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Microwave-Assisted Green Synthesis of Coumarin-3-Carboxylic Acids Using Aromatic N-Oxides and Meldrum's Acid in Ionic Liquid (TEAA)

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Abstract: Meldrum's acid and its derivatives have been widely utilised as synthones for the preparation of pharmacologically important compounds. Variety coumarin-3-carboxylic acids were synthesized of using variety of aromatic nitrones and Meldrum's acid without any catalyst in ionic liquid under microwave irradiation. The reaction followed an addition-elimination pathway, yielding the desired coumarin-3-carboxylic acids in excellent amounts under environmentally friendly reaction conditions.

Keywords: Meldrum's acid, ionic liquid (TEAA), Aromatic N-oxides, Coumarin-3-carboxylic acids, MWI.

Introduction:

From past half century, Meldrum's acid and its derivatives have been a hot synthone for the synthesis of pharmacologically significant heterocyclics such as coumarines, indoles, benzothiophenes, pyridines and benzofuranes.[1-2] Particularly, arylidene products of this molecule serve as Michael acceptors, along with acceptor of organometallic reagents and serves as dienophiles in cycloaddtion reactions.[2-3] In addition, 2-oxo-2*H*-benzopyran-3-arboxylic acids (Coumarin-3-carboxylic acids) are key precursor for the synthesis of coumarins, which acts as a vital building block for molecules/natural products exhibiting diverse pharmacological activities.[4] Coumarin derivatives extensive applications in the production of perfumes and cosmetics.[5]

The synthesis of coumarin-3-carboxylic acid derivatives of Meldrum's acid and arylidene derivatives, Knoevenagel reaction has been a simplest way and to a achieve this catalysts like sodium hydroxide, pyridine, piperidine, piperidinium acetate, triethyl ammonium formate, ionic liquid, surfactants, K_3PO_4, $Zr(O_3POK)$, $ZnCl_2$, light, nano-particles coupled with a variety of

conditions such as thermal heating, grinding, microwave irradiation, and ultrasound irradiation are used.[6-7] Further, synthesis of these derivatives require highly sophisticated reaction conditions to avoid subsequent Michael addition/formation of bis-adduct.[2,8] Overall these already reported procedures are not very efficient, require expensive catalysts, volatile solvents, harsh reaction conditions, and leave harmful waste on aqueous work-up. Therefore, there is still scope for better development of green sustainable processes in view of environment concerns. Herein we report first ever reaction of aldonitrones with Meldrum's acids affording facile production of coumarin-3-carboxylic acids.

Nitrones are well known 1,3-dipoles and are extensively explored for the synthesis of five membered heterocycles particularly, *via* [3+2] cycloaddition reaction.[9] Hamana *et al.* reported reactions of heterocyclic nitrones under acidic conditions and obtained only condensed products.[10] In the present protocol we disclose the first ever use of aryl nitrones as aldehydes equivalents[11] for the selective synthesis of coumarin-3-carboxylic acids under environmentally benign reaction condition using ionic liquid TEAA (Triethylammonium acetate) and microwave irradiations (MWI). The reaction proceeds *via* addition-elimination way and then cyclisation with dehydration to afforded the desired products in very good to excellent yields.

Results and Discussion

For a pilot reaction, a mixture of freshly prepared nitrone (10 mmol) **1a** and Meldrum's acid (10 mmol) **2** and ionic liquid (TEAA) (5.0 mL) were irradiate under microwave irradiations (MWI) without the use of any catalyst. Progress of reaction carried out via thin layer chromatography (TLC). After the reaction completion, reaction mass was cooled and then add 5.0 mL distilled water drop wise with stirring and obtained crude product was filtered and wash with cold water obtained product **3a** then recrystallized with EtOH:Water to yield pure coumarin-3-carboxylic acids **3a** in 90% yield (**Scheme 1**). Obtained product then further characterized by physical and spectral analysis data.

As far as mechanism is concerned, reaction proceeds *via* nucleophilic addition of **2** on **1a-f** with subsequent elimination of amine part of **1a-f,** after addition-elimination, unstable arylidene product undergoes cyclization and subsequent dehydration leading to the formation of coumarin-3-carboxylic acids **3a-f**.

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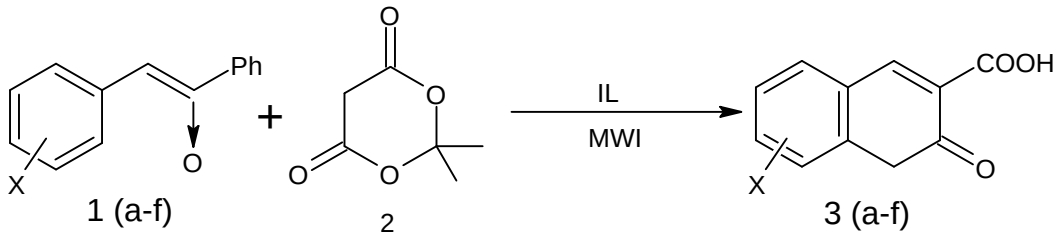

X= H, -CH_3,-Cl, OH, -OCH_3

Scheme 1: Synthesis of coumarin-3-carboxylic acids using IL (TEAA) and MWI via Addition-elimination reaction of aromatic nitrones and Meldrum's acid.

