**FRUIT JUICES: NATURAL AND BIOCATALYST FOR ENVIRONMENTALLY BENIGN ORGANIC SYNTHESIS**

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**1. ABSTRACT**

 Application of fruit juices as a natural and biocatalyst allows mild and highly selective transformation and synthesis in a facile and environmentally friendly manner. Moreover, fruits are inexpensive and easily available in the market, and its juice can be extracted easily which can be used as catalyst in the organic transformations.  Fruit juice of lemon, pineapple, tamarind, Acacia concinna, Sapindum trifolistus, and coconut is extensively used in organic synthesis. A simple, efficient and green procedure for the synthesis of 3-carboxycoumarins has been developed which involves the treating of aromatic aldehydes with Meldrum’s acid (2,2-dimethyl-1,3-dioxan-4,6-dione) and catalyzed by lemon juice at room temperature. This Knoevenagel condensation of various aromatic aldehydes with Meldrum’s acid using lemon juice for synthesis of 3-carboxycoumarin and its derivatives under ‘Grindstone Chemistry’ which is one of the ‘Green Chemistry Techniques may be considered as an excellent improvement over the existing methods. The protocol is much more efficient as the reactions are carried out at room temperature, yields are also quite high and the reactions go to completion within 20 min. All the compounds were characterized by their melting points and IR spectra. Various derivatives of 3-carboxycoumarin can be synthesized by this method.

# 2. INTRODUCTION

Among various green chemistry aspects, selection of catalysts for mild running of chemical reaction with optimum yield is most important part of the reaction procedure. Fruit juice plays an important role as a biocatalyst in many of the chemical reactions and this biocatalyst follows all the parameters of green chemistry. The multicomponent reactions are the most important

tools in organic transformations and pharmaceuticals. The concept of “Green Chemistry” has been widely accepted to complete the basic scientific challenges of protecting human health and environment [1]. In order to complete these needs, chemical reactions are proceeds in solvent-free [2-3], water as a solvent [4], ionic liquids [5], biobased chemicals [6] and supercritical fluids [7] as green solvents. The increasing interest in fruit juice because these are available at low cost and non-toxic agents that can carry out an organic transformation in an environmentally benign manner. Fruit juice acts as homogenous catalyst for various organic reactions in easy and smooth way. The development of new strategies for the preparation of complex molecules in neat conditions is a challenging area of organic synthesis. Many exothermic reactions can be accomplished in high yield by just grinding solids together using mortar and pestle, a technique known as ‘Grindstone Chemistry’ which is one of the ‘Green Chemistry Techniques’. Reactions are initiated by grinding, with the transfer of very small amounts of energy through friction. In addition to being energy efficient Grindstone Chemistry also results in high reactivity and less waste products.

**Fruit juice (Figure-1) plays an important role as a biocatalyst in many of the chemical reactions and this biocatalyst follows all the parameters of green chemistry.**

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**Figure-1 Various Fruit juices**

3-Carboxycoumarins also known as coumarin-3-carboxylic acids constitute an important class of compounds because of their enormous applications, as these are the required intermediates for the synthesis of number of natural products with various biological activities [8]. These compounds have been used for the synthesis of modified cephalosporins [9], pencillins [10],

Isoureas [11] and oxygen-bridged tetrahydropyridones [12] compounds with specific inhibition activity of α-chymotrypsin and human Leukocyte elastase [13-14]. In recent reports, 3-carboxycoumarin derivatives have been found to be potent and selective inhibitors to monoamine oxidase and showed marked potency in inhibiting cancer cell invasion in vitro and tumor growth in vivo [15-17]. Their metal complexes also exhibited good biological properties [18-19]. 3-Carboxycoumarins have been used as fluorescent probes and triplet sensitizers [20-21] and also have wide applications in the perfume and cosmetic industry [22]. Due to their important role in various fields, lot of emphasis has been laid on their synthesis [23-25].

