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

 Garima Choudhary1, Priya1 and Sarita Khaturia1

1Department of Chemistry , School of Liberal Arts and Sciences, Mody University of Science and Technology, Lakshmangarh, Sikar 332311, Rajasthan, India.

 Author/s email addresses: **saritarajkhatri@gmail.com**

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**1. ABSTRACT**

 The use of fruit juices as a natural and biocatalyst allows easy and environmentally safe conversion and synthesis with high selectivity. In addition, the fruit is inexpensive and readily available in the market, and its juice can be easily extracted, which can be used as a catalyst in organic transformations. In organic synthesis, the juice of lemon, pineapple, tamarind, acacia Kancin, sapindum three-leaf, and coconut is widely used. A simple, efficient, and environmentally friendly procedure for the synthesis of 3-carboxycoumarins was developed, involving the treatment of aromatic aldehydes with Meldrum's acid (2,2-dimethyl-1,3-dioxane-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 the synthesis of 3-carboxycoumarin and its derivatives in "Grindstone Chemistry", which is one of the methods of "Green Chemistry", can be considered as a remarkable improvement over existing methods. The protocol is much more efficient since the reactions are carried out at room temperature, the yields are also quite high and the reactions are completed within 20 minutes. All compounds were characterized by melting points and IR spectra and various 3-carboxycoumarin derivatives can be synthesized by this method.

# 2. INTRODUCTION

For the protection of human health and the environment [1], chemical reactions are carried out without solvents [2-3], water as a solvent [4], ionic liquids [5], biological chemicals [6] and supercritical fluids [7] as green solvents. Growing interest in fruit juices because they are available at low cost and non-toxic agents that can carry out organic transformation in an environmentally beneficial way. Fruit juice acts as a homogeneous catalyst for various organic reactions in a light and smooth manner. The development of new strategies for the preparation of complex molecules under clean conditions is a challenging area of ​​organic synthesis. Many exothermic reactions can be performed in high yield simply by grinding the solids in a mortar and pestle, a method known as "Whetstone Chemistry", which is one of the "green chemistry methods". The reactions are initiated by grinding with very little energy being transferred through friction. In addition to energy efficiency, Grindstone Chemistry also provides high reactivity and less waste.

**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 due to their enormous applications, as they are essential intermediates for the synthesis of a number of natural products with different biological activities [8]. These compounds were used for the synthesis of modified cephalosporins [9], penicillins [10],

Isoureas [11] and tetrahydropyridones [12] with oxygen bridges with specific activity of inhibiting α-chymotrypsin and elastase of human leukocytes [13-14]. In recent reports, 3-carboxycoumarin derivatives have been shown to be potent and selective monoamine oxidase inhibitors and have shown marked efficacy in inhibiting cancer cell invasion in vitro and tumor growth in vivo [15-17]. Their metal complexes also showed good biological properties [18-19]. 3-Carboxycoumarins have been used as fluorescent probes and triplet sensitizers [20–21], and are also widely used in the perfumery and cosmetic industries [22]. Due to their important role in various fields, much attention is paid to their synthesis [23-25].

As a rule, these compounds were obtained by condensation of substituted 2-hydroxybenzaldehydes with malonic acid, ethyl cyanoacetate, malononitrile [26–29] in the presence of piperdine [30], piperdine acetate [31], ammonium acetate [32], sulfuric acid. adsorbed on silica [33], L-proline [34] and ionic liquids [35]. The use of Meldrum's acid was found to be much better in terms of yield. Recently, they were obtained by condensation of 2-hydroxybenzaldehydes with Meldrum's acid in water-ethanol medium using visible light [36], under catalyzed phase transfer conditions using triethylbenzylammonium chloride (TEBAC) [37] and potassium phosphate in ethanol [38]. Some of the above-mentioned conditions have disadvantages, such as the use of harsh and hazardous chemicals, mainly organic solvents, longer reaction times, elevated temperatures, and low yields. Due to their volatile nature, organic solvents affect human health and cause enormous damage to the environment. These drawbacks led us to develop a safe, environmentally friendly and more efficient method for the synthesis of 3-carboxycoumarins. In recent years, the milling technique has been considered an important tool for conducting the reaction under solvent-free conditions with minimal costs and maximal yields [39-41]. It has also attracted much attention due to its atom economy and ease of operation compared to conventional methods. In continuation of our work on the development of an environmentally 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 using lemon juice during grinding. a condition (Figure-2) that avoids the use of hazardous chemicals and organic solvents at any stage of the reaction, including processing (Scheme 1). Thus, chemists have been strongly motivated to explore simpler and more environmentally friendly synthetic strategies for further research and development.

