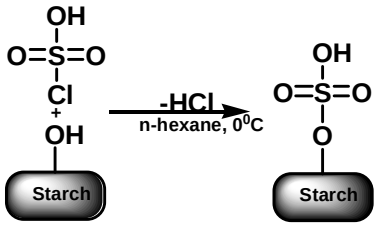
Due to extending our interest in the development of practical, safe, and environmentally friendly procedures for several important organic transformations[38-40] we set out to develop a solvent-free preparation of coumarins using an inexpensive and non-polluting catalyst. We have recently used melamine-formaldehyde resin supported H^+ (MFRH) as a promoting agent in the synthesis of coumarins.[41]Herein we are gratified to report an efficient and a convenient method for the synthesis of 4-substituted coumarinsusing starch sulfuric acid (SSA)catalyst in the Pechmann condensation reaction of phenols with β-ketoesters under solvent-free conditions (Scheme 1).



Scheme 1

Starch sulfuric acid is readily prepared by the dropwise addition of chlorosulfonic acid to mixture of starch in n-hexane at 0 ºC. It is important to note that, this reaction is easy and clean without any work-up procedure due to HCl gas is evolved from the reaction vessel immediately. This white homogeneous, nonhygroscopic solid acid is stable under reaction conditions(Scheme 2).



Scheme 2

To study the effect of catalyst loading on the Pechmann condensation reaction of phenols with β-ketoesters the reaction of resorcinol with ethyl acetoacetate was chosen as a model reaction (Table 1). The results show clearly that starch sulfuric acid(SSA)is an effective catalyst for this transformation and in the absence of catalystafter 7 h, at 80 ºConly 25% of the expected productwas obtained when after workup and recrystallization of the crude product from ethanol (TABLE 1, Entry 1). To improve the yield andoptimize the reaction conditions, the same reaction was carriedout in the presence of a catalytic amount of 0.02 g of SSA undersimilar conditions. Surprisingly, a significant improvement wasobserved and the yield of productwas dramatically increased to 85%after stirring; the mixture was stirred for only 30 min (Entry 2). Withthis optimistic result in hand, we further investigated the bestreaction conditions using different amounts of SSA. An increase in the quantity of SSA from 0.02 g to 0.05 g not only decreased the reaction time from 30 min to 5 min, but also increased the product yield slightly from 85% to 90% (Entry 3). Although the use of excess amount of 0.05 g of SSA permitted the reaction time to be decreased to 3 min, the yield unexpectedly decreased to 75% and 72% respectively (Entries 4, 5). A possible explanation for the low product yield is that the starting material or the product may have been destroyed during the reaction when an excess amount (0.1 g) of SSA was used in the exothermic reaction and that 0.05 g SSA was sufficient to catalyze the reaction effectively.

TABLE 1 : Conversion of resorcinol to the corresponding coumarin with ethyl acetoacetate in the presence of different amounts of SSA[a]

Entry	Starch sulfuric acid (g)	Time (min)	Yield (%)[b]
1	0	7 h	25
2	0.02	30	85
3	0.05	5	90
4	0.1	3	75
5	0.12	3	72

[a]Reaction conditions: resorcinol (1 mmol), ethyl acetoacetate(1.1mmol), 80ºC, solvent-free; [b]Isolated yield.

The model reaction was also examined in various solvents as well as under solvent-free conditions in the presence of 0.05g of SSA (TABLE 2). The yield of the reaction under solvent-free conditions was the highest

TABLE 2 : Conversion of resorcinol to the corresponding coumarin in differentsolvents and under solvent-free conditions

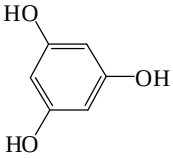
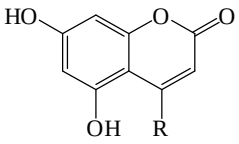
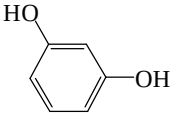
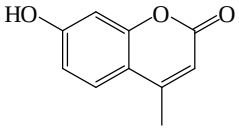
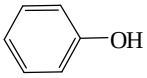
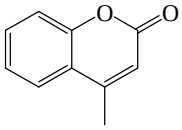
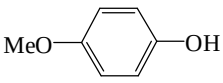
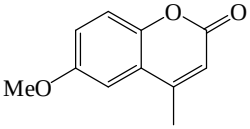
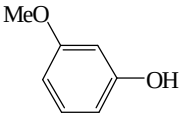
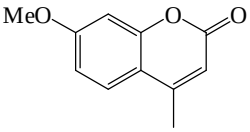
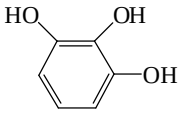
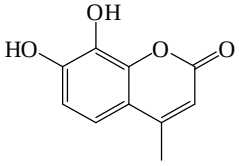
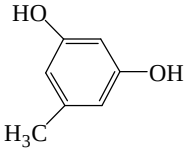
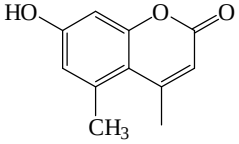
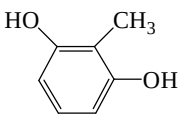
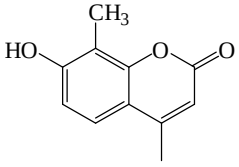
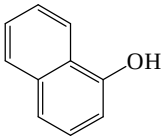
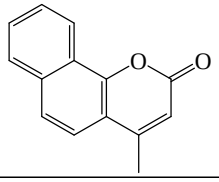
Entry	Solvent[a]	Yield[b](%)
1	EtOH	75
2	H_2O	50
4	n-Hexane	68
5	CH_3CN	65
6	Solvent-free[c]	80

