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Salicylic acid an efficient organocatalyst for synthesis of coumarins

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ABSTRACT. Various substituted coumarins were synthesized in high yield and purity by direct reaction of substituted phenol and β-keto esters in the presence of a catalytic amount of salicylic acid under solvent-free conditions. This method is simple, cost-effective, short reaction time, simple work-up procedure, and avoid the use of transition metals.

Keywords: Coumarins; Pechmann condensation; β-Keto esters; Phenol; Organocatalysis

INTRODUCTION

Coumarins (1-benzopyran-2-one) are chemical compounds in the benzopyrone class of organic compounds found in many plants. Coumarinic compounds are a class of lactones structurally constructed by a benzene ring fused to α-pyrone ring, and essentially possess-conjugated system with rich electron and good-charge-transport properties. They represent an important family of naturally occurring and synthetic oxygen containing heterocycles bearing a typical benzopyrone framework [1]. They are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals, and in the preparation of insecticides, optical brightening agents, dispersed fluorescent and tunable laser dyes [2]. Coumarin and its derivatives have numerous bioactivities

such as antimicrobial [3], antithrombotic [4], anticoagulant, antipsoriasis activity [5], anticancer[6], anti-HIV[7], antioxidant activity, antiproliferative activity [8], inhibitory activity on viral proteases [9], estrogen like effects[10], and central nervous system modulating activities[11]. Coumarins also act as intermediates in the synthesis of furocoumarins, chromenes, coumarones and 2-acetylresorcinols [12].

Literature data reveal that Coumarins were synthesized using Perkin reaction [13], Knoevenagel condensation [14], Reformatsky reaction [15], Intramolecular Wittig reaction [16] and Pechmann condensation [17]. The Pechmann synthesis of coumarins is reported by $BiCl_3$ [18], chloroaluminate ionic liquid [19], $HClO_4.SiO_2$[20], $Y(NO_3)_3.6H_2O$ [21], *p*-TSA [22], W/ZrO_2[23], Oxalic acid under microwave irradiation[24], $ZrCl_4$[25]. However, reported some of the methods have shortcomings like longer reaction time, low to moderate yield, expensive catalyst, catalyst preparation required, hazardous solvent and toxic solvent. To overcome these problems, there is the need to develop new chemical methodology for the synthesis of coumarin.

Salicylic acid (2-hydroxybenzoic acid) is a plant phenolic acid, which exists in willow bark, willow leaves as well as in poplar and birch trees [26]. The Salicylic acid has been successfully employed as the organocatalyst for organic transformations and the synthesis of some organic molecules, such as oxidation of alkenes [27], the Hantzsch multicomponent reaction [28], diarylmethanones [29], α-arylketones [30], hydrodeamination of aromatic amines [31], the Sonogashira-type cross-coupling [32], ring opening polymerization of ε-caprolactone [33], pyrrolidine derivatives [34], 2,3-dihydroquinazolin-4(*1H*)-ones[35], homoallyic alcohols [36], and 3, 3'-bis(indoly)methanes [37]. Here we are reporting salicylic acid as an organocatalyst for the synthesis of coumarin via Pechmann condensation between phenol and β-ketoester under solvent free conditions.

EXPERIMENTAL SECTION

All the reagents and chemicals were obtained from commercially available sources and used without further purification. Melting points were measured open capillary method and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-500 MHz spectrophotometer using $CDCl_3$ as the solvent and TMS as an internal standard. The purity of newly synthesized compounds and the development of the reaction were monitored by TLC on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light.

General procedure for preparation of coumarin:

A mixture of substituted phenols (5 mmol), ethyl acetoacetate (5 mmol) and salicylic acid (0.05 mmol) was taken in 50mL RB flask. The reaction mixture was heated at 100-110°C for respective time given in **Table 3**. The Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled at room temperature and neutralized with 10% sodium bicarbonate. The product was precipitated out from the reaction mixture. The precipitated product was filtered on the suction pump followed by washing with water and finally with 10mL ice cold ethanol. The crude product, which was purified by recrystallization in ethanol and afford the pure product. The structure of products was confirmed by IR, ^{1}HNMR, ^{13}CNMR and HRMS. All the products were known and their spectral data match with the literature.

