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Solid Phase Synthesis of Substituted Coumarin-3-Carboxylic Acids via the Knoevenagel Condensation

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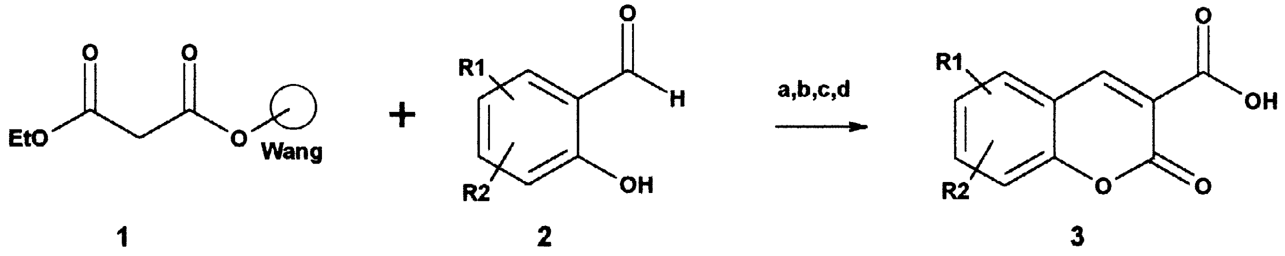
Abstract: A solid phase synthesis of substituted coumarin-3-carboxylates using the Knoevenagel condensation reaction between ethyl malonate bound to the Wang resin and *ortho*-hydroxyarylaldehydes is described. The reaction has been shown to proceed cleanly to give the desired products.

Keywords: combinatorial chemistry; coumarins; Knoevenagel condensation; solid-phase synthesis

The preparation of small organic molecules using solid phase organic synthesis has become increasingly important in the past few years for the rapid supply of a large number of highly diverse compounds for screening in the pharmaceutical and agrochemical industries. The relative ease of automation of chemistry on solid support along with the decreased need for tedious purification methods has resulted in its choice for this purpose. The Knoevenagel condensation on solid phase has been described for cyanoacetamides,[1] unsymmetrical malonamic esters,[2] malonates,[2] and β-ketoesters.[3] In 1898, Knoevenagel described the solution phase synthesis of coumarins by the condensation of malonic acid with *ortho*-hydroxyarylaldehydes.[4] Herein, we describe the use of this Knoevenagel condensation reaction on solid support to prepare substituted coumarin-3-carboxylic acids in a mild and facile manner with very good purity.



a) Piperidine/pyridine, RT, 16 h; b) Wash Resin; c) Repeat Steps 1,2; d) TFA/CH_2Cl_2

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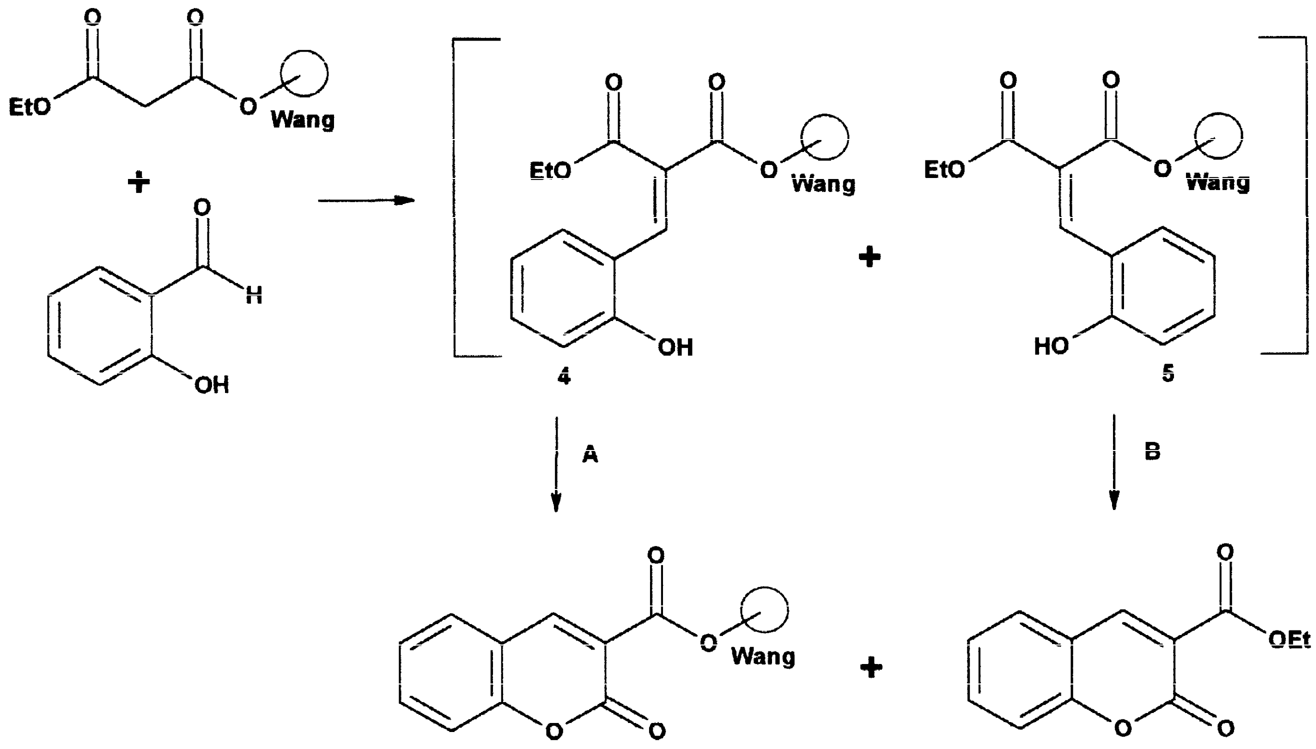
The reaction sequence is illustrated above in which ethyl malonate attached to the Wang resin (**1**) was suspended in pyridine, treated with a substituted *ortho*-hydroxyarylaldehyde (**2**) and a catalytic amount of piperidine. The cleanest and most consistent results were obtained when the resin was treated under these conditions, washed, and again subjected to the reaction conditions. The coumarin-3-carboxylic acids (3) were isolated in high purity after cleavage with trifluoroacetic acid/methylene chloride.[5] The products were obtained as solids in 7-29 milligram quantities; the purity of each was measured by HPLC at both 214 and 254 nm as shown in Table I. No extra purification steps were performed and there were no major impurities in the HPLC chromatogram; only baseline impurities were observed. All of the compounds were characterized by ^{1}H NMR, ^{13}C NMR and LC-MS.

