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One pot synthesis of coumarin derivatives via pechmann condensation catalyzed by pTSA under solvent free conditions and antifungal activities of the compounds

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Abstract
A rapid and efficient solvent free synthesis of coumarin derivatives by Pechmann condensation reactions of substituted phenols with β keto ester using para toluene sulphonic acid (pTSA) as a catalyst. Synthesis of coumarin derivatives has been occurred with the help of grinding techniques and comparison has been done with conventional method in which 73% H_2SO_4 has been used. Unique/key features of this grinding method includes short reaction time, ecofriendly, good to excellent yield, non toxic and easy to handle. These compounds were screened for their antifungal activity. These synthesized compound were characterized by IR, ^{1}HNMR and melting point.

Keywords: coumarin; solvent free; pTSA; grinding technique and antifungal activity

1. Introduction
Coumarin is a heterocyclic compound, which play an important role in the realm of natural products and synthetic organic chemistry. Coumarins are also found in many plants. Coumarins are synthesized by Pechmann (Pechmann and Duisberg, 1884) [2], Perkin, Witting and Reformastsky reaction (Brufola *et al*., 1996) [1]. Among these, the Pechmann reaction has been the most widely used method. Since it proceeds from very simple starting materials and gives good yield of variously substituted coumarins. Coumarins are classified as a member of the benzopyrone family all of which consist of a benzene ring joined to a pyrone ring. Coumarins owe their class name to 'Coumarou', the vernacular name of the tonka bean (Dipteryxodorata Wild, Fabaceae), from which coumarin, it was isolated in 1820 (Bruneton, 1999) [4]. Coumarins comprise a very large class of compounds found throughout the plant kingdom. They are found at high levels in some essential oils, particularly cinnamon bark oil (7,000 ppm), cassia leaf oil (up to 87,300 ppm) and lavender oil. Coumarin is also found in fruits (e.g. bilberry, cloudberry), green tea and other food such as chicory (Lake, 1999) [5]. Coumarins are naturally occurring compound and found in various plants in large quantities. Coumarins are biologically active compound used in various aspects of cosmetics, medicines and pharmaceutical industries (Muley *et al.* 1979) [6]. They are recently used in anti-tuberculosis anti- HIV and active drug (Kirkiacharian *et al.* 2002) [7]. Coumarin and its derivatives are biologically and pharmacologically active compounds with a wide range of properties. Owing to their diverse pharmacological properties and natural sources of origin, coumarin play an important role in the synthesis of natural products (Chen *et al.* 2012) [8]. Coumarin find widespread application in a broad range of fields, including foods, cosmetics, as dispersive fluorescent laser dyes, as light activated compounds in the fields of medicine, and as anticoagulants in the production of pesticide (Weigt *et al.* 2012) [9]. Now a days, organic synthesis has been oriented towards the development of new environmentally benign procedures so as to achieve the goals of green chemistry (Tanka *et al.* 2000 and Gu, 2012) [10, 11].

2. Materials and method
2.1 Synthesis of compounds
Method A (Grinding method)
A mixture of substituted phenols and ethyl acetoacetate was ground with dry p-toluene sulphonic acid in a mortar by pestle for few minutes untill the color of the reaction mixture has

been taken place. The reaction mixture was kept at room temperature for 30 minutes. The completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ice cold water. The solid thus separated out was filtered, washed with water and recrystallized from ethanol to afford compound.

Method B (Conventional method)
A mixture of substituted phenols and ethyl acetoacetate has been taken in round bottom flask in ice bath. To this mixture sulphuric acid (15 ml; 73%) was added dropwise with constant stirring, keeping the temperature below 5°C and reaction mixture left overnight at room temperature. It was poured over crushed ice and the solid that separated out was filtered, washed with water and dried. It was crystallized from ethanol to give compound.

Result
2H-1-benzopyran-2-ones (coumarins) are very versatile classes of heterocycles and intermediates for the preparation of organic compounds due to their variety of biological activities. For the preparation of these compounds and their derivatives, different organic solvents and reagents are being used which are quite hazardous to environment and human health due to their volatile nature. Since last few years attempts has been made successfully for ecofriendly synthesis viz. microwave irradiation synthesis and synthesis by grinding methods. In present studies, synthesis of above mentioned classes of compounds has been carried out by grinding methods. All the synthesized compounds were also evaluated against *Aspergillus awamori* and *Sclerotium rolfsii* fungi to test their efficiency and to establish structure activity relationship (SAR). This chapter is divided into two sections which are described here.