RESULTS AND DISCUSSION

The Pechmann reported the condensation reaction between phenol and β-keto ester to afford coumarin in the presence of Lewis acid or Bronsted acid. Based on this concept, we have various organic acids in our hand like gallic acid, benzoic acid, salicylic acid, 4-amino benzoic

acid, cinnamic acid, pTSA, sulphanilic acid, 4-hydroxy benzoic acid, oxalic acid, 5-sulphosalicyclic acid, oxalic acid, succinic acid, citric acid, L-cystine, L-argenine. The condensation between phenol and ethyl acetoacetate were considered as a model reaction to find the best catalyst for this reaction. The model reaction was performed in 50mL RB flask using 5mmol of phenol and 5mmol of ethyl acetoacetate and acid catalyst 0.5mmol under solvent-free condition at 100-110ºC and results are summarized in **Table 1**.

From **Table 1** it is observed that salicylic acid was found an efficient catalyst for synthesis of coumarin with 95% yield. Phthalic acid, p-amino benzoic acid, cinnamic acid, sulphanilic acid, pTSA, p-hydroxybenzoic acid, oxalic acid, benzoic acid, 5-sulphosalicyclic acid, succinic acid gave the product in moderate to low yield and long reaction time. Gallic acid, L-argenine, L-cystine and citric acid did not give the desired product.

Table 1 Effect of oragno acid catalysis on pechmann condensation between phenol and ethyl acetoacetate[a]

Sr. No	Catalyst	product	Time in Hrs.	% Yield[b]
1.	Phthalic acid	**3a**	3:30	37
2.	Gallic acid	**3a**	12:00	NR[c]
3.	*p*-amino benzoic acid	**3a**	3:00	52
4.	Cinnamic acid	**3a**	3:20	44
5.	Sulphanilic acid	**3a**	7:00	18
6.	PTSA	**3a**	6:20	18
7.	Salicylic acid	**3a**	1:00	95

8.	*p*-Hydroxy benzoic acid	**3a**	3:10	32
9.	Oxalic acid	**3a**	6:00	18
10.	Benzioc acid	**3a**	3:10	60
11.	5-sulphosalicylic acid	**3a**	7:45	28
12.	L-argenine	**3a**	12:00	NR[c]
13.	L-cystine	**3a**	4:40	NR[c]
14.	Succinic acid	**3a**	10:15	30
15.	Citric acid	**3a**	12:00	NR[c]

[a] Reaction condition: phenol(5 mmol), ethyl acetoacetate (5 mmol), organic acid (0.05mmol), under solvent free at 100 – 110°C; [b] isolated yield; [c] NR No Reaction

Next we study the effect of solvent on this reaction. For searching the best solvent, we used model reaction between phenol and ethyl acetoacetate using salicylic acid as an acid catalyst in solvents like ethanol, water, n-hexane, THF, DCM, DMF, MeCN, $CHCl_3$ and solvent free condition at 100 – 110°C. The results of this study are summarized in **Table 2** and a solvent free condition was good for this reaction. Therefore, all further reactions were carried out using 0.05mmol of salicylic acid under solvent free conditions at 100 – 110°C

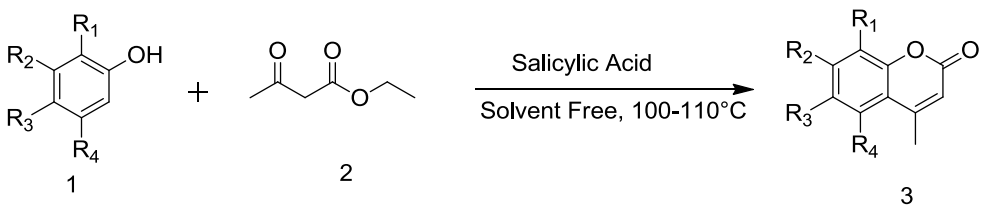
Table 2 Optimization of solvents for Pechmann condensation catalyzed by Salicylic acid[a]

