Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1755–1758

TETRAHEDRON LETTERS

A convenient synthesis of coumarin-3-carboxylic acids via Knoevenagel condensation of Meldrum's acid with *ortho*-hydroxyaryl aldehydes or ketones

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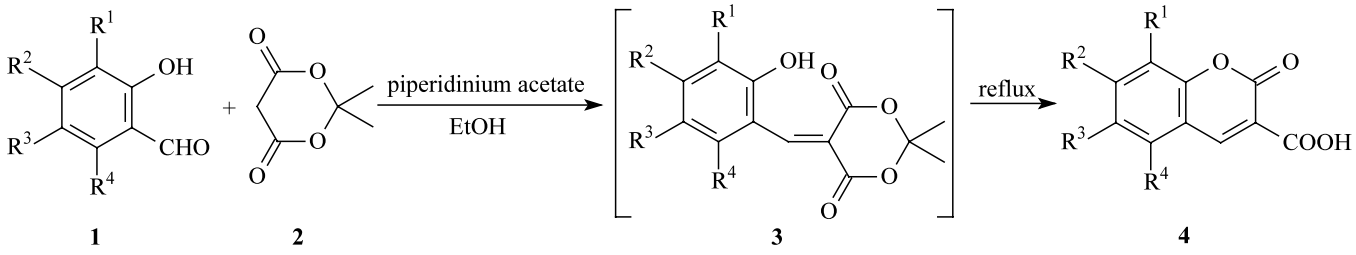
Received 7 January 2003; accepted 13 January 2003

Abstract—Coumarin-3-carboxylic acids were obtained in high yields with excellent purity from *ortho*-hydroxybenzaldehydes and Meldrum's acid after a 2 h reflux in ethanol. The less reactive ketones were first reacted with alcoholic ammonia to form ketimines, which were then condensed with Meldrum's acid to generate 4-alkylcoumarin-3-carboxylic acids in moderate yields.

Coumarin-3-carboxylic acids (2-oxo-2*H*-benzopyran-3-carboxylic acids) are important initial compounds for the synthesis of coumarins, which are well known natural products for their diverse biological activities.[1] Coumarin derivatives have a broad range of applications in the pharmaceutical, perfume, and cosmetic industries.[2] Some carboxycoumarins have been used as fluorescent probes[3,4] and triplet sensitizers.[5,6]

Coumarin-3-carboxylic acids are traditionally prepared via Knoevenagel condensation[7] of *ortho*-hydroxyaryl aldehydes with malonic acid,[7,8] malonic ester,[8,9] or cyanoacetic ester.[10] In 1988, Armstrong et al.[11] developed a two-step method for the synthesis of coumarin-3-carboxylic acids. 2-Methoxybenzaldehydes were condensed with Meldrum's acid in DMF, followed by cyclization in the presence of sulfuric acid. Since then, several one-pot procedures have been reported using Meldrum's acid as the condensation reagent.[12–15] The reaction is catalyzed by sodium hydroxide,[13] clays,[14] or lithium salts.[15] A solid phase approach has also been described.[16]

In an effort to find suitable fluorescent probes for peptides and proteins in our laboratory, we have found that coumarin-3-carboxylic acids can be readily prepared from 2-hydroxybenzaldehydes and Meldrum's acid under the classic conditions for Knoevenagel condensation.[7] Equal molar equivalents of 2-hydroxybenzaldehydes (**1**) and Meldrum's acid (**2**) were first incubated in the presence of a catalytic amount of piperidinium acetate at room temperature, followed by reflux in ethanol (Fig. 1). The synthesis was easy because the reactants dissolved quickly, and the prod-



1 **2** **3** **4**

Figure 1. One-pot synthesis of coumarin-3-carboxylic acids.

