International Journal of Engineering Technology Science and Research
IJETSR
www.ijetsr.com
ISSN 2394 – 3386
Volume 4, Issue 9
September 2017

Mechanochemical Synthesis of Coumarin-3-carboxylic acid using Water Extract of Papaya

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ABSTRACT: The coumarin-3-carboxylic acid is a blockbuster heterocycle containing in many active biological, coumarin-3-carboxylic acidderivatives are also reported in the action of plant growth hormones and growth regulators. The synthesis of 3-carboxycoumarinisreported by many researchers group using various catalytic methods, but such systems are required tedious work-up and use of toxic reagents. Herein, we are developed green protocol for the synthesis of 3-carboxycoumarin using pestle and mortar in the presence of water extract of papaya (WEP) at room temperature. The reaction proceeds vigorously by mechanical ground at about 7-12 min, the product is separated as a solid about 80-85% yield. The final product is recrystallized, the physical constants are comparable with reported literature and characterized by FT-IR, ^{1}H- ^{13}C-NMR and mass spectrometry.

KEY WORDS:3-Carboxycoumarin, Mechanochemical, Water extract of papaya, Room temperature, Green chemistry.

INTRODUCTION: Coumarin (2-oxo-2*H*-1-benzopyran) and their derivatives are important heterocyclic moiety[1] present in many structural motif both in numerous natural product and potential pharmacological activities in the synthetic compounds. Their widely used in pharmaceuticals[2], agrochemicals, cosmetics, insecticides, optical brighteners[3], fluorescence sensors, and molecular photonic devices.
Coumarin-3-carboxylic acids or 3-carboxycoumarins (2-oxo-2*H*-chromene-3-carboxylic acids or 2-oxo-2*H*-1-benzopyran-3-carboxylic acids) represent a pronounced group of coumarin-heterocyclic[1] compounds exhibited wide range of applications[4]. The reported literature reveals that, coumarin-3-carboxylic acids derivatives find applications as synthons of numerous natural and semi-synthetic pharmacological agents. The ester [5] and amide derivatives of coumarin-3-carboxylic acid have been evaluated to possess efficient inhibitory activity against cancer cell invasion *in vitro* and tumor growth *in vivo* [2]. The complexes of some selected metal have been reported beneficial biological effects. Apart from these applications, coumarin-3-carboxylic acids have been widely used in photoelectric devices as a sensitizers and fluorescent probes[3]. Hence, chemists have been greatly motivated to explore simple and greener synthetic strategies for the subsequent research and development.

Various naming reaction type methods are known for the synthesis of substituted coumarins in the literature employing different starting material[6]. Some of the recent efficient methods utilize several heterogeneous[6] as well as transition, metal catalysis[7], solid phase synthesis and ionic liquids[8]. Most of the procedures suffer from harsh reaction conditions, such as the use of stoichiometric amount of minerals[9],[10], Lewis acids or toxic reagents[11]-[13], often under high temperatures and with longer reaction times and low yields. Thus, it is clearly evident that development of newer simple reaction condition and faster with greener protocols is required.

The organic transformations using biocatalysts are more efficient and generate lower waste than traditional chemical methods[14]-[17]. Hence biocatalytical transformations using edible plants[18], plant roots[19], plant tuber[20] and extract of plant leaves are being applied in many organic reactions. Recently in the literature reported aqueous extract of acacia pods, water extract of rice straw ash[21] and water extract of banana[21] are

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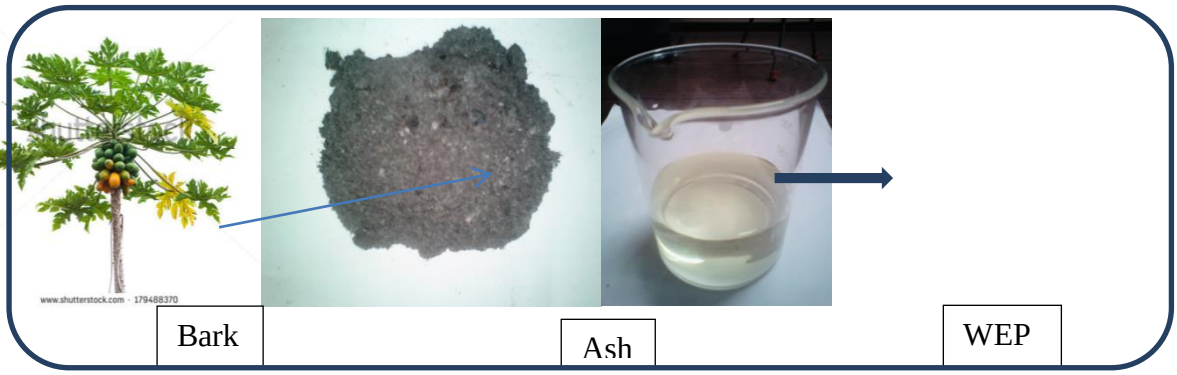
used as biocatalysts in many organic transformations. Herein, we reported green chemistry protocol for the synthesis of Coumarin-3-carboxylicusing pestle and mortar in the presence of water extract of papaya(WEP) at room temperature.

