LETTER

Aqueous-mediated green synthesis of 3-carboxycoumarins using grinding technique

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A simple, efficient and green procedure for the synthesis of 3-carboxycoumarins has been developed which involves the grinding of 2-hydroxybenzaldehydes with Meldrum’s acid (2,2-dimethyl-1,3-dioxan-4,6-dione) in aqueous moist conditions at room temperature. The protocol is much more efficient as the reactions are carried out at room temperature and yields are also quite high. All the compounds were characterized by their IR, 1H NMR and mass spectral data and compared with authentic samples.

Keywords: Grinding technique; 3-carboxycoumarin; 2-hydroxybenzaldehyde; Meldrum’s acid; green synthesis

Introduction

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 (1). These compounds have been used for the synthesis of modified cephalosporins (2), pencillins (3), isoareas (4) and oxygen-bridged tetrahydropyridones (5) compounds with specific inhibition activity of α-chymotrypsin and human Leukocyte elastase (6, 7).

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 (8–10). Their metal complexes also exhibited good biological properties (11, 12).

3-Carboxycoumarins have been used as fluorescent probes and triplet sensitizers (13, 14) and also have wide applications in the perfume and cosmetic industry (15).

Due to their important role in various fields, lot of emphasis has been laid on their synthesis (16–18). Generally, these compounds have been obtained by the condensation of substituted 2-hydroxybenzaldehydes with malonic acid, ethylenoacetate, malonitrile (19–22, 17) in the presence of piperidine (23), piperidine acetate (24), ammonium acetate (25), sulfmeric acid adsorbed over silica (26), l-proline (27) and ionic liquids (28).

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 (29), under the phase transfer catalyzed condition using triethylbenzyl ammoniumchloride (TEBAC) (30) and potassium phosphate in ethanol (31).

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 (32–34). 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 in aqueous medium using the grinding technique (35), we report a simple and efficient protocol for the synthesis of 3-carboxycoumarins under a grinding condition which avoids the use of hazardous chemicals and organic solvents at any stage of the reaction including work-up (Scheme 1).

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Results and discussion
A mixture of 2-hydroxybenzaldehyde and Meldrum’s acid moist with few drops of water was ground in a mortar using pestle without using any catalyst. The progress of the reaction was monitored by thin layer chromatography after every 5 min and the reaction was found to be almost completed in 20 min. The reaction mixture was further left at room temperature for an hour and worked up by diluting the reaction mixture with ice-cold water to give 3-carboxycoumarin in 90% yield whose structure was confirmed by its spectral data and comparison of melting point with the literature value (Table 1). Solvent effect on the reaction was also studied by using other solvents such as ethanol, dichloromethane and 1,4-dioxane but best yields were obtained by using water as solvent (Table 2). So it appears that in the present case water is the best solvent in the presence of which the dissociation of Meldrum’s acid takes place which generates the nucleophilic species attack the aldehydic carbon to give arylidene derivatives, which is further cyclized by nucleophilic attack of OH group on the carbonyl moiety and gave the intermediate and subsequent proton transfer gave 3-carboxycoumarin 3 (Scheme 2). Moreover, to illustrate the efficiency and generality of the present protocol, some of the results of our method were compared with literature methods (Table 3). Thus, it is evident that the present protocol is superior to the reported methods in terms of time and yield of the product, without using organic solvents at any stage of the reaction, including work-up.

Experimental design
Melting points were determined in open capillaries and are uncorrected. All the compounds were identified from their IR, 1H NMR and mass spectral data. IR spectra were recorded on Perkin-Elmer spectrum BX series FT-IR spectrophotometer with KBr pellets. 1H NMR spectra were recorded on Bruker Avance (400 MHz) instrument using tetramethyl silane as the internal standard. Mass spectra were recorded on Bruker-Daltonich mass spectrometer. All the chemicals were obtained from commercial sources and used without further purification. The reactions were carried out in a porcelain mortar and pestle.

