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A Facile Solid –phase Synthesis of 3-Carboxycoumarins

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Abstract: 3-Carboxycoumsrins were synthesized via the solid phase synthesis conviently. The resin bound cyclic malonic ester reacted with o-methoxy or o-hydroxybenzaldehydes. Then cyclization was processed under H_2SO_4 to afford the products in excellent purities and yields.

Keyword: Resin bound cyclic malonic ester, solid phase synthesis, 3-carboxycoumarin.

Solid phase synthesis (SPOS) has drawn the attention because it is a powerful method for accelerating the process of drug discovery and the product can be easily purified with a simple wash of the resin[1]. Coumarins display a broad rang of biological activities. They have been successfully prepared by the reaction of o-methoxybenzaldhydes with Meldrum's acid via solution-phase synthesis[2] and others. Also Meldrum's acid is a versatile reagent. In connection with our recent studies on the application of Meldrum's acid towards the synthesis of heterocyclic compounds[3a,b], in this paper, our interest in Meldrum's acid prompted us to exploit this highly acidic methylene compounds to prepare 3-carboxycoumarin via solid-phase synthesis under the mild condition.

We use the resin-bound cyclic malonic ester **2**[4] condensating with o-methoxy-benzaldehydes or o-hydroxybenzaldehydes in DMF without catalyst, then cyclization in H_2SO_4 to afford the 3-carboxycoumarin (**scheme 1**). Knoevenagel condensation of carbonyl compounds with active methylene compounds is generally catalyzed by bases or lewis acids, We carry out this reaction in DMF without catalyst, resin-bound cyclic malonic ester swelled in dry DMF, the o-methoxybenzaldehydes or o-hydroxyben-zaldehydes was added and stirred at 60°C for 10 h to afford the resin **3**. Then, concentrated sulfuric acid was added to the resin **3** at 0°C and the mixture was stirred for 5 h at room temperature, the resin was filtred and washed with AcOEt, the filtrate was washed with NaOH to pH 6, the solvent was evaporated to afford the product 3-carboxycoumarins in good yields and excellent purity **(Table 1)**.

In summary, we have developed a solid phase synthesis route for the preparation of 3-Carboxycoumarins. The procedure we followed has some advantage over the thermal procedure, such as the mild condition and convience in handing and the recycling of the resin.

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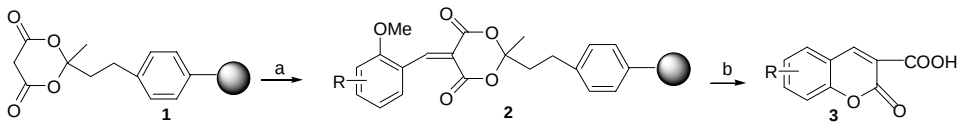
Scheme 1



a. DMF, o-methoxybenzaldhydes or hydroxybenzaldehydes, 60°C, 10h b. conc. H_2SO_4, 0°C~rt°C, 5h

Table Yield and purities of substituted 3-carboxycoumarins

Entry	R	Yield(%)[a]	Purity(%)[b]
3a	2-methoxy	65	>95
3b	2-hydroxy	64	>95
3c	2,4-dimethoxy	68	>95
3d	2,5- dimethoxy	71	>95
3e	2- methoxy -5-Br	73	>95
3f	2- methoxy -5-Cl	70	>95
3b	2-hydroxy	63[c]	>95[c]

a. The crude yields are based on the loading of the cyclic malonic ester resin 1.
b. determined by ^{1}H NMR. c the recovered resin was used

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