Similarly, a variety of nitrones **1a-f** obtained from aromatic aldehydes **1a-f** were reacted with Meldrum's acid (**2**) under similar conditions with similar successes (**Scheme 1**). Nitrones bearing electron donating group and withdrawing on aryl ring did not have significant effect either on rate of reaction or on yields of the coumarin-3-carboxylic acids **3a-f** (**Table 1**).

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

Entry	X	Product[a]	Time (min)	Yield (%)[b]	Melting point (°C)
1	H	**3a**	10	90	190-192
2	2-OH	**3b**	17	87	196-198
3	5-Cl, 2-OH	**3c**	19	86	218-120
4	6-Me	**3d**	16	85	158-159
5	8-Me	**3e**	16	84	155-156
6	7-OMe	**3f**	18	82	187-188

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

[b] Isolated yields after recrystallization.

Experimental Section

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Reagent-grade chemicals were purchased from a commercial source and used without further purification. Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. ^{1}H NMR spectra were recorded on a BRUKER AVANCE II 300 NMR Spectrometer using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

General procedure for the synthesis of 2-oxo-2*H*-chromene-3-carboxylic acids (3a-f):

A mixture of nitrone (10 mmol), Meldrum's acid (10 mmol) and ionic liquid (TEAA) (5.0 mL) were irradiate under microwave irradiations (MWI) without the use of any catalyst for time (see Table 1). The progress of reaction was monitored *via* thin layer chromatography. After the reaction completion, reaction mass was cooled and then add 5.0 mL distilled water drop wise with stirring and obtained crude product was filtered and wash with cold water obtained product **3a-f** then recrystallized with EtOH:Water to yield pure coumarin-3-carboxylic acids **3a-f** (for yield see table 1). Obtained product then further characterized by comparison of their melting points and spectral (IR, ^{1}H NMR & Mass Spectra) data with those of authentic samples. The representative characterized data of products was identical with those described in the literature and shown as below.

Spectral Data of representative compounds:

2-oxo-2H-chromene-3-carboxylic acid (3a): White poder; mp 190-191 °C; IR (KBr): 3417, 3055, 2919, 1743, 1679, 1610, 1565, 1420, 1371, 1202 cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) (δ/ppm): 8.70 (s, 1H, H4), 7.86 (dd, J = 7.65 Hz, 1H, H5), 7.69 (td, J = 7.87 Hz, 1H, H7), 7.41 (t, J = 6.3 Hz, 1H, H6), 7.35 (d, J = 7.65 Hz, 1H, H8); MS: (m/z) 190 (M^+).

6-Methyl-2-oxo-2H-chromene-3-carboxylic Acid (3d): White powder; mp 158-159 °C; IR (KBr): 3420, 3050, 2918, 1740, 1675, 1609, 1560, 1422, 1370, 1200 cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) (δ/ppm): 8.62 (s, 1H, H4), 7.64 (s, 1H, H5), 7.51 (d, J = 8.4 Hz, 1H, H8), 7.32 (dd, J = 8.4 Hz, 1H, H7), 2.34 (s, 3H, H9); MS: (m/z) 204 (M^+).

8-Methyl-2-oxo-2H-chromene-3-carboxylic Acid (3e): White needless, mp 155-156 °C; IR (KBr): 3418, 3053, 2920, 1744, 1680, 1615, 1561, 1423, 1370, 1203 cm^{-1}; ^{1}H NMR (300 MHz; DMSO-

d_6) (δ/ppm): 8.67 (s, 1H, H4), 7.70 (d, J = 7.95 Hz, 1H, H5), 7.56 (d, J = 7.05 Hz, 1H, H7), 7.26 (t, J = 7.65 Hz, 1H, H6), 2.33 (s, 3H, H9); MS: (m/z) 204 (M^+).

7-Methoxy-2-oxo-2H-chromene-3-carboxylic Acid (3f): White powder, mp 187-188 °C; IR (KBr): 3418, 3057, 2918, 1745, 1675, 1616, 1568, 1427, 1373, 1211 cm^{-1}; ^1H NMR (300 MHz; DMSO-d_6) (δ/ppm): 8.72 (s, 1H, H4), 7.81 (d, J = 9.0 Hz, 1H, H5), 7.02 (d, J = 8.1 Hz, 1H, H6), 6.99 (s, 1H, H8), 3.87 (s, 3H, H9); MS: (m/z) 220 (M^+).

Conclusion:

In conclusion, we have developed a simple and rapid procedure for the synthesis of 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones and coumarin-3-carboxylic acids *via* simple addition-elimination reaction followed by cyclization and dehydration. The present protocol has following synthetic features: in contrast to known methods, this procedure does not need any external catalyst, a variety of nitrones can be employed, Meldrum's acid afforded the Coumarin products selectively without the formation of any other side-products/bis-products, this method produces good to excellent yields in shorter reaction time, and it seems that reaction is auto-catalyzed because eliminating-part of nitrone acts as catalyst.

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