Entry	**Solvents**	**Time in hrs**	**% Yield[b]**
1.	Chloroform	4:25	72
2.	Ethanol	6:00	No Reaction
3.	Toluene	4:20	75
4.	DMSO	5:20	22
5.	DMF	4:40	-

6.	Water	4:30	73
7.	Solvent Free	1:00	95

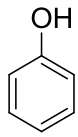
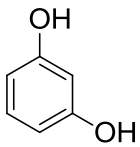
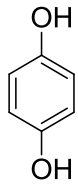
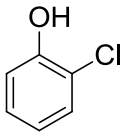
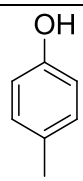
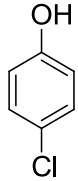
[a] Raction condition: phenol (5mmol), ethyl acetoacetate (5mmol), salicylic acid (0.05mmol), and 10 mL above solvent under thermal condition; [b] isolated yield

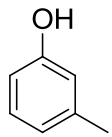
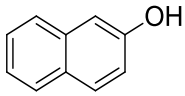
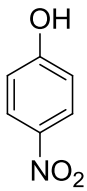
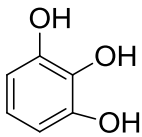
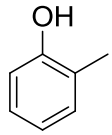
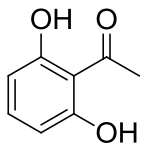
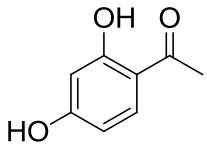
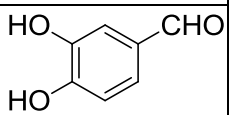
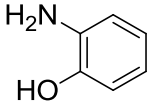
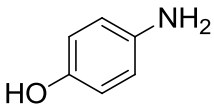
With the optimized reaction conditions in hand, the convenience of this method were well evaluated using a variety of phenol, so various substituted coumarins were synthesized with this simple approach (**Scheme 1**). The results are summarized in **Table 3**. The nature and position of functional groups on the phenyl ring affected the reaction time and yield of product. The results indicated that phenol containing functional groups such as methyl, methoxy, amino group afforded high yield of product. Nitro, aldehyde and ketone group afforded moderate yield of product

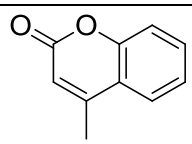


Scheme 1. Synthesis of coumarin

Table 3 Synthesis of substituted coumarins using salicylic acid as catalyst

Sr. No	Phenols	Product	Time (min)	% Yield[b]	M.P[0]C
1.		**3a**	60	95	110-120
2.		**3b**	45	92	182-190
3.		**3c**	120	89	240
4.		**3d**	140	65	160-165
5.		**3e**	40	92	240-245
6.		**3f**	100	84	187-190

7.		**3g**	80	89	192
8.		**3h**	45	90	155
9.		**3i**	240	40	157-160
10.		**3j**	130	68	236-240
11.		**3k**	300	62	120-122
12.		**3l**	190	67	145-147
13.		**3m**	230	72	167-168
14.		**3n**	400	45	192-194
15.		**3o**	270	40	167-170
16.		**3p**	110	78	190-195

17.		**3q**	270	77	124-126

[a] Reaction condition: phenol (5 mmol), β-ketoester (5 mmol), salicylic acid (0.05 mmol) under solvent free condition heat at 100-110^{0}C; [b] Isolated yield

CONCLUSIONS

Here, we reported the use of salicylic acid an efficient catalyst for Pechmann condensation reaction between substituted phenol and ethyl acetoacetate under solvent free media. The merits of this method are excellent yield, good purity, hazardous chemical avoided, simple work-up, no environmental hazards and easy available and inexpensive catalyst, moderate to high yield.

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