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**Figure-2: GRINDING TECHNIQUE**

**3. SYNTHESIS**

The study was carried out to identify a new green method for the synthesis of 3-carboxycoumarin and its derivatives in order to compare it with the previously existing green method. The grinding technique is considered effective for the solvent-free synthesis of 3-carboxycoumarin with minimum cost and maximum yield, but the only drawback of this method is the long reaction time, which takes about 20 minutes. grinding Meldrum's acid and 2-hydroxybenzaldehyde wet (lemon juice) with an additional waiting period of 40 minutes. A new method using lemon extract as a catalyst was discovered to increase the reaction rate.

**Table 1. Coumarin-3-carboxylic acid derivatives (3a-c)**

|  |  |  |  |
| --- | --- | --- | --- |
| **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 (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):

 A fresh lemon was cut with a knife, and then the pieces were pressed by hand using a homemade press to obtain the juice. The juice was then filtered through a cotton/muslin cloth and then through filter paper to remove the solid material and obtain a clear juice which was used as a catalyst.

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

A mixture of 2-hydroxybenzaldehydes (1, 4.16 mmol) and Meldrum's acid (2, 4.16 mmol) moistened with 2 ml of lemon juice was triturated in a mortar with a pestle at room temperature for 20 minutes and the reaction mixture was allowed to stand at room temperature. temperature for 40 minutes. The progress of the reaction was checked by the method of thin-layer chromatography. The reaction mixture was diluted with ice water. The solid that separated was vacuum filtered, washed with water and recrystallized from ethanol to give 3-carboxycoumarins.

6. FUTURE SCOPE

Natural juices contain various acids that act as a natural acid catalyst in organic synthesis. These reactions were carried out at room temperature and in the absence of solvent. In this study, we reported a simple, faster, and environmentally friendly method for the synthesis of coumarin-3-carboxylic acids via Knoevenagel condensation by a mechanochemical method. Natural fruit juice is used as a biocatalyst in the synthesis of coumarin compounds, and the grinding technique is quite clean, fast and efficient. This procedure offers several advantages, including time savings, biocatalytic, clean reactions, and very easy processing, and does not require the use of organic solvents. Various 3-carboxycoumarin derivatives that may have potential biological activity can be synthesized by this method.

**REFERENCES**

 [1] Achatz S, Domling A. *Bioorg. Med.Chem. Lett.* 2006; 16(24):6360-6362.

[2] Himaja M, Poppy D, Asif K. Int. J. Res. Ayurveda & Pharm. 2011; 2:1079.

[3] Tanaka K, Toda F. Chem. Rev. 2000; 100(3):1025-1074.

[4] Narayan S, Muldoon J, Finn MG, Fokin VV, Kolb HC, Sharpless KB. Angew. Chem. Int. Ed. 2005; 44: 3275-3279.

[5] Plechkova NV, Seddona KR.Chem. Soc. Rev. 2008; 37: 123-150.

 [6] Gu Y, Jerome F. Chem Soc Rev. 2013; 42:9550-9570.

[7] Poliakoff M, Licence P. Phil. Trans. R. Soc. 2015; A373:20150018.

[8] Murray, R.D.H.; Mendez, J.; Brown, S.A. The Natural Coumarins; John Wiley & Sons: New York, 1977.

[9] Bonsignore, L.; Cittiglia, F.; Elkhaili, H.; Jehl, F.; Lavagna, S.M.; Loy, G.; Manna, F.; Monteil, H.; Pompei, D.; Secci, D. Farmoco. 1998, 53, 425–430.

[10] Bonsignore, L.; De Logu, A.; Lavagna, S.M.; Loy, G.;Secci, D. Eur. J. Med. Chem. 1994, 29, 479–485.

[11] Bonsignore, L.; Cottiglia, F.; Lavagna, S.M.; Loy, G.; Secci, D. Heterocycl. 1999, 50, 469–478.

[12] Jonsson, D.; Erlandsson, M.; Unden, A. Tetrahedron Lett. 2001, 42, 6953–6956.

[13] Pochet, L.; Doucet, C.; Thierry, N.; Schynts, M.; Boggeto, N.; Pirotte, B. J. Med. Chem. 1996, 39,2579–2585.

[14] Doucet, C.; Pochet, L.; Thierry, N.; Pirotte, B.; Delarge, J.; Rebound, R.M. J. Med. Chem. 1999, 42, 4161–4171.

[15] Chimenti, F.; Secci, D.; Bolasco, A.; Chimenti, P.; Granese, A.; Befani, O.; Turini, P.; Alcaro, S.; Ortuso, F. Bioorg. Med. Chem. Lett. 2004, 14, 3697–3703.

