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Synthesis of coumarins via Pechmann reaction using $Cr(NO_3)_3$. $9H_2O$ as a Catalyst under microwave irradiation

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ABSTRACT

$Cr(NO_3)_3$. $9H_2O$ is used as an efficient catalyst in the reaction of phenols with ethyl acetoacetate (via Pechmann reaction) in solvent-free media leads to the formation of coumarin derivatives using microwave irradiation in excellent yields with good purity.

Keywords: Coumarins, $Cr(NO_3)_3$. $9H_2O$**,** Pechmann reaction, microwave irradiation

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INTRODUCTION

Coumarin and its derivatives have attracted great interest because of their importance in the synthetic organic and medicinal chemistry. Coumarins are naturally occurring polyphenolics and its derivatives form an important class of benzo-pyrones which are distributed widely in plants, fungi and bacteria. Coumarin and its derivatives possess significant biological activities such as antitumor [1], anti-HIV [2], antioxidative [3], antimicrobial [4], anticancer[5] activity, antifungal, anticoagulant, antispasmodic and anticholerostatic activity including HIV-1–specific reverse transcriptase inhibitor properties [6-11].

Coumarins have been synthesized by several routes, including Pechmann [12], Perkin [13], Knoevenagel [14], Reformatsky [15], Wittig reactions [16] and by flash vacuum pyrolysis [17]. Among these, the Pechmann reaction is the most widely used method, because the reaction involves the use of simple starting materials like phenols and ß-keto esters in the presence of acidic conditions. Various acids have been used to carry out this reaction [18]. The Pechmann reaction is one of the most widely applied method for synthesizing coumarins using different catalysts such as Amberlyst ion-exchange resins[19], montmorillonite K-10[20], nafion resin silica nanocomposites [21], nanocrystalline sulfated-zirconia[22], furic acid[23], trifluoroacetic acid[24], phosphorus pentoxide[25], sulfonic acid functionalized SBA-15 silica [26], $ZrCl_4$ [27] and $TiCl_4$ [28]. However, most of these procedures require difficulties in workup, harsh reaction conditions, a large amount of catalyst, long duration, microwave irradiation, and high temperature to complete the reaction. Therefore, the search continues for a better catalyst for the synthesis of coumarins. Herein, we have focused our attention on $Cr(NO_3)_3$. $9H_2O$ as catalyst in the synthesis of coumarins using microwave irradiation.

MATERIALS AND METHODS

Melting points were determined in open-end capillaries and are uncorrected. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz. Chemical shifts are given in ppm (δ) and spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets.

General Procedure for the Preparation of Coumarins:

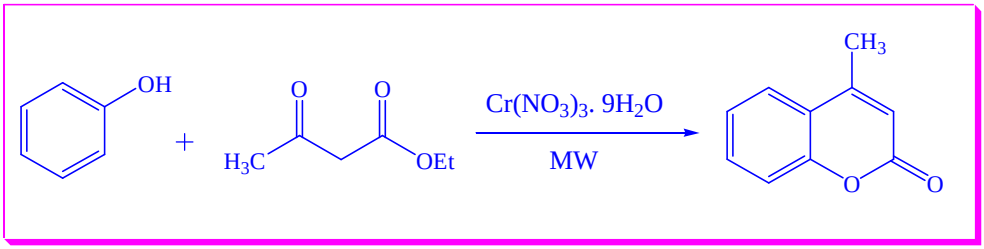
To a mixture of the phenolic compound (10 mmol) and ethyl acetoacetate (1.3g 10 mmol), $Cr(NO_3)_3$. $9H_2O$ (10 mmol) was added and the mixture was inserted in a microwave oven and heated at 450 W for the appropriate time (TLC). After completion, the reaction mixture was cooled to room temperature and poured into crushed ice, stirred for 10-15 min. The resultant product was collected by filtration under suction, washed with ice cold water (30 ml) and then recrystallized from hot ethanol to afford pure coumarins as colorless prisms.

