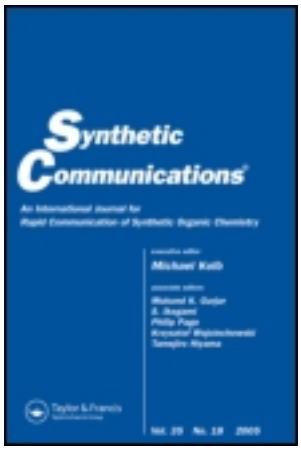

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Available online: 15 Aug 2006

To cite this article: M. N. Deshmukh, Rahila Burud, Carmen Baldino, Philip C. M. Chan & Jifeng Liu (2003): A Practical and Environmentally Friendly Preparation of 3-Carboxycoumarins, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:19, 3299-3303

To link to this article: http://dx.doi.org/10.1081/SCC-120023987

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 19, pp. 3299–3303, 2003

A Practical and Environmentally Friendly Preparation of 3-Carboxycoumarins

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ABSTRACT

The condensation of salicylaldehydes with Meldrum's acid in water at 75°C to produce 3-carboxycoumarin derivatives is described.

Coumarin carboxylic acid derivatives display a large number of biological properties[1] (anticoagulant[2] and triplet sensitizer[3]) due to which a considerable amount of work in the synthesis of 3-carboxycoumarin derivatives has been reported. There are several methods available for their synthesis such as condensation[4] of salicylaldehydes with malonate esters at 150–155°C, treating salicylaldehydes with ethyl cyanoacetate[5]

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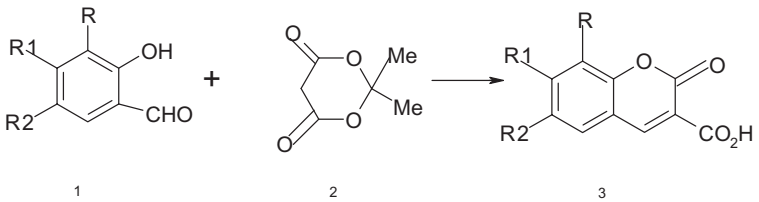
DOI: 10.1081/SCC-120023987 0039-7911 (Print); 1532-2432 (Online)

in presence of NaOEt or KOH at room temperature for 40–80 h followed by hydrolysis with HCl, treatment of dipotassium *o*-methoxybenzylidene malonate with trifluoroacetic acid–trifluoroacetic anhydride,[6] reaction of salicylaldehydes with Meldrum's acid in the presence of an alkaline condensing agent[7] at 0.025–0.25 mol/mol aldehyde in water, reaction of *o*-methoxybenzaldehydes with Meldrum's acid followed by cyclization of the resulting benzylidene derivatives in conc. sulfuric acid,[8] refluxing *o*-hydroxybenzaldehydes with 2,2-pentamethylene-1,3-dioxane-4,6-dione in acetic acid in presence of pyridine,[9] reaction of salicylaldehydes with dimedone followed by acetal cleavage with ammonium acetate[10] and reaction of *o*-hydroxy or *o*-methoxybenzaldehydes or acetophenones with Meldrum's acid in the presence of catalysts (kaolinitic clays, EPZ10 and EPZG) using focused microwaves.[11]

Although these methods are suitable for the synthesis of 3-carboxycoumarins, the long reaction time at elevated temperatures and the use of large amount of organic solvents, organic and inorganic bases which eventually results in generation of large amount of toxic waste during quenching procedure are problematic. Therefore, we decided to develop a eco-friendly, efficient alternative method for the synthesis of 3-carboxycoumarins which is described herein.

We present in this article a general method for the preparation of 3-carboxycoumarin derivatives (3) (Sch. 1). Thus, the reaction of salicylaldehydes (1) with Meldrum's acid (2) in water at 75°C provides 3-carboxycoumarin derivatives (3). The reaction proceeds to completion in 2 h and the product precipitates during the course of the reaction and is separated by filtration.

