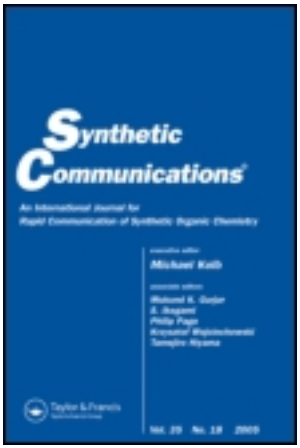

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Ionic Liquid–Mediated Synthesis of Coumarin-3-carboxylic Acids via Knoevenagel Condensation of Meldrum's Acid with *ortho*-Hydroxyaryl Aldehydes

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Abstract: A simple, efficient, and green protocol for synthesis of coumarin-3-carboxylic acids is described via Knoevenagel condensation of Meldrum's acid with *ortho*-hydroxyaryl aldehydes in [Hmim]Tfa ionic liquid, which was found to give better results than other ionic liquids. Furthermore, ionic liquid is easily reused without any appreciable loss in activity.

Keywords: Bronsted acidic ionic liquid, coumarin-3-carboxylic acids, Knoevenagel condensation, Meldrum's acid, recyclability

Various methods have been reported in the literature for the synthesis of coumarin-3-carboxylic acid derivatives.[1–3] In 1988, Armstrong et al. developed a two step method for the synthesis of coumarin-3-carboxylic acids involving Knoevenagel condensation of 2-methoxybenzaldehydes with Meldrum's acid in dimethytlformamide (DMF) followed by cyclization with H_2SO_4.[4] A solid-phase synthesis has also been reported for condensation of 2-methoxybenzaldehydes with Meldrum's acid in the presence of an excess of ZnO at 80 °C followed by cyclization in the presence of cold H_2SO_4.[5] Later on, many one-pot methods have been reported involving condensation of *ortho*-hydroxyarylaldehyde and

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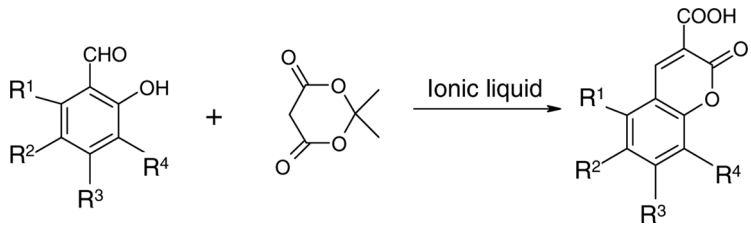


Scheme 1. Knoevenagel condensation of salicylaldehyde with Meldrum's acid.

Meldrum's acid in the presence of a solid acid catalyst under microwave irradiation,[6] by grinding a reaction mixture with ammonium acetate and keeping it overnight,[7] and by use of piperidinium acetate in ethanol under reflux conditions.[8] Some uncatalyzed routes have also been developed involving heating the reaction mixture in an aqueous medium.[9,10] A solid-phase synthesis has also been reported using ethylmalonate tethered to Wang resin in pyridine as solvent.[11]

We have earlier reported an ecofriendly methodology for the Knoevenagel condensation of Meldrum's acid and aldehydes mediated by ionic liquid.[12] As an extension of this work, we have studied the one-pot synthesis of coumarin-3-carboxylic acids by Knoevenagel condensation of *ortho*-hydroxyarylaldehydes and Meldrum's acid followed by intramolecular cyclization (Scheme 1).

The condensation of salicylaldehydes and Meldrum's acid were studied in different ionic liquids for optimization of the product yield with gas chromatographic analysis (Table 1). (Conversions in all cases were monitored with respect to decay of aldehyde by GC. A gas chromatograph Nucon 5765 equipped with FID and RH-17 capillary column was employed for analysis. The column was programmed initially at 50 °C with a gradient of 10 °C/min to 280 °C. The detector and injector temperature was set at 300 °C.) Although it was expected from our previous investigations, the actual isolated yields obtained after the usual workup procedure

Table 1. Knoevenagel condensation of Meldrum's acid and salicylaldehyde in different ionic liquids