Synthesis and characterization of compounds
2.1.1 7-hydroxy-4-methyl-2H-1-benzopyran-2-one (6)
IR (KBr): 3280 (OH), 1715 (C=O), 1380 (C-CH_3)
^{1}HNMR ($CDCl_3$) : 2.35 **(**s, 3H, C_4 - CH_3); 6.04 (s, 1H, C_3 - H); 6.78 (s, 1H, C_8 - H); 6.81 (d, J = 8.5 Hz, 1H, C_5 -H), 7.52 (d, J = 8.5 H z, 1H, C_6-H

2.1.2 5, 7 - dihydroxy-4 methyl-2H-1- benzopyran-2-one (7)
IR (KBr): 3320 (OH), 1690 (C = O), 1375 (C-CH_3)
^{1}HNMR ($CDCl_3$): 2.38 (s, 3H, C_4 -CH_3); 6.01 (s, 1H, C_3 -H) 6.65 (s, 1H, C_8 -H); 6.75 (s, 1H, C_6 -H)

2.1.3 4, 5, 7-trimethyl- 2H-1- benzopyran -2-one (8)
IR (KBr): 1716 (C = O), 1490 (C-CH_3)
^{1}H NMR ($CDCl_3$): 2.17 (s, 9H, 3xCH_3), 6.74 (s, 1H, C_3-H), 6.82 (s, 1H, C_6-H), 6.97 (s,1H,C_8-H).

2.1.4 4, 5, 6 -trimethyl-2H-1-benzopyran-2-one (9)
IR (KBr): 1690 (C = 0) 1360 (C -CH_3)
^{1}HNMR ($CDCl_3$): 2.18 (s, 9H, 3xCH_3), 6.61 (s,1H,C_3-H)
Analysis found: C,73.17; H, 7.31%; $C_{12}H_{12}O_2$
Required: C, 72.9; H, 7.10%

2.1.5 7-benzoyloxy-4-methyl-2H -1-benzopyran-2-one (10)
IR (KBr): 1738 (ester, C=O); 1720 (coumarin C=O)
^{1}HNMR ($CDCld_3$): 2.46 (s, 3H, CH_3); 6.29 (s, 1H, C_3 -H); 7.20 -8.20 (m, 3H, Ar-H) Molecular formula, $C_{17}H_{12}O_3$ Required: C,76.98; H,4.10%

2.1.6 5, 7-dibenzoyloxy-4-methyl-2H-1-benzopyran-2-one (11)
IR (KBR): 1735 (ester, C=O), 1690 (coumarin, C=O) Molecular formula, $C_{24}H_{16}O_6$ Required: C, 73.98; H4.10%

2.1.7 3–acetyl -2H-1- benzopyran-2-one (13)
A mixture of salicylaldehyde (12) (2.44g; 20m mole), ethyl acetoacetate (5) (2.60g; 20 m mole) dry pyridine (20 ml) and piperidine (0.3 ml) in a 100 ml round bottom flask was heated on oil bath at 140°C for 4 hrs. The Completion of reaction was monitored by TLC. The reaction mixture was cooled and poured on ice water and neutralized with conc. HCl. The solid thus separated out was filtered, washed with water and crystallized from ethanol to give 3 -acetyl- 2H - 1-benzopyran - 2 - one (13);
Yield: 85%
M.P.: 117-119 °C
IR(KBR): 1705 (C=O)