[16] Kempen, I.; Hemmer, M.; Counerotte, S.; Pochet, L.; de Tullio, P.; Foidart, J.M.; Blacher, S.; Noël, A.; Frankenne, F.; Pirotte, B. Eur. J. Med. Chem. 2008, 43, 2735–2750.

[17] Kempen, I.; Papapostolou, D.; Thierry, N.; Pochet, L.; Counerotte, S.; Masereel, B.; Foidart, J.M.; Reboud-Ravaux, M.; Noel, A.; Pirotte, B. Br. J. Cancer. 2003, 88, 1111–1118.

[18] Karaliota, A.; Kretsi, O.; Tzougraki, C. J. Inorg. Biochem. 2001, 84, 33–37.

[19] Creaven, B.S.; Egan, D.A.; Kavanagh, K.; McCann, M.; Noble, A.; Thati, B.; Walsh, M. Inorg. Chim. Acta. 2006, 359, 3976–3984.

[20] Peroni, E.; Caminati, G.; Baglioni, P.; Nuti, F.; Chelli, M.; Papini, A.M. Bioorg. Med. Chem. Lett. 2002, 12, 1731–1734.

[21] Specht, D.P.; Martic, P.A.; Farid, S. Tetrahedron. 1982, 38, 1203–1211.

[22] Meuly, W.C. K-Othmer Encylopedia of Chemical Technology; John Wiley & Sons: New York, 1979. Vol. 7, 3rd ed., pp 196–206.

[23] Wiener, C.; Schroeder, C.H.; Link, K.P. J. Am. Chem.Soc. 1957, 79, 5301–5303.

[24] Watson, B.T.; Christiansen, G.E. Tetrahedron Lett. 1998, 39, 6087–6090.

[25] Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. J. Org. Chem. 1999, 64, 1033–1035.

[26] Maggi, R.; Bigi, F.; Carloni, S.; Mazzacani, A.; Saroti, G. Green Chem. 2001, 3, 173–174.

[27] Shirokova, E.A.; Segal, G.M.; Torgov, I.V. Bioorganic heskaya Khimiya. 1988, 14, 236–242.

[28] Bandgar, B.P.; Uppalla, L.S.; Kurule, D.S. Green Chem.1999, 1, 243–245.

[29] Bandgar, B.P.; Uppalla, L.S.; Sadavarte, V.S. J. Chem. Res. 2002, 1, 40–41.

[30] Creaven, B.S.; Egan, D.A.; Kavanagh, K.D.; McCann, M.; Noble, A.; Thati, B.; Walsh, M. J. Inorg. Biochem.2007, 101 (8), 1108–1119.

[31] Song, A.;Wang, X.; Lam, K.S. Tetrahedron Lett. 2003,44, 1755–1758.

[32] Scott, J.L.; Raston, C.L. Green Chem. 2000, 2, 245–247.

[33] Hekmatshoar, R.; Rezaei, A.; Bheshtiha, S.Y.S.Phosphorus, Sulfur Silicon Relat. Elem. 2009, 184, 2491–2496.

[34] Karade,N.N.; Gampawar, S.V.; Shinde, S.V.; Jadhav,W. N. Chin. J. Chem. 2007, 25, 1686–1689.

[35] Darvatkar, N.B.; Deorukhkar, A.R.; Bhilare, S.V.; Raut, D.G.; Salunkhe, M.M. Synth. Commun. 2008, 38, 3508–3513.

[36] Ghosh, S.; Das, J.; Chattopadhyay, S. Tetrahedron Lett.2011, 52, 2869–2872.

[37] Yang, L.; Gao, W. Synth. Commun. 2012, 42, 2067–2074.

[38] Undale, K.A.; Gaikwad, D.S.; Shaikh, T.S.; Desai, U. V.; Pore, D.M. Indian J. Chem. 2012, 51B, 1039–1042.

[39] Sharma, D.; Makrandi, J.K.; Kumar, S. Green Chem. Lett. Rev. 2009, 2, 53–55.

[40] Aakeroy, C.B.; Sinha, A.S.; Epa, K.N.; Spartz, C.L.; Desper, J. Chem. Commun. 2012, 48, 11289–11291.

[41] Sharma, D. Res Chem Intermed. 2015, 41, 927–933.

[42] Sachdeva, H.; Saroj, R.; Khaturia, S.; Singh, HL. Journal of the Chilean Chemical Society 2012, 57 (1), 1012-1016

[43] Sachdeva, H.; Saroj, R.; Khaturia,; Dwivedi,D. Green Processing and Synthesis 1(5) 2012; 1: 469–477,