Entry	Ionic liquid	Time	Conversion (%)
1	[bmim]PF_6	36 h	56
2	[hmim]BF_4	16 h	70
3	[bmim]BF_4	16 h	74
4	[Hmim]Tfa	45 min	95

(addition of water to the reaction mixture followed by filtration) were found to be much less as compared with percentage conversion. Even after carrying out the workup procedure very carefully, the isolated yields could not be improved. We have attributed this reduction in isolated yields to the loss of product during workup procedure, which was supported by the presence of product in the filtrate as indicated by thin layer chromatographic (TLC) analysis of the filtrate. Although product is expected to be insoluble in aqueous filtrate, its partial solubility in it can be due to presence of acetone, which is one of the side products formed in the reaction. Thus in the modified workup procedure, before the addition of water to the reaction mixture, the acetone that is formed is removed under reduced pressure. As expected, improved yields were observed as shown in Table 2 (entry 1). To generalize the protocol, we have used various substituted salicylaldehydes. Good yields were observed in almost all cases (Table 2).

The ionic liquid [Hmim]Tfa in the aqueous filtrate obtained after the workup can be easily recycled by removing the water on a rotary evaporator. As indicated in Table 3, recycled ionic liquid gave good yields even after the fourth cycle.

In conclusion, coumarin-3-carboxylic acids can be prepared in an efficient, expeditious, and environmentally benign manner by Knoevenagel condensation of salicylaldehydes and Meldrum's acid mediated by [Hmim]Tfa. The protocol avoids use of hazardous organic solvents such as dimethyl formamide (DMF), high temperature, and acidic catalysts. Furthermore, the ionic liquid can be easily reused without any appreciable loss in activity.

EXPERIMENTAL

Meldrum's acid and ionic liquids were prepared as per the procedures reported in the literature. The aldehydes were purchased from Sd Fine Chemicals and Aldrich and were used as received. The products were characterized by ^{1}H NMR and mass spectroscopy (MS) techniques. ^{1}H NMR was recorded on a Jeol (300-MHz) instrument using DMSO-d_6 as solvent. Mass spectra was recorded on Schimadzu QP-2010 spectrophotometer.

Typical Procedure

In a typical experiment, 1 mmol of salicylaldehyde was added to 200 mg of [Hmim]Tfa in 50-ml round-bottom flask equipped with an efficient magnetic stirrer. Stirring was continued until a homogeneous mixture formed at room temperature. To this, 1 mmol of Meldrum's acid was

Table 2. Knoevenagel condensation of *ortho*-hydroxy benzaldehydes and Meldrum's acid

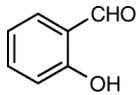
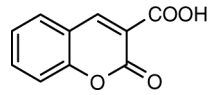
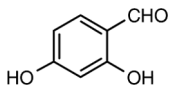
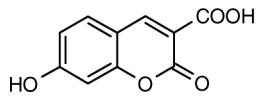
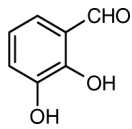
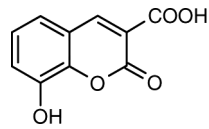
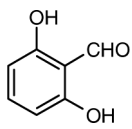
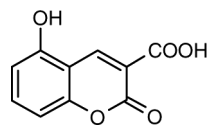
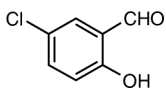
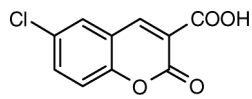
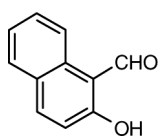
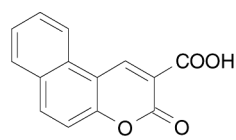
Entry	Aldehyde	Product	Reaction time (min)	Conversion (%)	Isolated yield (%)
1			45	95	90
2			45	88	85
3			45	99	90
4			45	97	90
5			45	75	65
6			60	80	75

Table 3. Recycling of [Hmim]Tfa

No. of cycles	Conversion (%)	Isolated yield (%)
1	95	90
2	95	88
3	94	88
4	94	86

added. The reaction was monitored using TLC. The stirring continued until the product precipitated out and the reaction mixture solidified. The acetone formed in the reaction was removed by applying the vacuum, and water was added to the reaction mixture, which dissolved the ionic liquid. The product was separated by filtration and purified if necessary by crystallization from ethanol or acetone. The products were characterized by ^{1}H NMR and MS techniques. The ionic liquid was recovered by removing the excess water from the filtrate under a vacuum in a rotary evaporator.