General procedure for synthesis of 3-carboxycoumarins 3a–3g
A mixture of 2-hydroxybenzaldehydes (1, 4.16 mmol) and Meldrum’s acid (2, 4.16 mmol) moist with 10 drops of water 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

Table 1. Synthesis of 3-carboxycoumarins.

| Compound | \( R_1 \) | \( R_2 \) | \( R_3 \) | Time/min (a + b) | Yield (%)\(^c\) | Mp (°C) | Lit. Mp (°C) |
|----------|----------|----------|----------|----------------|---------------|---------|--------------|
| 3a       | H        | H        | H        | 20 + 40        | 90            | 190–191  | 191–192 (24) |
| 3b       | H        | Br       | H        | 20 + 40        | 92            | 195–196  | 199 (36)     |
| 3c       | H        | Cl       | H        | 20 + 40        | 86            | 120–121  | 120–121 (24) |
| 3d       | H        | CH\(_3\) | H        | 20 + 40        | 90            | 165–166  | 166–167 (18) |
| 3e       | H        | OCH\(_3\)| H        | 20 + 40        | 92            | 207–208  | 206–207 (18) |
| 3f       | OCH\(_3\)| H        | H        | 20 + 40        | 87            | 175–176  | 177 (36)     |
| 3g       | OCH\(_3\)| H        | OCH\(_3\)| 20 + 40        | 85            | 235–236  | 234–237 (36) |

\(^a\) Grinding time.  
\(^b\) Time at which the reaction mixture was kept at room temperature.  
\(^c\) Isolated yields.
was filtered at vacuum, washed with water and recrystal-
ized from ethanol to give 3-carboxycoumarins.

**Spectral characterization of 3-carboxycoumarins**

3-Carboxycoumarin \(3a\). IR \(\nu_{\text{max}, \text{cm}^{-1}}\, \text{KBr}\): 3415 (OH), 1745 (C=O), 1685 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\), ppm): 7.42–7.82 (m, 3H, H-6, H-7, H-8), 7.92–7.94 (dd, \(J = 8.0\) Hz & \(J = 2.0\) Hz, 1H, H-5), 8.74 (s, 1H, H-4), 13.25 (s, 1H, COOH); MS: \(m/z\) 190.04 (M\(^+\)).

6-Bromo-3-carboxycoumarin \(3b\). IR \(\nu_{\text{max}, \text{cm}^{-1}}\, \text{KBr}\): 3310 (OH), 1742 (C=O), 1712 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\), ppm): 7.65 (d, \(J = 8.0\) Hz, 1H, H-8), 7.80–7.82 (dd, \(J = 8.0\) Hz & \(J = 2.0\) Hz, 1H, H-7), 8.10 (d, \(J = 2.0\) Hz, 1H, H-5), 8.45 (s, 1H, H-4), 12.95 (s, 1H, COOH); MS: \(m/z\) 269.95 (M\(^+\)).

6-Chloro-3-carboxycoumarin \(3c\). IR \(\nu_{\text{max}, \text{cm}^{-1}}\, \text{KBr}\): 3195 (OH), 1748 (C=O), 1678 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\), ppm): 7.48 (d, \(J = 8.0\) Hz, 1H, H-8), 7.73–7.75 (dd, 1H, \(J = 8.0\) & \(J = 2.0\) Hz, H-7), 7.95 (d, \(J = 2.0\) Hz, 1H, H-5), 8.82 (s, 1H, H-4), 13.65 (s, 1H, COOH); MS: \(m/z\) 226 (M\(^+\)).

6-Methyl-3-carboxycoumarin \(3d\). IR \(\nu_{\text{max}, \text{cm}^{-1}}\, \text{cm}^{-1}\, \text{KBr}\): 3195 (OH), 1748 (C=O), 1678 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\), ppm): 2.45 (s, 3H, H-8), 7.92–7.94 (dd, \(J = 8.0\) Hz & \(J = 2.0\) Hz, 1H, H-5), 8.74 (s, 1H, H-4), 13.25 (s, 1H, COOH); MS: \(m/z\) 190.04 (M\(^+\)).