Generally, these compounds have been obtained by the condensation of substituted 2-hydroxybenzaldehydes with malonic acid, ethylcyanoacetate, malononitrile [26–29] in the presence of piperdine [30], piperdine acetate [31], ammonium acetate [32], sulfuric acid adsorbed over silica [33], L-proline [34] and ionic liquids [35]. Use of Meldrum’s acid was found to be much superior in terms of yields. Recently, these have been obtained by condensation of 2-hydroxybenzaldehydes with Meldrum’s acid in aqueous-ethanol medium using visible light [36], under the phase transfer catalyzed condition using triethylbenzylammoniumchloride (TEBAC) [37] and potassium phosphate in ethanol [38]. Some of the above-mentioned conditions possess shortcomings such as use of harsh and hazardous chemicals mainly organic solvents, longer reaction time, elevated temperature and poor yields. The organic solvents due to their volatile nature affect the human health and cause extreme damage to our environment. These shortcomings led us to develop a safe, environmentally benign and more efficient method for the synthesis of 3-carboxycoumarins. In recent years the grinding technique has been considered to be an important tool to carry out the reaction under solvent-free conditions with minimum cost and maximum yield [39–41]. It also got much attention due to its atom economy and operational simplicity as compared to conventional methods. In continuation of our work on the development of eco-friendly procedure for the synthesis of organic compounds using the grinding technique [42-43], we report a simple and efficient protocol for the synthesis of 3-carboxycoumarins by using lemon juice under a grinding condition **(Figure-2)** which avoids the use of hazardous chemicals and organic solvents at any stage of the reaction including work-up **(Scheme 1).** Hence, chemists have been greatly motivated to explore simple and greener synthetic strategies for the subsequent research and development.

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**Figure-2: GRINDING TECHNIQUE**

**3. SYNTHESIS**

The research was carried out to discover a novel green method for synthesis of 3-carboxycoumarin and its derivatives to compare it with former existing green method. The grinding technique has been considered to be an efficient to carry out the synthesis of 3-Carboxycoumarin under solvent-free conditions with minimum cost and maximum yield but the only drawback of this method is long duration of the reaction, it takes about 20 minutes of grinding of Meldrum’s acid and 2-hydroxybenzaldehyde in moist condition (lemon juice) with additional 40 minutes waiting period. In order to increase the rate of reaction a novel method using extract of lemon as a catalyst was discovered.

**Table 1. Synthesis of coumarin-3-carboxylic acid derivatives (3a-c) in presence of lemon juice.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Entry** | **R** | **Yield (%)** | **M.P. (ºC)****Found** |
| **3a**  | **R1=H, R2=H, R3=H**  | **85**  | **190-192**  |
| **3b**  | **R1=H, R2=Cl, R3=H**  | **90**  | **116-118**  |
| **3c**  | **R1=H, R2=OCH3, R3=H**  | **90**  | **193-195**  |

**4. SPECTRAL STUDIES**

**Table 2. IR Spectral data of coumarin-3-carboxylic acid derivatives (3a-c)**

|  |  |
| --- | --- |
| **Entry**  | **IR (cm-1)** |
| **3a** | **3-Carboxycoumarin****3415 (OH), 1745 (C=O), 1685 (C=O)** |
| **3b** | **6-Bromo-3-carboxycoumarin****3310 (OH), 1742 (C=O), 1712(C=O)** |
| **3c** | **6-Methoxy-3-carboxycoumarin****3152 (OH), 1726 (C=O), 1688 (C=O)** |

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 **Figure: (3b) 6-Bromo-3-carboxycoumarin**

**5. GENERAL PROCEDURE**

**Preparation of Lemon Juice (Citrus limonium):**

 Fresh lemon was cut by using knife and then pieces were pressed manually using domestic presser to extract juice. Then juice was then filtered through cotton/muslin cloth and then through filter paper to remove solid material and to get clear juice which was used as a catalyst.

**General procedure for synthesis of 3-carboxycoumarins (3a–c):**

A mixture of 2-hydroxybenzaldehydes (**1**, 4.16 mmol) and Meldrum’s acid (**2**, 4.16 mmol) moist with 2 ml of lemon juice was ground in a mortar by a pestle at room temperature for 20 minutes and the reaction mixture was left at room temperature for 40 minutes. The completion of the reaction was checked by thin layer chromatography. The reaction mixture was diluted with ice-cold water. The solid that separated out was filtered at vacuum, washed with water and recrystallized from ethanol to give 3-carboxycoumarins.

**6. CONCLUSION**

Natural juices contain various acids act as natural acid catalyst in organic synthesis. These

reactions were carried out at room temperature and under solvent free conditions. In the present investigation, we reported simple, faster and greener method for the synthesis of coumarin-3- carboxylic acids via Knoevenagel condensation by mechanochemical method. The naturally available fruit juice is used as biocatalyst in synthesis of coumarin compounds and grinding technique is fairly clean, rapid and efficient. This procedure offers several advantages including time saving, bio-catalytic, clean reactions, and very easy work-up, and it is free from usage of organic solvents. Various derivatives of 3-carboxycoumarin can be synthesized by this method which may have potential biological activities.

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