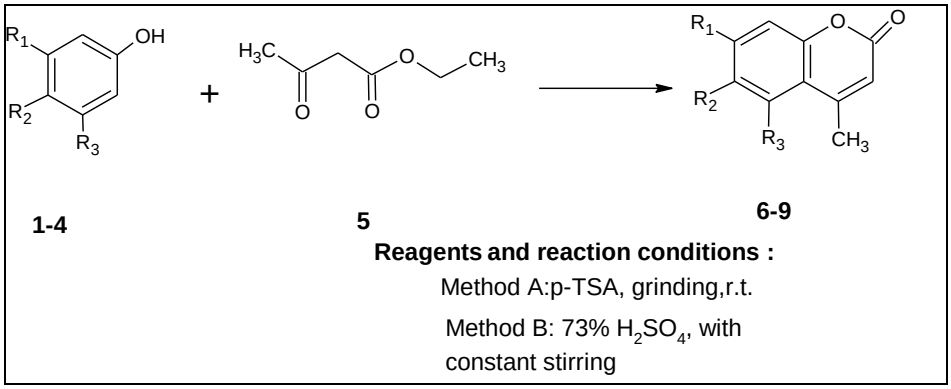
2.1.8 3-(-2-bromoacetyl)-2H-1-benzopyran-2-one (14)
Method A: (Grinding by NH_4Br-$(NH_4)_2S_2O_8$
A mixture of 3- acetyl - 2H - 1 - benzopyran - 2 - one (**13**) (0.38g; 20 m mole), Ammonium bromide (0.4g, 40m mole) and ammonium persulphate (1.1g; 5.0m mole) with 10 drops of water was ground in a mortar by a pestle at room temperature for 15 min. The completion of the reaction was monitored by TLC. The reaction mixture was diluted with ice cold water. The solid that separated was filtered, washed with water and recrystallized from ethanol to afford 3-(-2-bromoacetyl)-2H-1-benzopyran-2-one (14).
Yield: 91%,
M.P.: 165-66°C
IR (KBr): 1732, 1675 (C = O); 765 (C -Br)
^{1}H NMR ($CDCl_3$): 4.27 (s, 1H, C_4-H), 6.98 (s, 1H, C_4-H), 7.01-7.23(m, 4H, Ar-H) Molecular formula, $C_{11}H_7O_3Br$ Required: C, 49.43; H, 2.62%

Method B (Grinding by NBS-$(NH_4)_2S_2O_8$
A mixture of 3 - acetyl - 2H - 1 benzopyran - 2 - one (**13**) (0.38g; 20m mole), NBS (3.8g; 20 m mole) and ammonium persulphate (1.1g; 5.0m moles) with few drops of water was ground in mortar by pestle at room temp. for 10 minutes. It was worked up as described above to give 3-(-2-bromoacetyl)-2H-1-benzopyran-2-one (14).
Yield: 93%,
M.P.: 165-66°C
IR (KBr): 1732, 1675 (C = O); 765 (C -Br)
^{1}H NMR ($CDCl_3$): 4.27(s, 1H, C_4-H), 6.98 (s, 1H, C_4-H), 7.01-7.23 (m,4H,Ar-H) Molecular formula, $C_{11}H_7O_3Br$ Required: C,49.43; H,2.62

3.1 Synthesis of 7-hydroxy-/5,7-dihydroxy-/4,5,7-trimethyl-/4,5,6-trimethyl-2H-1-benzopyran-2-ones (6-9)
Method A: (Grinding method)
Synthesis of substituted-2H-1- benzopyran-2-ones (6 - 9) have been carried out by grinding a mixture of resorcinol (1), Phloroglucinol (2), 3,5-dimethylphenol (3), 3,4 dimethylphenol (4) and ethyl acetoacetate (5) with p-toluene sulphonic acid (p -TSA) in a mortar by pestle (Scheme 4.1). The physical and analytical data have been given in (table 3.1)

Method B: (Conventional method)
Resorcinol (1), Phloroglucinol (2), 3, 5- dimethyl phenol (3) and 3, 4-dimethyl phenol (4) when reacted with ethyl

acetoacetate (5) in equimolar ratio in presence of 73% sulphuric acid afforded -7-hydroxyl-4-methyl-2H-1-benzopyran-2- one (6), 5, 7- dihydroxy-4-methyl-2H-1-benzopyran-2-one (7), 4, 5, 7-trimethyl-2H-1-benzopyran-2-one (8) and 4,5,6-trimethyl-2H-1-benzopyran-2-ones (9) in good yields (Scheme 4.1). The physical and analytical data of these compounds (6-9) have been given in (table 3.1).



