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Environmentally positive and energy proficient synthesis of coumarin by the Pechmann reaction via microwave irradiation

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Coumarins have been synthesized by microwave irradiation in solvent free reaction condition, and excellent yields of coumarins have been obtained with high purity. Pechmann method is a revere reaction which is one of the easy and forthright scheme used to produce coumarins. IR and NMR spectroscopy have been used to confirm the successful synthesis of coumarins by Pechmann reaction. Use of commercially accessible low-cost catalyst makes this procedure very fascinating from a cost-effective point of view. An easygoing and capable microwave synthesis technique has been evolved for condensation of β-ketoester and substituted phenol in the presence of catalytic quantity of oxalic acid at extensive temperature range to give the resultant substituted 4-methyl-2*H*-chromen-2-one in elevated output.

Keywords: β-Ketoester, Microwave irradiation, Oxalic acid, Pechmann condensation, Substituted phenols

Coumarins are placed under the class benzopyrones of heterocyclic compounds having physiological and pharmacological activities. They are widespread in plants, they are also isolated from tonka bean, which also gave them their name (from a French comarou)[1]. Various natural products such as organic and medicinal useful compounds contain coumarins as main structural unit[2]. Usually they are used as linker in agrochemicals, cosmetic and drugs[3] and in the synthesis of insecticides, optical brightening agents[4], dispersed fluorescent and tunable dye lasers[5]. Coumarins are recognized to have several biological activities such as antifungal, platelet aggregation[6], antibacterial[7], anticancer[8], antioxidative properties[9], anticoagulant, anhelmentic, hypnotic[4], inhibitory of steroid 5- reductase[10], anti-inflammatory and anti-HIV activities[11]. Additionally coumarins act as main component of fluorocoumarins, chromenes, coumarones, and various medicinal plant[12]. These properties make coumarins especially attractive target for organic chemists to prepare a number of designs of bioactive compounds.

Microwave irradiation is used as a tool for proficient synthesis of various compounds. The solvent-free conditions make reaction time shorter which is suitable for the synthesis of heterocyclic compounds[13-17].

In the present work coumarin derivatives have been synthesized in solvent free conditions starting from substituted phenols along with methyl acetoacetate and ethyl acetoacetate in the presence of catalyst. Coumarin and its derivatives can be synthesized by various schemes that consist of Perkin reaction[18], Knovenegal reaction[19], Wittig reaction[20], Pechmann reaction[21], and Reformatsky reaction[22]. Between these reactions Pechmann scheme is mainly used for the research of substituted coumarins as it achieve with very straightforward primary resources and gives excellent yields of coumarin derivatives.

Traditionally the route consists of the condensation of phenols with *β*-ketoesters in the presence of a range of reagents to produce excellent yields of 4-substituted coumarins[23]. Synthesis of heterocyclic compounds by microwave assisted process is widely adopted these days because of convenient operating condition. Preparation of heterocyclic compound have been reported in the presence of promoters, like polyaniline sulfate salt[24,25], heteropoly acids[26], zeolites[27], amberlyst 15[28], montmorillonite clay[29], nafion-H[30], potassium dihydrogen phosphate[31], $Zn[(L)\text{-proline}]_2$ catalyst[32], FeF_3 and various solid acid catalysts[33-37]. Large amount of solid support (promoters) used in the reaction results in the production of huge quantity of poisonous waste. Furthermore Pechmann reactions have also been conducted by using $CuFe_2O_4$ nano particles[38], chloro aluminate ionic liquids[39-43], melamine formaldehyde resin supported H^+ ion catalyzed[44], ionic liquid

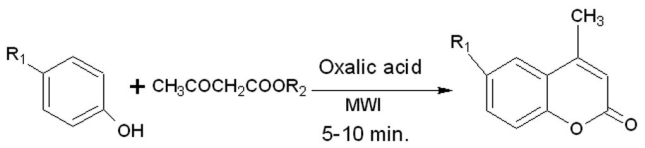
catalyzed[45], but a few of these reported methods have various disadvantages such as moisture reactive or extremely harmful to atmosphere, unpleasant experimental process and reagents are high-priced as well. A mild and effective catalyst for the synthesis of coumarins is very desirable. Performing organic reactions in aqueous medium is paying interest because of useful water properties. It will be considerably harmless, economical, non-hazardous and environmental friendly as compared to organic solvents[46]. In addition, the catalyst system can be reused by means of the water soluble catalyst and the insoluble products can be separated by easy filtration. In continuation of this newly incorporated change our investigation further proposes improvement for novel synthetic methodology. One-pot condensation of phenol derivatives with β- ketoesters in presence of oxalic acid were used for synthesis of coumarins. This is an innovative, suitable and proficient method for the synthesis of coumarins.