RESULT AND DISCUSSION:

In the present work water extract of papaya bark has selected as reaction media in place of external base. The WEP has been prepared by taking bark of papaya, dried and subjected to combusting with open flame to ash and resulted ash suspended in distilled water about 2hours at room temperature followed by filtration. The resulted filtrate is abbreviated as water extract of papaya (**Figure 1**). The model reaction**(scheme-1)** between salicyldehyde (1mmol) and Meldrum's acid (1mmol) taken in a pestle, added WEP (5%) about 2-4 mL grounded till reaction, the reaction completion is monitored by TLC. The reaction is completedabout 7-12 min at room temperature, after completion 5mL of water is added, the precipitated product is filtered, and recrystallized in ethanol solvent. The isolated product is tabulated in T**able-1**with observed physical constant is compared with the literature data are found satisfactory. Further the concentration of WEP was selected based on the reported literature [22]used in other organic reactions. The model reaction is also carried out in the absence of WEP and no reaction found in TLC. The other most important observation of this work, the reaction takes place in mechanical pestle and mortar ground. After ground about 7-12 min at room temperature, the product separation is done by simple dilution with water and it is not requiredacid hydrolysis has reported in other biocatalyst method, where isolation of product required acid hydrolysis. A survey of the recent literature reveled that WEP contain carbonates of K, Na, Ca and Mg as major constituents [22] along with a host of other trace elements. It is a cheap available in nature for the extraction, and rich in carbonates of alkali and alkaline earth metals. These interesting properties of WEP tempted us to use it as an eco-friendly basic catalyst for the organic synthesis especially for the important coumarin derivatives. Our group is also under developing more eco-friendly synthetic methods for other biologically active molecule synthesis.

Figure -1: Water Extraction of papaya



Scheme -1: General reaction of synthesis of 3-carboxycumarin

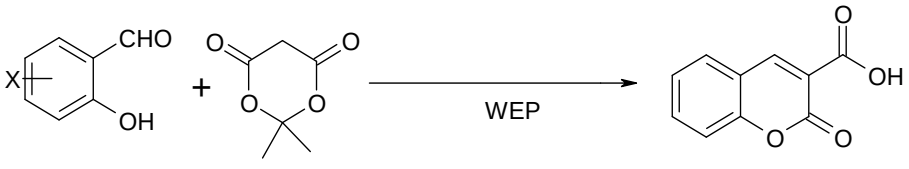


Table-1: Physical and experimental data of Coumarin-3-carboxylic derivatives.

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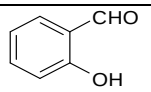
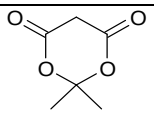
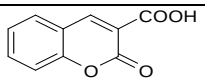
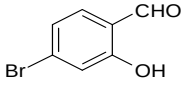
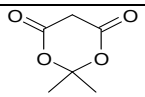
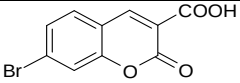
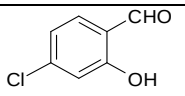
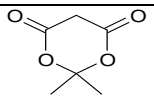
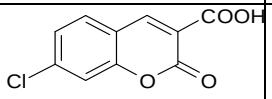
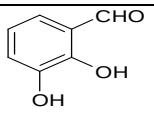
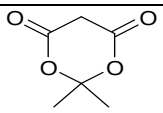
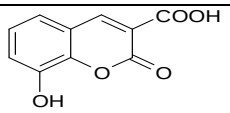
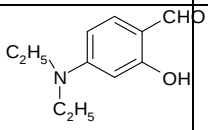
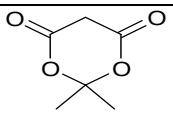
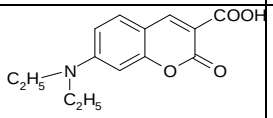
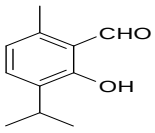
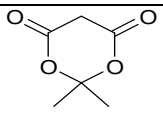
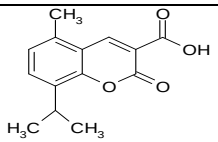
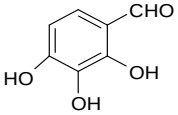
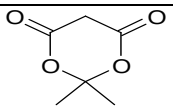
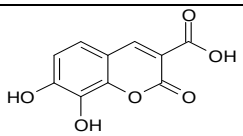
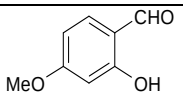
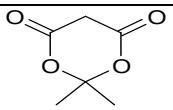
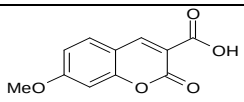
Entry	Reactants		Product	Time in min(R.T)	Yield (%)	MP in (°C)
1				8	92	188-190
2				10	88	194-196
3				7	89	116-118
4				8	92	202-204
5				11	87	209-211
6				10	81	212-214
7				12	83	204-206
8				9	90	193-195