Table I

	2			HPLC Purity (%)	
Entry	R1	R2	Yield of **3** (%)	214 nm	254 nm
a	H	H	36	90	82
b	3-Cl	H	39	93	>98
c	3-MeO	H	16	92	>98
d	3-Br	5-Br	36	74	95
e	3-Br	5-Cl	39	69	90
f	3-I	5-I	34	92	97
g	4-OH	H	28	96	>98
h	4-MeO	H	40	68	87
i	4-MeO	6-MeO	40	70	80
j	5-Br	H	35	83	91
k	5-MeO	H	35	97	>98
l	5-Cl	H	39	97	>98
m	5-  -6		37	>98	96

Our results and others have shown that the Knoevenagel condensation between alkyl malonates attached to the Wang resin and variously substituted arylaldehydes proceeds to give mixtures of the E:Z isomers in good yields.[2a, 6] In the case of *ortho*-hydroxyarylaldehydes we have found evidence to suggest that these also undergo the Knoevenagel condensation to give a mixture of the E and Z isomers (**4**, **5**) as shown in the following scheme. A suspension of the resin-bound ethyl malonate (**1**) in pyridine was treated with excess 2-hydroxybenzaldehyde and piperidine. HPLC analysis of the solution phase after 16 hours showed ethyl-3-coumarin carboxylate and excess *ortho*-hydroxybenzaldehyde. The pyridine and piperidine were then removed from the reaction in vacuo and the residue was treated with TFA/CH_2Cl_2. HPLC analysis of this mixture showed both ethyl-3-coumarin carboxylate and the coumarin-3-carboxylic acid in an approximately 1:1 ratio.[7] These results suggest that both **4** and **5** are generated as intermediates in approximately the same ratio and that the subsequent ring closure between the *ortho*-hydroxy group and the respective carbonyl group proceeds to give two different products. The arylhydroxy group of the E isomer (**4**) adds to the carbonyl to give the coumarin-3-carboxylate which remains attached to the resin (Pathway A). Ring closure of the Z isomer (**5**) results in autocleavage from the resin to give the ethyl coumarin-3-carboxylate in the solution phase (Pathway B). These data suggest that the maximum yield of coumarin-3-carboxylate that may be obtained by this method is limited to less than 100 percent. In light of these results, the yields of the products listed in Table I are encouraging. At the present time we are exploring the option by which the hydroxy group of an *ortho*-hydroxyarylaldehyde is selectively attached to the malonate resin by an ester linkage and the ring closure to the coumarin is formed directly by the Knoevenagel condensation.



In summary, we have developed a very simple synthesis of coumarin-3-carboxylic acids utilizing the Knoevenagel condensation between a resin-bound ethyl malonate and *ortho*-hydroxyarylaldehydes. The ease of this synthesis makes it very suitable for automation and the high purity of the isolated product should allow it to be considered for use in a multiple-step solid phase synthesis.

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References and Notes

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5. Preparation of **1**: Wang Resin (1 eq), purchased from Bachem with a loading of 0.92 mmol/g, was washed with DMF (3x), methylene chloride (3x) and dried in vacuo. To this was added ethyl potassium malonate (10 eq.) followed by N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride (10 eq) and the reaction was allowed to shake at RT for 16 h. The resin was filtered and washed: (9/1) DMF/H_2O (3x), DMF (3x), methylene chloride (3x). Preparation of **3a-m**: **1** (1 eq.) was suspended in pyridine, to this was added *ortho*-hydroxyarylaldehyde (20 eq) and piperidine (40 μL). The reaction was allowed to shake for 16 h at RT, the resin was filtered, washed: (9/1) DMF/H_2O (3x), DMF (3x), methylene chloride (3x); retreated with the reagents, and washed again as described. The resin was suspended in TFA/CH_2Cl_2 (1/2) and shaken for 1 h. The reaction was filtered, the resin washed with methylene chloride (2x) and the filtrate was evaporated to give product.
6. Using the same synthetic method as described in note 5, in two independent experiments, 2-methoxybenzaldehyde and 2,3-methylenedioxybenzaldehyde were allowed to react with Wang resin-bound methyl malonate. After cleavage, 1.4:1 and 1.6:1 mixtures of the E/Z isomers were obtained in 61%, 83% yield respectively; both with 94% purity as measured by HPLC (254 nm).
7. 2-hydroxybenzaldehyde, ethyl-3-coumarin carboxylate, and coumarin-3-carboxylic acid were correlated by HPLC retention times with authentic samples.