Experimental Section

General method used for the synthesis of coumarin derivatives

A combination of phenol derivatives (10 mmol) and β- ketoester (10 mmol) with oxalic acid as a catalyst (1 g) in the absence of solvent was stirred at room temperature and performed inside a domestic microwave oven for an appropriate time (5-10 min) (Scheme 1). The progress of the reaction was checked by TLC. After finishing point of the reaction, the resultant crude product was filtered and then recrystallized with hot ethanol-water to get pure product. The physical facts (MP, IR, NMR) of these well-known synthesized compounds from our synthetic routes were found to be the similar among those reported in the literatures[31-33,47,48].

Synthesized coumarin derivatives were evaluated for physical properties such as physical state and melting point. All chemicals used were of analytical grade. The melting points of the synthesized derivatives were determined through open capillary tube method using paraffin bath and are uncorrected.



Scheme 1 — Pechmann condensation

All the synthesized derivatives were subjected to TLC analysis on silica gel G plates using benzene-acetone (5:5) as developer detected by iodine vapors. The chromatoplates were prepared by using silica gel G. All the synthesized compounds were subjected to IR spectroscopic analysis by using Shimadzu Fourier Transform Infra Red spectrophotometer (KBr in cm^{-1}) (School of Pharmaceutical, RGPV Bhopal M.P.). ^1H NMR analysis of respective samples of the synthesized coumarin derivatives was carried by ^1H NMR spectrometer and peaks are expressed in terms of ppm (Bruker AMX200 and Bruker DRX400 instrument) (IIT Delhi). Microwave irradiations were carried out on domestic microwave oven (Bajaj 700 W, 2450 MHz) (Table 1).

Results and Discussion

The oxalic acid holds the Pechmann reaction in gentle reaction conditions. The Pechmann reaction was carried out employing microwave irradiation, in the presence of oxalic acid as a catalyst. The use of the catalyst effectively assist the reaction at low reaction temperature in solvent-free conditions. This condensation reaction not only conserve the straightforwardness of the Pechmann reaction but also gives excellent yields of the coumarin derivatives and to a great level decreases environmental pollution. Spectral analysis of products supported the success of the MW-mediated condensation reaction.

Spectral data of coumarin derivatives

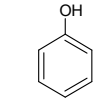
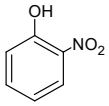
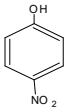
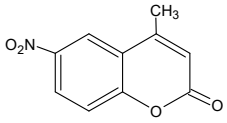
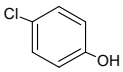
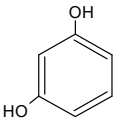
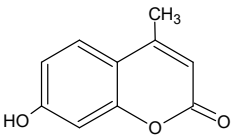
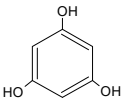
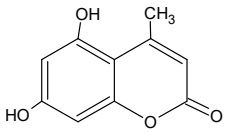
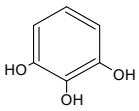
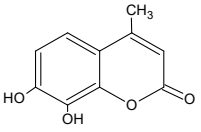
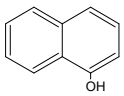
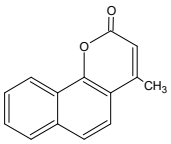
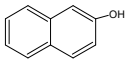
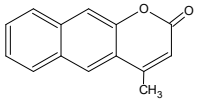
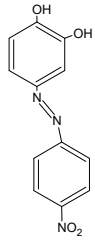
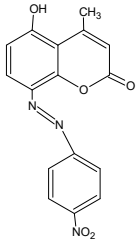
4-Methyl-6-nitro coumarin (Entry 3): IR (υ in cm^{-1}): 3323.35 (-OH str.)1514, 1494 (aromatic ring), 1610 (C=O), 1589, 1334 (-NO_2), 1284, 1217, 1163 (C-O); ^1H NMR: δ 2.362 (s, 3H, CH_3), 7.601 (d, 1H, H_7), 6.8 (dd, 1H, H_6) 3.339 (1H, H_3 aromatic).

