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A SUSTAINABLE MICROWAVE-ASSISTED SYNTHESIS OF COUMARIN-3-CARBOXYLIC ACIDS FROM AROMATIC N-OXIDES AND MELDRUM'S ACID IN 1-ETHYL-3-METHYLIMIDAZOLIUM ([emim]) IONIC LIQUID

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Abstract : Meldrum's acid and its analogues are important synthons for preparing biologically active molecules. As part of the current investigation, a set of coumarin-3-carboxylic acids was prepared via reactions between different aromatic N-oxides and Meldrum's acid in 1-ethyl-3-methylimidazolium ([emim]) ionic liquid under microwave radiation, in the absence of any external catalyst. The reaction mechanism follows an addition-elimination pathway to give the coumarin-3-carboxylic acids in good yields. The proposed methodology features several benefits such as reduced reaction times, ease of handling, lack of catalytic activation, and environmentally friendly reaction systems.

IndexTerms - **: Meldrum's acid; Aromatic N-oxides; Coumarin-3-carboxylic acids; Ionic liquid (1-ethyl-3-methylimidazolium [emim]); Microwave irradiation; Green synthesis.**

I. INTRODUCTION

During the past half-century, Meldrum's acid and its analogues have been discovered to be useful synthons for the preparation of a variety of bioactive heterocycles including coumarins, indoles, benzothiophenes, pyridines, and benzofurans.[1-2] The arylidene derivatives of Meldrum's acid are effective Michael acceptors, act as acceptors for metal-organic compounds, and behave as dienophiles in cycloaddition reactions.[2-3] The prepared compounds include the 2-oxo-2*H*-benzopyran-3-carboxylic acids (coumarin-3-carboxylic acids), which are useful intermediates for preparing coumarin derivatives that are essential building blocks in many bioactive natural products and biologically active compounds with various biological activities.[4] Coumarin derivatives also play a crucial role in the industrial production of perfumes and cosmetics among others.[5]

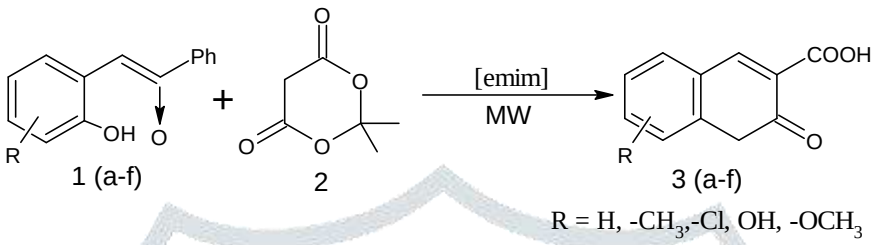
The traditional preparation of coumarin-3-carboxylic acid derivatives by starting from Meldrum's acid and arylidene compounds has generally involved the application of the Knoevenagel condensation process. Various catalysts, such as sodium hydroxide, surfactants, potassium phosphate (K_3PO_4), zirconium compounds, zinc chloride ($ZnCl_2$), pyridine, piperidine, piperidinium acetate, triethylammonium formate, ionic liquids and nanoparticles, have been explored under various reaction conditions, including thermal heating, grinding, microwave, and ultrasonic irradiations.[6-7] Many of these approaches rely on strictly controlled conditions for their successful implementation to avoid the occurrence of side reactions, such as Michael addition reactions to afford bis-adducts.[2,8] In addition, numerous procedures exhibit shortcomings in terms of the use of costly catalysts, toxic organic solvents, vigorous reaction conditions, and hazardous waste generation during aqueous purification. It is therefore imperative to develop more sustainable and efficient synthetic methodologies in consideration of growing environmental and sustainability issues.

Nitrones are well-known examples of 1,3-dipoles and have received much attention toward the formation of five-membered heterocycles by means of [3+2] cycloaddition reactions.[9-10] Recently, nitrones have been identified as useful replacements for aldehydes, thereby increasing their scope in synthetic transformations.[11] In this regard, we now describe an

efficient and sustainable methodology for the preparation of coumarin-3-carboxylic acids based on the use of aromatic N-oxides and Meldrum's acid using [emim] ionic liquid under environmentally friendly conditions. This method involves an addition-deprotonation-cyclization-dehydration pathway leading to the formation of coumarin-3-carboxylic acids in very good to excellent yields.

II. RESULTS AND DISCUSSION

For the synthesis of the model compound, a solution of freshly prepared nitrone **1a** (10 mmol) and Meldrum's acid **2** (10 mmol) was dissolved in [emim] ionic liquid (5.0 mL) and subjected to Microwave irradiation (MW) in the absence of any external catalyst. The course of the reaction was determined using TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and treated with distilled water (5.0 mL) with continuous stirring. The isolated crude product was filtered and washed with cold water, providing compound **3a** that was crystallized from an ethanol-water mixture, giving pure coumarin-3-carboxylic acid **3a** in a yield of 92%. The structure of the obtained compound was confirmed using physical and spectral methods.



Scheme 1: Synthesis of coumarin-3-carboxylic acids using IL [emim] under MW via Addition-elimination reaction of aromatic nitrones and Meldrum's acid.

As far as the reaction mechanism is concerned, the conversion is considered to involve the nucleophilic attack of Meldrum's acid **2** on nitrone derivatives **1a-f**, followed by elimination of the amine group from the nitrone unit. The formed labile arylidene product undergoes intramolecular ring closure and dehydration to give the desired coumarin-3-carboxylic acids **3a-f**.

In order to investigate the general applicability of the designed synthetic protocol, a number of nitrones **1a-f**, synthesized from diverse aromatic aldehydes, were subjected to the optimized reaction parameters using Meldrum's acid **2**. The reaction proceeded efficiently under identical conditions to furnish the desired coumarin-3-carboxylic acids **3a-f** in high yields (**Scheme 1**). It is important to mention that the presence of both electron-donating and withdrawing groups on the aromatic ring did not have any drastic effect on the duration of reaction or the yield of products (**Table 1**).