[a]The reactions were carried out in the presence of resorcinol (1 mmol), ethyl acetoacetate; (1.1 mmol), and SSA (0.05 g) at 65ºC for 10 min; [b]Isolated yield; [c]Catalyst was reused for three times

and the reaction time was the shortest.

To study substituent effects on the reactivity of the phenol, the reactions were performed on a variety of phenols. The reactions worked well and the results are illustrated in TABLE 3. Substrates having electron-donating groups in *para*to the site of electrophilic substi-

TABLE 3 : Starch sulfuric acid catalyzed synthesis of coumarins[a]

Entry	Substrate	Product	Time (min)	Yield[b] (%)	Mp(^{0}C)(found)	Mp(^{0}C)(lit)
						
1		R= CH_3	10	95	274-276	280-281[25]
2		R= CH_2Cl	15	85	178-180	187–189[25]
3		R= Ph	15	78	239-241	243–246[25]
4		R= Furyl	20	70	244-246	254–255[14b]
5			5	90	180-182	185-187[26]
6			25	80	76-78	78–80[26]
7			15	75	160-162	164–166[28]
8			10	92	170-172	171[27]
9			10	90	236-238	241–243[25]
10			10	85	248-250	256–257[26]
11			15	82	258-260	263-265[25]
12			20	80	150-152	154–156[26]

[a]**Reaction conditions: phenol (1 mmol), β-ketoesters (1.1mmol), SSA (0.05 g) and 80°C;** [b]**Isolated yield**

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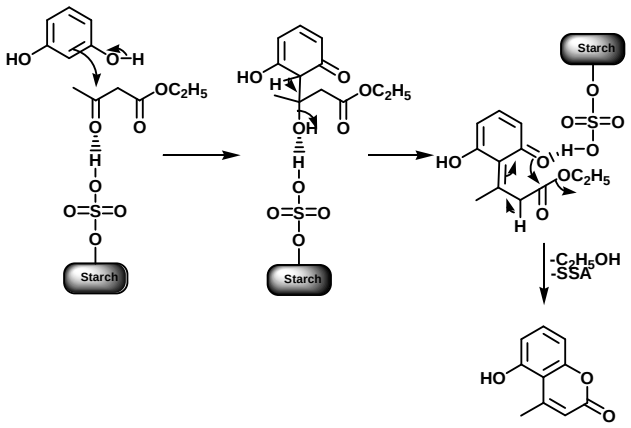
tution gave maximum yields at 80ºC in the minimum time. Methoxyphenols (entries 7,8) showed no detectable demethylation under the given conditions.Simple phenol without any substituents (entry 6) required longer reaction duration, as no electron-donating group is present. Similarly,1-naphthol (entry 12) requires longer reaction time, due to the presence of another phenyl ring. Togeneralize the protocol, we also attempted the condensationreaction using a further variety of β-ketoesters suchas ethyl 4-chloroacetoacetate, ethyl benzoylacetate and ethyl furoacetate (TABLE 3, entries 2-4). In allthese cases, good yields of the corresponding coumarinderivatives were obtained.

It is an established fact in the literature that Pechmann reaction proceeds throughtrans-esterification and intramolecularhydroxyalkylation, followed by dehydration. These three steps are all typical acid-catalyzed reactions. Therefore, the outcome of the Pechmann reaction depends very much on the Brønsted acidity of the catalysts. We have given a plausible mechanism for the Pechmann condensation of phenols andβ–ketoesters by starch sulfuricacid in Scheme 3.



Scheme 3

To show the merit of starch sulfuric acid in comparison with other reported catalysts, we summarized some of the results for the synthesis of coumarins via Pechmann condensation obtained by other workers. It is clear from TABLE 4 that the current method is simpler, efficient, and less time consuming for the synthesis of coumarin derivatives.

In conclusion, we describe a mild and convenient method for the preparation of some coumarins by the Pechmanncyclocondensation reaction of phenols and β-ketoesters using cheap, non-toxic, recyclable, easily available and solid support biodegradable acid catalyst under solvent-free conditions. Additionally, this new reaction might be a useful tool for high-throughput organic synthesis.

TABLE 4 : Comparison of the efficiencies of various catalysts used in the synthesis of coumarins via Pechmann condensation.