Table 2. Effect of solvent on the yields of 3-carboxycoumarin \(3a\).

| Sr.No. | Solvent     | Time (min) | Yield (%) |
|--------|-------------|------------|-----------|
| 1      | EtOH        | 20 + 40    | 70        |
| 2      | CH\(_2\)Cl\(_2\) | 20 + 40    | 58        |
| 3      | 1,4-Dioxane | 20 + 40    | 60        |
| 4      | H\(_2\)O     | 20 + 40    | 90        |

Table 3. Comparison of the results of the reactions carried out with different catalysts for the synthesis of 3-carboxycoumarins with the present method.

| Entry | Catalyst                                      | Time | Temp. (°C) | Yield (%) | Ref. |
|-------|-----------------------------------------------|------|------------|-----------|------|
| 1     | Pyridine/piperidine                           | 16 h | room temp  | 16-40     | (17) |
| 2     | EPZ10                                         | 3–6 min | MW       | 64-82     | (21) |
| 3     | LiClO\(_4\)                                   | 50–75 sec | MW     | 79-90     | (22) |
| 4     | H\(_2\)O                                      | 2 h  | 75         | 65-92     | (37) |
| 5     | [Hmim]Tfa                                      | 45 min | room temp | 65-90     | (28) |
| 6     | EtOH-H\(_2\)O                                 | 20 min | hv       | 89        | (29) |
| 7     | [Hmim]Tfa                                      | 5 h  | room temp  | 63-73     | (38) |
| 8     | [Hmim]Tfa                                     | 2 h  | room temp  | 61-98     | (24) |
| 9     | H\(_2\)SO\(_4\)/DMF                           | 30-45 min | 120   | 80-92     | (26) |
| 10    | 1,1,3,3-N,N,N',N'-tetramethylguanidinium trifluoroacetate | 1–4 min | MW       | 74-83     | (39) |
| 11    | K\(_2\)PO\(_4\)/EtOH                          | 30–60 min | room temp | 81-94     | (30) |

*Present method.
CH₃), 7.18 (d, J = 8.0 Hz, 1H, H-8), 7.20–7.23 (dd, J = 8.0 Hz & J = 2.0 Hz, 1H, H-7), 7.38 (d, J = 2.0 Hz, 1H, H-5), 8.60 (s, 1H, H-4), 12.92 (s, 1H, COOH); MS: m/z 206.6 (M⁺).

6-Methoxy-3-carboxycoumarin (3e). IR (νmax, cm⁻¹, KBr): 3152 (OH), 1726 (C=O); 1H NMR (400 MHz, CDCl₃, δ, ppm): 3.23 (s, 3H, OCH₃), 7.15 (d, J = 8.0, 1H, H-7), 7.35–7.38 (dd, J = 2.0 Hz, 1H, H-5), 8.62 (s, 1H, H-4), 12.95 (s, 1H, COOH); MS: m/z 222.05 (M⁺).

7-Methoxy-3-carboxycoumarin (3f). IR (νmax, cm⁻¹, KBr): 3320 (OH), 1738 (C=O); 1H NMR (400 MHz, CDCl₃, δ, ppm): 3.90 (s, 3H, OCH₃), 7.05–7.15 (m, 2H, H-6, H-8), 7.86 (d, J = 2.0 Hz, 1H, H-5), 8.75 (s, 1H, H-4), 12.85 (s, 1H, COOH); MS: m/z 222.05 (M⁺).

5,7-Dimethoxy-3-carboxycoumarin (3g). IR (νmax, cm⁻¹, KBr): 3345 (OH), 1748 (C=O), 1682 (C=O); 1H NMR (400 MHz, CDCl₃, δ, ppm): 3.88 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 6.52 (d, J = 2.0 Hz, 1H, H-8), 6.64 (d, J = 2.0 Hz, 1H, H-6), 8.55 (s, 1H, H-4), 12.96 (s, 1H, COOH); MS: m/z 252.06 (M⁺).

Conclusions
In conclusion, it can be stated that the present method for the synthesis of 3-carboxycoumarins in the aqueous medium using the grinding technique is fairly clean, rapid and efficient. This protocol is an eco-friendly one, as it avoids the use of hazardous solvents at any stage of the reaction.

Disclosure statement
No potential conflict of interest was reported by the author.

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