Compound No.	R_1	R_2	R_3
1, 6	OH	H	H
2, 7	OH	H	OH
3, 8	CH_3	H	CH_3
4, 9	H	CH_3	CH_3

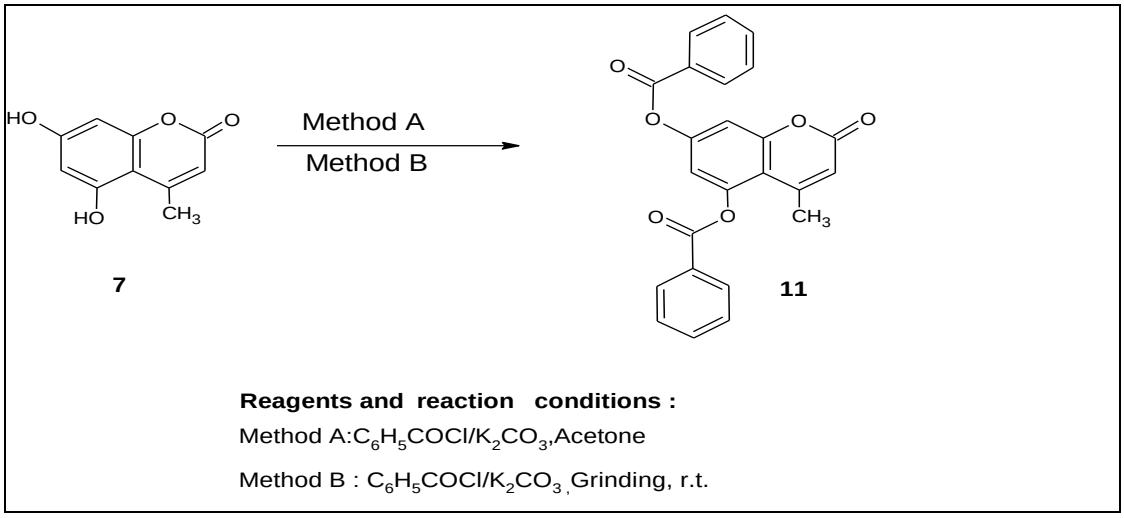
Scheme 3.1 Synthesis of 7-hydroxy-/ 5, 7-dihydroxy-/ 4, 5, 7-trimethyl-/ 4, 5, 6-trimethyl -2H-1-benzopyran-2- ones **(6-9)** by grinding and conventional method.

Table 3.1: Physical and analytical data of substituted -2H-1- benzopyran-2-ones (6 - 9).

Compound No.	Conventional method			Grinding method		
	Time (Hr.)	Yield (%)	m.p. (ºC)	Time (min.)	Yield (%)	m.p. (ºC)
6	Left overnight	85	183-184	12	86	183-184
7	Left overnight	81	298-299	10	83	298-300
8	Left overnight	87	173-174	12	89	172-174
9	Left overnight	80	175-176	12	86	175-176

3.2 Synthesis of 7-benzoyloxy-/5, 7-dibenzoyloxy-4-methyl-2H-1-benzopyran-2-ones (10, 11)

Benzoylation of 7-hydroxy-4-methyl-2H-1-benzopyran-2-one (6) and 5,7-dihydroxy-4-methyl-2H-1-benzopyran-2-one (7) with benzoyl chloride by conventional as well as grinding method has been carried out to afford compounds 10 and 11 respectively (Scheme 3.2). Details of physical and analytical data have been given in (table 3.2).



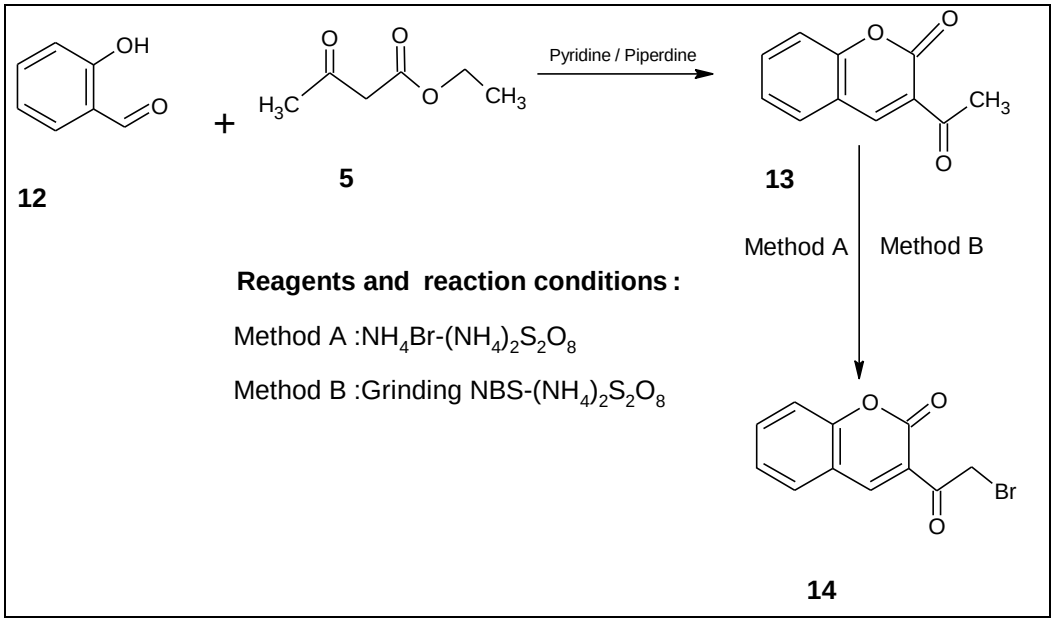
Scheme 3.2 Synthesis of 7-benzoyloxy-4-methyl-/5,7-dibenzoyloxy-4-methyl-2H-1-benzopyrans (10, 11) has been carried out by conventional and grinding method.