Table 1. Synthesis of coumarin-3-carboxylic acids (**3a-f**)[a] using IL [emim] under MW via Addition-elimination reaction of aromatic nitrones and Meldrum's acid.

Entry	R	Product[a]	Time (min)	Yield (%)[b]	Melting point (°C)
1	H	**3a**	09	92	190-192
2	4-OH	**3b**	15	88	196-198
3	5-Cl	**3c**	18	87	218-120
4	5-Me	**3d**	14	86	158-159
5	3-Me	**3e**	14	85	155-156
6	4-OMe	**3f**	18	84	187-188

[a] Reaction conditions: **1a-f** (10 mmol) and **2** (10 mmol), were irradiate under MW in IL[emim]. The products were characterized by spectral techniques like IR, ^{1}H NMR and Mass.
[b] Isolated yields after recrystallization.

III. EXPERIMENTAL SECTION

All reagents were commercially acquired and utilized without further purification. The melting points were determined using open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin–Elmer 240C infrared spectrometer using the potassium bromide (KBr) pellet technique. ^{1}H NMR spectra were recorded on a Bruker Avance II 300 MHz NMR spectrometer with TMS used as an internal standard in DMSO-d_6. Chemical shifts (δ) are indicated in ppm. Mass spectra were measured via the standard electron impact (EI) method. The course of reactions was followed by thin-layer chromatography (TLC) carried out on silica gel G plates (Merck).

General Procedure for the Synthesis of 2-oxo-2H-chromene-3-carboxylic Acids (3a–f):

The mixture of nitrone (10 mmol), Meldrum's acid (10 mmol), and 1-ethyl-3-methylimidazolium ([emim]) ionic liquid (5.0 mL) was irradiated with microwaves (MWI) in the absence of any external catalyst for the suitable time period (refer to Table 1). The progress of the reaction was monitored via thin-layer chromatography (TLC).
Once the reaction was completed, the reaction mixture was cooled to room temperature. Subsequently, distilled water (5.0 mL) was slowly added under constant stirring conditions. The precipitated crude product was filtered off and purified with cold water to yield products 3a-f. The crude products were crystallized with ethanol-water solvent system to provide pure coumarin-3-carboxylic acids (3a-f) in satisfactory to excellent yields (refer to Table 1). Melting points of the prepared compounds were

measured, and their spectral properties (IR, ^{1}H NMR, and mass spectra) were compared with that of authentic samples from the literature sources. Spectral data for some representative compounds are listed below.

Spectral Data of Representative Compounds:

2-oxo-2H-chromene-3-carboxylic acid (3a): White powder; mp 190–191 °C**.**

IR (KBr, cm^{-1}): 3417, 3055, 2919, 1743, 1679, 1610, 1565, 1420, 1371, 1202**;** ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.70 (s, 1H, H-4), 7.86 (dd, J = 7.65 Hz, 1H, H-5), 7.69 (td, J = 7.87 Hz, 1H, H-7), 7.41 (t, J = 6.3 Hz, 1H, H-6), 7.35 (d, J = 7.65 Hz, 1H, H-8). MS (m/z): 190 (M^+).

6-Methyl-2-oxo-2H-chromene-3-carboxylic Acid (3d): White powder; mp 158–159 °C.

IR (KBr, cm^{-1}): 3420, 3050, 2918, 1740, 1675, 1609, 1560, 1422, 1370, 1200; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.62 (s, 1H, H-4), 7.64 (s, 1H, H-5), 7.51 (d, J = 8.4 Hz, 1H, H-8), 7.32 (dd, J = 8.4 Hz, 1H, H-7), 2.34 (s, 3H, CH_3). MS (m/z): 204 (M^+)**.**

8-Methyl-2-oxo-2H-chromene-3-carboxylic Acid (3e): White needles; mp 155–156 °C**.**

IR (KBr, cm^{-1}): 3418, 3053, 2920, 1744, 1680, 1615, 1561, 1423, 1370, 1203**;** ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.67 (s, 1H, H-4), 7.70 (d, J = 7.95 Hz, 1H, H-5), 7.56 (d, J = 7.05 Hz, 1H, H-7), 7.26 (t, J = 7.65 Hz, 1H, H-6), 2.33 (s, 3H, CH_3). MS (m/z): 204 (M^+).

7-Methoxy-2-oxo-2H-chromene-3-carboxylic Acid (3f): White powder; mp 187–188 °C.

IR (KBr, cm^{-1}): 3418, 3057, 2918, 1745, 1675, 1616, 1568, 1427, 1373, 1211; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.72 (s, 1H, H-4), 7.81 (d, J = 9.0 Hz, 1H, H-5), 7.02 (d, J = 8.1 Hz, 1H, H-6), 6.99 (s, 1H, H-8), 3.87 (s, 3H, OCH_3). MS (m/z): 220 (M^+)**.**

IV. CONCLUSION

In conclusion, an efficient, rapid and environmentally friendly protocol have been developed for the synthesis of coumarin-3-carboxylic acids via addition–elimination, cyclization and dehydration of aromatic nitrone derivatives with Meldrum's acid in [emim] ionic liquid under microwave irradiation. In comparison with the previously reported methods, the present method has several advantages such as catalyst-free reaction conditions, wide range of substrate scope, high selectivity of the desired coumarin products without formation of undesired by-products such as bis-adducts, significantly reduced reaction times, and high to excellent yields. In addition, the reaction seems to proceed through an auto-promoted pathway, possibly by the catalytic effect of the free nitrone derivative.

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