Entry	Catalyst	Conditions/T (ºC)	Time (min)	Yield (%)	Reference
1	Oxalic acid	Solvent-free/80	35–65	87–97	22
2	Silica-bonded S-sulfonic acid	Solvent-free/80	10–15	84–90	23
3	$ZrCl_4$	Solvent-free/25	5–10	90–98	25
4	LiBr	Solvent-free/75	15–90	66–92	28
5	$Cu(CH_3CN)_4PF_6$	Solvent-free/25	5–35	90–98	30
6	$PEG\text{-}SO_3H$	Solvent-free/25	10–60	78–91	32
7	starch sulfuric acid	Solvent-free/80	5–25	70–95	This paper

EXPERIMENTAL

All chemicals and analytical grade solvents were purchased from Merck or Fluka chemical company. Melting points of all coumarins were determined in open glass capillaries on Mettler9100 melting point apparatus.^{1}H NMRand spectra were recorded on a Bruker250MHzspectrometer. Infrared (IR) spectra were recorded using a 4300 Shimadzu FT-IR spectrometer. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. All products were characterized by comparison of their ^{1}H NMR, IR and mass spectra with thoseof authentic samples.

Preparation of starch sulfuric acid

To a magnetically stirred mixture of 5.0 g of starch in 20 mlof n-hexane, 1.0 g of chlorosulfonic acid (9 mmol) was added dropwise at 0 ºC during 2 h. HCl gas was removed from the reactionvessel immediately. After the addition was complete, the mixturewas stirred for 2 h. Then the mixture was filtered and washed with30

ml of acetonitrile and dried at room temperature to afford 5.25 gof starch sulfuric acid as a white powder. Sulfur content of thesamples by conventional elemental analysis, was 0.55mmol/g for starch sulfuric acid. The number of H^+ sites on the starch-SO_3H wasdetermined by acid–base titration was 0.50 meq/g. This value corresponds to about 90% of the sulfur content, indicating thatmost of the sulfur species on the sample are in the form of the sulfonic acid groups.

Typical experimental procedure for the synthesis ofcoumarins

A mixture of phenol (1 mmol), β-ketoester (1.1mmol) and starch sulfuric acid (0.05 g) was ground and heated to 80ºC. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and extracted with EtOAc (2×5mL).The solution was concentrated and the crude product was recrystallized from ethanol yielding each of purecoumarins.All the coumarin derivatives are well known in literature and were identified by comparison of their physical and spectral data.

4-(Chloromethyl)-5, 7-dihydroxy-2H-chromen-2-one:(2)

^{1}H NMR (250 MHz, DMSO-d_6): 5.11 (s, 2H, CH_2Cl), 6.25 (d, J = 2.60, 1H, ArH), 6.29(d, J = 2.60, 1H, ArH), 6.35 (s, 1H, C=CH), OH not observed, IR (KBr): 3157, 1655 cm^{-1}. EIMS: *m/z:* 226 (M^+).

5,7-Dihydroxy-4-phenyl-2H- chromen-2-one:(3)

^{1}H NMR (250 MHz, DMSO-d_6): 5.74 (s, 1H, C=CH), 6.15 (d, J = 2.55, 1H,ArH), 6.26 (d, J = 2.55, 1H,ArH),7.31–7.38 (m, 5H,ArH), OH not observed, IR (KBr): 3155, 1660 cm^{-1}. EIMS: *m/z:*255.

5,7-Dihydroxy-4-trifluoromethyl-2H-chromen-2-one:(4)

^{1}H NMR (250 MHz, DMSO-d_6): 6.24 (d, J = 2.62, 1H, ArH), 6.34 (d, J = 2.62, 1H, ArH), 6.50 (s, 1H, C=CH), OH not observed, IR (KBr): 3158, 1665 cm^{-1}. EIMS: *m/z*: 246 (M^+).

7-Hydroxy-4-methyl-2H-chromen-2-one:(5)

^{1}H NMR (250 MHz,DMSO-d_6): 2.65 (s, 3H, Me), 6.41 (s, 1H, C=CH), 6.91–7.72 (m, 3H, ArH), ArH3155, 1690 cm^{-1}. EIMS: *m/z*: 176 (M^+)

7-Methoxy-4-methyl-2H-chromen-2-one:(8)

^{1}H NMR ($CDCl_3$): 2.59(s, 3H, Me), 4.22 (s, 3H, OMe), 6.51 (s, 1H, C=CH), 7.01–7.51 (m, 3H, ArH), IR, (KBr): 1685 cm^{-1}. EIMS: *m/z*: 190 (M^+).

7,8-Benzo-4-methyl-2H-chromen-2-one:(12)

^{1}H NMR ($CDCl_3$): 2.71 (s, 3H, Me), 6.51 (s, 1H, C=CH), 7.50–8.91 (m, 6H, ArH), IR, (KBr): 1675 cm^{-1}. EIMS: *m/z*: 210 (M^+).

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