CONCLUSION: Herein we reported simple, faster and greener method for the synthesis of coumarin-3-carboxylic acids via Knoevenagel condensation by mechanochemical method. This procedure offers several advantages including time saving, bio-catalytic, clean reactions, andvery easy work-up, and it is free from usage of organic solvents. The generality of this method has been demonstrated by the successful conversion of substrates into substituted 3-carboxycumarins in 80-85% yieldsin 7-12 minute reaction completion.

SOME SELECTED SPECTRAL DATA

Entry 1: 2-Oxo-2H-chromene-3-carboxylic acid
^{1}H NMR (400 MHz, DMSO-d_6):7.13 (d, 2H), 7.65 (d, 1H), 7.81 (d,1H), 8.80 (s,1H), 13.00 (s,1H). ^{13}C NMR(100 MHz, DMSO-d6):115.94, 115.80, 118.88, 122.4,129.92, 134.80, 147.47, 153.12, 156.85, 163.67. ESI-MSm/z $[M+H]^{+}$=Theoretical: 190.15 found: 191.11.

Entry2: 6-Bromo-2-oxo-2H-chromene-3-carboxylic acid

^{1}H NMR (400 MHz, DMSO-d6) 6.94 (d, 1H), 7.32 (d, 1H), 7.85(s, 1H), 10.19 (s, 1H), 10.85 (s,1H). ^{13}CNMR (100 MHz, DMSO-d_6): 116.35, 118.60, 120.50, 122.50, 130.99, 131.18, 146.01, 153.26, 159.18, 163.36. ESI–MS m/z $[M+H]^+$= found: 268.77.

Entry 8: 7,8-Dihydroxy-2-oxo-2H-chromene-3-carboxylic acid
^{1}H NMR (400 MHz, DMSO-d6): 6.21 (d, 1H), 6.32 (d,1H), 8.75 (s, 1H), 11.00 (d, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 94.10, 98.58, 102.88, 107.30, 144.23, 156.32, 157.12, 159.35, 162.89, 166.76. ESI–MS m/z $[M+H]^+$= Theoretical: 244.13,found: 245.14.

ACKNOWLEDGMENTS:

KK is thankful to the UGC for the award of Major Research Project {(UGC-MRP:F.43-181/2014 (SR)} and VGST, Govt. of Karnataka for SMYSR award.The authoris also acknowledge the Department of Science and Technology for the award of DST-FIST to theDepartment of Chemistry, RCUB.

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23]GENERAL PROCEDURE: In a mortar salicyldehyde (1mmol) Papaya bark extract(2-3 mL), Meldrum's acid (1mmol) added and ground for about 2-3 min.The solid mass formation takes place and continued ground till the completion of reaction about 7-8 min.The reaction progress is monitored by TLC, the reaction mixture is triturated with water (5mL) filtered. The crude product is recrystallized with ethanol.The products are characterized by FT-IR, 1H-, ^{13}C-NMR and Mass spectrometry.The product synthesized is tabulated in theTable-1 with physical constants observed.
24]PREPARATION OF WATER EXTRACT OF PAPAYA (WEP): WEP solution is prepared by papaya bark collected and chopped in to small pices, washed with waterthen dried in sun light shade, and followed burning them to ash using burner. The burnt ash (5 g)is then soaked with distilled water (100 mL) about 2 hrs and filtered. The filtrate is named as WEP solution.