A wide range of salicylaldehyde derivatives have been condensed with Meldrum's acid in water at 75°C (Table 1). We believe that the salicylaldehyde with Meldrum's acid first form *o*-hydroxybenzylidene Meldrum's acid, followed by cyclisation to **3**.



1 2 3

Scheme 1. (a) $R = R_1 = R_2 = H$; (b) $R = OMe$, $R_1 = R_2 = H$; (c) $R_1 = OMe$, $R = R_2 = H$; (d) $R_2 = OMe$, $R = R_1 = H$; (e) $R = F$, $R_1 = R_2 = H$; (f) $R_2 = Cl$, $R = R_1 = H$.

Table 1.

Salicylaldehyde used	3-Carboxycoumarin obtained	Yield (%)[a]	M.p. (°C)	HPLC purity[e] area (%)
1a	3a	84	192[b]	99
1b	3b	92	219	99
1c	3c	65	203[c]	99
1d	3d	80	188[d]	98
1e	3e	82	168	98
1f	3f	73	195	95

[a]Isolated yield; products fully characterized by spectroscopic data (IR, NMR, MS).
[b]Lit.[8] 191–192°C.
[c]Lit.[8] 192–193°C.
[d]Lit.[8] 179–180°C.
[e]HPLC conditions; Column: C18 Licrocart; Mobile phase: [Acetonitrile–Buffer (pH = 3) 4.5:5.5]; Flow rate: 1 mL/min; UV: 254 nm.

In conclusion, the present report describes an efficient and practical method to prepare 3-carboxycoumarin derivatives **3**. We have shown that the condensation of salicylaldehydes with Meldrum's acid occurs in water by heating at 75°C for 2 h providing 3-carboxycoumarins in excellent yield. The significant advantage of this methodology is the ease of isolation of the product. The method is eco-friendly as it does not involve the use of any organic solvent or base/acid in the reaction. The products are isolated by filtration. In light of its operational simplicity and simple experimental work-up procedure, the present method is expected to have broad synthetic utility.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Brucker 200 MHz spectrometer and the chemical shifts are expressed in δ relative to TMS as internal standard. The starting salicylaldehyde derivatives and Meldrum's acid were purchased from Aldrich Chemical Co.

General Procedure for the Preparation of 3-Carboxycoumarins

Salicylaldehyde (**1a**, 0.244 g, 2 mmol), Meldrum's acid (**2**, 0.288 g, 2 mmol), and water (10 mL) were stirred at 75°C for 2 h. The reaction was cooled to room temperature, solid filtered, and washed with cold water to get 3a (0.336 g). The precipitate was dried at suction and characterized by spectral data.

The 3-carboxycoumarins thus obtained were found to be 95–99% pure by HPLC.

3b. ^{1}H NMR ($CDCl_3$): δ 8.92 (s, 1H, H-4), 7.44–7.25 (m, 3H, Aromatic), 4.03 (s, 3H, OMe). Anal. calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 60.21; H, 3.78.

3e. ^{1}H NMR ($CDCl_3$): δ 8.97 (s, 1H, 4-H), 7.70–7.40 (m, 3H, ArH). Anal. calcd. for $C_{10}H_5FO_4$: C, 57.61; H, 2.58. Found: C, 57.75; H, 2.69.

3f. ^{1}H NMR ($CDCl_3$): δ 8.88 (s, 1H, 4-H), 7.85–7.70 (m, 2H, ArH), 7.46 (d, 1H, ArH). Anal. calcd. for $C_{10}H_5ClO_4$: C, 53.39; H, 2.40; Cl, 15.76. Found: C, 53.53; H, 2.58; Cl, 15.89.

ACKNOWLEDGMENTS

We thank Dr. M. K. Gurjar for encouragement and fruitful discussions.

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Received in the USA March 12, 2003

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