RESULTS AND DISCUSSION

To study the feasibility of the $Cr(NO_3)_3$. $9H_2O$ catalyzed Pechmann condensation, the reaction of phenolic compound with ethyl acetoacetate was selected as a model. The results indicated that only 10 mmol of $Cr(NO_3)_3$. $9H_2O$ could effectively catalyze the reaction which could be completed under microwave irradiation. Comparing with other catalysts $Cr(NO_3)_3$. $9H_2O$ has some advantages such as ease of handling, low catalyst loading. Any excess of $Cr(NO_3)_3$. $9H_2O$ beyond this loading did not show any substantial improvement in the yield. So 10 mmol of $Cr(NO_3)_3$. $9H_2O$ chosen as the optimal loading of the catalyst. 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 (scheme 1).

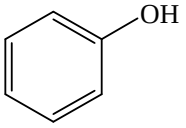
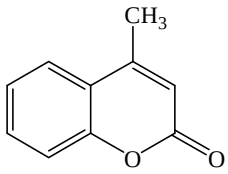
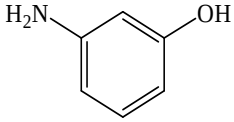
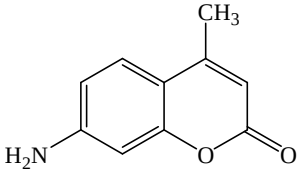
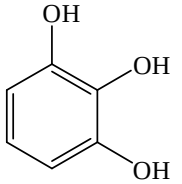
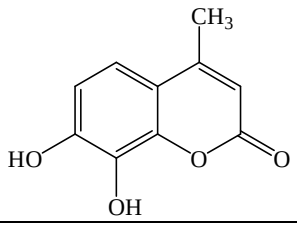
As indicated in Table 1, the reaction works easily for a vast range of phenols with electron-donating groups with ethyl acetoacetate and reaction does not give good yields in the case of phenols with electron withdrawing groups like nitro (Table 1, entries 9–10).

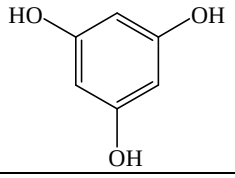
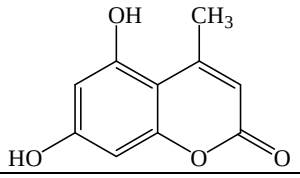
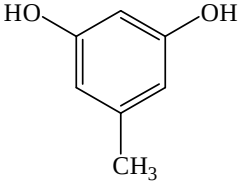
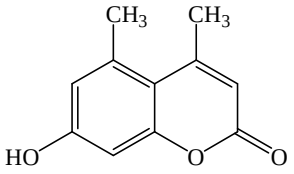
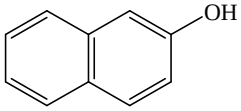
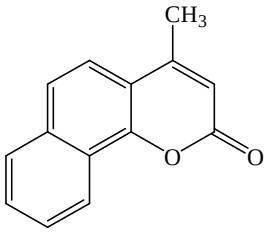
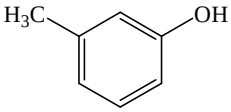
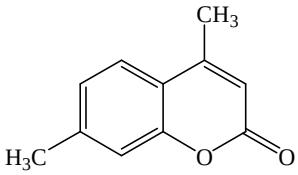
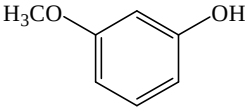
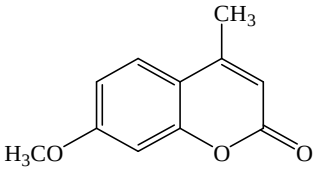
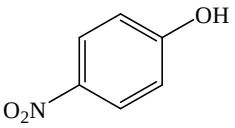
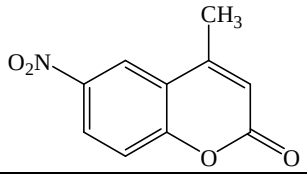
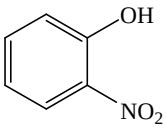
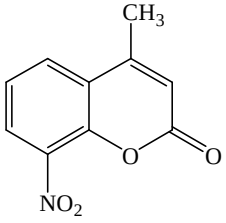
Scheme 1