Table 3.2: Physical and analytical data of 7-benzoyloxy-/ 5, 7-dibenzoyloxy-4-methyl-2H-1-benzopyrans (10,11).

Compound No.	Conventional method			Grinding method		
	Time (Hrs.)	Yield (%)	M.P. (ºC)	Time (Min.)	Yield (%)	M.P. (ºC)
10.	4	83	117-18	5	84	117-18
11.	4	81	126-27	7	83	126-27

3.3 Synthesis of 3-acetyl-2H-1-benzopyran-2-one and 3-(2-bromoacetyl)-2H-1-benzopyran-1-one (13-14).

In this reaction salicylaldehyde (12) and ethyl acetoacetate (5), dry pyridine and piperidine were refluxed on oil bath at 140 ºC temperature. The reaction mixture was cooled and poured on ice water and neutralized with HCL, worked up as usual to afford compound 13 (Scheme 4.3). Bromination of compound (13) in presence of ammonium bromide-ammonium persulphate and NBS afforded 3-(2-bromoacetyl)-2H-1-benzopyran-2-one (14) in good yield (Scheme 3.3). The physical and analytical data of above compounds have been given in table 3.3



Scheme 3.3 Synthesis of 3-Acetyl-2H-1- benzopyran-2-one (13) and 3-(2-bromo acetyl-2H-1-benzopyran-2-one (14).

Table 3.3: Physical & analytical data of 3-acetyl-2H-1-benzopyran-2-one (13) and 3-(2 -bromoacetyl-2H-1-benzopyran-2-one (14).

Compound No.	NH_4Br / $(NH_4)_2S_2O_8$			$NBS/(NH_4)_2S_2O_8$		
	Time (min)	Yield (%)	M.P. (ºC)	Time (min)	Yield (%)	M.P. (ºC)
14	15	91	165-68	10	93	165-68

4. Bioevaluation The synthesized compounds have been screened for their antifungal activity against *Aspergillus awamori* and *Sclerotium rolfsii* fungi by poisoned food techniques (Tuit, 1968) at 10, 50, 100 and 200 µg/ml concentrations. The data are presented in (table 4.1)

Table 4.1 Antifungal activity of 7-hydroxy-/ 5, 7-dihydroxy-/4, 5, 7-trimethyl-/4, 5, 6 -trimethyl-2H-1-benzopyran-2-ones (6-9) and related compounds (10, 11, 13, 14)

%age growth inhibition								
Compound no.	Fungi							
	Aspergillus awamori (con.) µg/ml				*Sclerotiun rolfsii* (con.) µg/ml			
	10	50	100	200	10	50	100	200
6	9	17	25	32	8	15	21	27
7	11	20	24	33	9	14	22	28
8	8	16	26	30	6	9	12	18
9	12	20	27	36	12	18	25	31
10	20	28	39	54	7	14	21	29
11	10	19	26	32	12	20	28	34
13	11	18	26	31	10	19	27	35
14	9	16	23	30	8	16	23	31

Conclusion

We have explained a novel methodology based on the grinding technique for the synthesis of substituted coumarin in ecofriendly manner. The special advantages of this method provide a one pot synthesis strategy, ecofriendly mechanism, easy and simple work up of the products. The synthesized compounds have been screened for their antifungal activity against *Aspergillus awamori* and *Sclerotium rolfsii* fungi.

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