Spectral Data of the Two Representative Compounds

2-Oxo-2H-benzopyran-3-carboxylic acid (entry 1): ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.4 (2H, m), 7.7 (2H, m), 8.7 (1H, s), 12.2 (1H, s, broad). ^{13}C NMR (DMSO-d_6): δ 116.1, 118.0, 118.3, 124.8, 130.2, 134.3, 148.4, 154.5, 156.7, 164.0. MS m/z (%): 190 (M^+, 45), 146 (100), 118 (80), 89 (50), 90 (35).

7-Hydroxy-2-oxo-2H-benzopyran-3-carboxylic acid (entry 2): ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.7 (1H, D20 exchangeble), 6.7 (1H, s), 6.8 (1H, d, $J = 9$ Hz), 7.7 (1H, d, $J = 9$ Hz), 8.6 (1H, s), 12.5 (1H, s, broad). ^{13}C NMR (DMSO-d_6): δ 101.8, 110.6, 112.5, 114.1, 132.1, 149.4, 157.0, 157.6, 164.0, 164.3. MS m/z (%): 206 (M^+, 85), 162 (100), 134 (75), 105 (35), 51(30).

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REFERENCES

1. Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurance, Chemistry and Biochemistry*; John Wiley & Sons: New York, 1982.
2. Meuly, W. C. *Kirk-Othmer Encyclopedia of Chemical Technology;* 3rd ed.; John Wiley & Sons: New York, 1979; vol. 7, pp. 196–906.
3. Chizhov, D. L.; Sosnovskikh, V. Y.; Pryadeina, M. V.; Burgart, Y. V.; Saloutin, V. I.; Charushin, V. N. The first synthesis of 4-unsubstituted 3-(trifluoroacetyl)coumarins by the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetoacetate followed by chromene-coumarin recyclization. *Synlett* **2008**, 281–285, and references cited therein.
4. Armstrong, V.; Soto, O.; Valderrama, J. A.; Tapia, R. Synthesis of 3-carboxycoumarins from o-methoxybenzylidene Meldrum's acid derivatives. *Synth. Commun.* **1988**, *18*(7), 717–725.
5. Rouessac, F.; Leclerc, A. An efficient preparation of coumarins. *Synth. Commun.* **1993**, *23*(19), 2709–2715.
6. Bandgar, B. P.; Uppalla, L. S.; Kurule, D. S. Solvent-free one-pot rapid synthesis of 3-carboxycoumarins. *Green Chem.* **1999**, 243.
7. Scott, J. L.; Raston, C. L. Solvent-free synthesis of 3-carboxycoumarins. *Green Chem.* **2000**, *2*, 245–247.
8. Song, A.; Wang, X.; Lam, K. S. A convenient synthesis of coumarin-3-carboxylic acids via knoevenagel condensation of meldrum's acid with ortho-hydroxyaryl aldehydes or ketones. *Tetrahedron Lett.* **2003**, *44*, 1755–1758.
9. Deshmukh, M. N.; Burud, R.; Baldino, C.; Chan, P. C. M.; Liu, J. A practical environmentally friendly preparation of 3-carboxycoumarins. *Synth. Commun.* **2003**, *33*(19), 3299–3303.
10. Maggi, R.; Bigi, F.; Carloni, S.; Mazzacani, A.; Sartori, G. Unanalyzed reactions in water, part 2: Preparation of 3-carboxycoumarins. *Green Chem.* **2001**, *3*, 173–174.
11. Watson, B. T.; Christiansen, G. E. Solid phase synthesis of substituted coumarin-3-carboxylic acids via the Knoevenagel condensation. *Tetrahedron Lett.* **1998**, *39*, 6087–6090.
12. Darvatkar, N. B.; Deorukhkar, A. R.; Bhilare, S. V.; Salunkhe, M. M. Ionic liquid–mediated Knoevenagel condensation of Meldrum's acid and aldehydes. *Synth. Commun.* **2006**, *36*, 3043–3057.