Scheme 1: The synthesis of substituted coumarins in the presence of $Cr(NO_3)_3$. $9H_2O$

Table 1: Synthesis of Coumarin derivatives (3a-j)

Entry	Phenolic compound	Product	Yield(%)
1			92
2			90
3			89

4			90
5			92
6			88
7			90
8			95
9			68
10			65

Spectral data for selected compounds.

7-Hydroxy-4-methyl-2H-chromen-2-one (3a):

IR (KBr): 3165, 1675, 1383, 1237, 1067, 985, 856, 758, 572, 525, 426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.52 (brs, 1H), 7.35 (d, J=8.4 Hz, 1H), 6.78 (d, J=8.0 Hz, 1H), 6.65 (s, 1H), 6.10 (brs, 1H), 2.29 (brs, 3H).

7-Amino-4-methyl-2H-chromen-2-one (3b):

IR (KBr): 3436, 3353, 3250, 1617, 1543, 1448, 1389, 1263, 1213, 1155, 1056, 835, 710, 649, 539, 452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J=8.0 Hz, 1H), 6.43 (dd, J=7.2 Hz, 1H), 6.42 (d, J=2.5 Hz, 1H), 6.12 (brs, 2H), 5.92 (s, 1H), 2.26 (s, 3H).

7,8-Dihydroxy-4-methyl-2H-chromen-2-one (3c):

IR (KBr): 3260, 1675, 1385, 1235, 1060, 985, 856, 758, 572, 525, 426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 6.10 (s, 1H), 6.80 (d, J=8.8 Hz, 1H), 7.10 (d, J=8.0 Hz, 1H), 9.30 (br, 1H), 10.04 (br, 1H).

5,7-Dihydroxy-4-methyl-2H-chromen-2-one (3d):
IR (KBr): 3185, 1675, 1380, 1227, 1067, 985, 856, 758, 572, 525, 426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.90–4.30 (br, s, 2H), 5.90 (s, 1H), 6.25(d, J=1.8 Hz, 1H), 6.35 (d, J=1.8 Hz, 1H).

7-Hydroxy-4,5-dimethyl-2H-chromen-2-one (3e):
IR (KBr): 3155, 1675, 1373, 1235, 1067, 985, 856, 758, 572, 525, 426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.50 (s, 3H), 3.34 (s, 1H), 6.00 (s, 1H), 6.54(s, 1H), 6.57 (s, 1H).

4-Methyl-2H-benzo[h]chromen-2-one (3f):
IR (KBr): 3250, 1675, 1383, 1237, 1067, 985, 856, 758, 572, 525, 426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H), 6.47 (s, 1H), 7.67–7.82 (m, 4H), 7.95–8.15 (m, 1H), 8.32–8.35 (m, 1H).

4,7-dimethyl-2H-chromen-2-one (3g):
IR (KBr): 3054, 1685, 1210, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.10–7.62 (m, 3H), 6.38 (s, 1H) 2.81(s, 3H), 2.60 (s, 3H).

7-Methoxy-4-methyl-2H-chromen-2-one (3h):
IR (KBr): 3045, 1680, 1566, 1215, 1078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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).

CONCLUSION

In conclusion we have developed a simple methodology for the preparation of coumarin derivatives by using $Cr(NO_3)_3$. $9H_2O$ as efficient catalyst using microwave irradiation. The advantage of this method are extremely mild reaction conditions, short reaction time, high yield.

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