7-Hydroxy-4-methyl coumarin (Entry 5): IR (υ in cm^{-1}): 3487 (-OH str.), 1516, 1452 (aromatic ring), 1666 (C=O), 1275, 1072 (C-O); ^1H NMR: δ 2.335 (s, 3H, CH_3), 10.502 (S, 1H, C_7OH), 6.085 (S, 1H), 6.685 (d, 1H), 6.798 (dd, 1H), 7.561 (d, 1H).

5,7-Dihydroxy-4-methyl coumarin (Entry 6): IR (υ in cm^{-1}): 3136 (-OH str.), 1668 (C=O), 1236, 1159, 1028 (C-O); ^1H NMR: δ 2.493 (s, 3H, CH_3), 5.670 (s, 1H, CH), 6.17 (d, 1H), 2.63 (d1H).

7,8-Dihydroxy-4-methyl coumarin (Entry 7): IR(υ in cm^{-1}): 692, 719, 1004, 1058, 1186 (C-O), 1384, 1433, 1512, 1597, (aromatic ring), 1645, (C=O), 2918, 3215, 3406; ^1H NMR: δ 2.334 (s, 3H, CH_3), 6.105 (s,1H), 6.824 (d,1H), 7.097 (d, 1H), 9.832 (brs,1H).

Table1 — Synthesis of coumarins using Pechmann condensations of phenols with ethyl acetoacetate/methyl acetoacetate in catalytic amount of oxalic acid

Entry	Phenol	Product	Reaction temp. (°C)	Reaction time (Min.)	Yield (%)	m.p. (°C)	R_f value
1		–	110-140	10-15	–	–	–
2		–	110-140	10-12	–	–	–
3			110-140	10	49	135-140	0.86
4		–	110-140	10-12	–	–	–
5			110-140	7	68	180-182	0.62
6			110-140	6	70	295-300	0.55
7			110-140	5	47	136-140	0.60
8			110-140	12	39	150-155	0.87
9			110-140	10	57	179-182	0.86
10			110-140	5	70	185-190	0.44

4-Methyl-2-*H* benzo coumarin (Entry 8): IR (υ in cm^{-1}): 3070, 1716, 1681, (C=O), 1593, 1560, 1471 (aromatic ring), 1273, 1082 (C-O); ^{1}H NMR: δ 2.512 (s, 3H, CH_3), 6.865 (s 1H), 7.295-7.718 (m, 4H, aromatic) 7.723-8.367 (m, 1H, aromatic).

4-Methyl-2-*H* benzo coumarin (Entry 9): IR (υ in cm^{-1}): 1629 (C=O), 1593, 1575, 1475 (aromatic ring), 1276, 1083 (C-O); ^{1}H NMR: δ 2.51 (s, 3H, CH_3), 6.486 (s, 1H), 7.262 (d, 1H), 7.318 7.601 (m, 2H), 7.723 (d, 1H).

4-(*p*-Nitro phenyl azo)-5-hydroxy-4-methyl coumarin (Entry 10): IR (υ in cm^{-1}): 3456 (NH), 3068 (-OH str.), 1625 (C=O), 1593, 1506 (aromatic ring), 1448 (N=N), 1220, 1199 (C-N); ^{1}H NMR: δ 2.507 (s, 3H, CH_3), 6.386-8.380 (m, 5H), 12.165 (s, 1H, -OH), 10.940 (s, 1H, NH).

Conclusion

When the reaction is conducted in Microwave method in solvent free condition the Pechmann reaction being an exothermic reaction liberates exhorbitant energy which is substantial energy for commencement of the whole reactions. The presented research is an attempt towards "Green Chemistry" for synthesis of biologically important coumarins. The significant aspect of our research is the development of environmentally gentle process which reduces the use of toxic chemicals and makes the synthetic chemistry more eco-friendly to the environment.

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