Keywords: coumarin-3-carboxylic acids; Knoevenagel condensation; Meldrum's acid.
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0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4039(03)00108-4

Table 1. One-pot synthesis of coumarin-3-carboxylic acids (Fig. 1)

Entry	R^1	R^2	R^3	R^4	Yield (%)	HPLC purity (%)		mp[a] (°C)
						(214 nm)	(254 nm)	
a	H	H	H	H	89	96	98	191–192
b	H	Et_2N	H	H	85	97	98	222–224
c	H	MeO	H	H	88	94	97	192–194
d	H	OH	H	H	89	95	97	261–263
e	H	MeO	H	MeO	98	95	98	235–237
f	H	H	Cl	H	85	96	98	120–121
g	H	H	Br	H	70	93	96	195–196
h	H	H	NO_2	H	88	92	95	234–235
i	MeO	H	NO_2	H	61	89	94	219–220
j	H	H	CH–CH=CH–CH		77	91	95	236–237

[a] Samples were recrystallized from aqueous acetone or ethanol.

ucts formed crystals in the solvent. After filtration and washing with ethanol, coumarin-3-carboxylic acids (**4**) were obtained in excellent yields and purity.[17] Their structures and yields are listed in Table 1.

Ten 2-hydroxybenzaldehydes bearing various substituents were used in our study. All of them, including those bearing electron-withdrawing substituents (Table 1, **1h** and **1i**), react readily with Meldrum's acid after reflux in ethanol for 2 h. Excess of Meldrum's acid should be avoided because it may react with the formed coumarin-3-carboxylic acid leading to a decrease in yield and purity.[18,19] The cyclization step was quick and the intermediate **3** was never isolated in all cases.

This one-pot procedure is convenient and straightforward with simple product isolation. No recrystallization is needed in most cases. Nevertheless, using this method, we failed to prepare 4-alkylcoumarin-3-carboxylic acids due to the lack of the ketone reactivity to nucleophilic attack compared to aldehydes. The *ortho*-hydroxyaryl ketones were recovered unchanged after the reaction. For the condensation with Meldrum's acid, ketones require either (i) activation by titanium tetrachloride[20] or (ii) replacement by the corresponding ketimines obtained from the reaction between a Grignard reagent and a nitrile.[21] The first method is not a good choice for our purpose as the phenolic hydroxyl group may deactivate the catalyst. In the second method, the preparation of ketimines is quite involved.

To avoid the use of Grignard reagents, we tried to prepare ketimines from ammonia and ketones directly. The ketimine products were used to react with Meldrum's acid without isolation and purification (Fig. 2). Ammonium hydroxide, ammonium acetate/ethanol, ammonia/methanol and ammonia/ethanol were tested as the ammonia source. In all cases except with ammonium acetate, ketimines can be readily formed. We prefer to use 7 M ammonia solution in methanol because it can be easily removed.

Several different *ortho*-hydroxyaryl ketones were mixed with 7 M ammonia solution in methanol overnight at room temperature. Some crystals were formed the next day. The solvent and excess ammonia were removed in vacuo. The removal of excess ammonia is important as it causes serious decomposition of Meldrum's acid. The residue was refluxed with Meldrum's acid in ethanol to generate the coumarin derivatives.

We found that the ketimine intermediates formed smoothly in all cases, but only those from alkyl phenyl ketones such as propiophenone were successfully condensed with Meldrum's acid. 4-Alkylcoumarin-3-carboxylic acids were obtained in moderate yields.[22] The yield of 4-methyl-5,6-benzocoumarin-3-carboxylic acid from 2′-hydroxy-1′-acetonaphthone was poor probably due to the strong steric hindrance. 2-Hydroxybenzophenones could be converted to the corresponding ketimines, but the latter did not react with Meldrum's acid at all. The ketones were recovered unchanged after reflux with Meldrum's acid in ethanol.

The structures and yields of 4-alkylcoumarin-3-carboxylic acids are shown in Table 2. Seven 4-alkylcoumarin-3-carboxylic acids were obtained in moderate

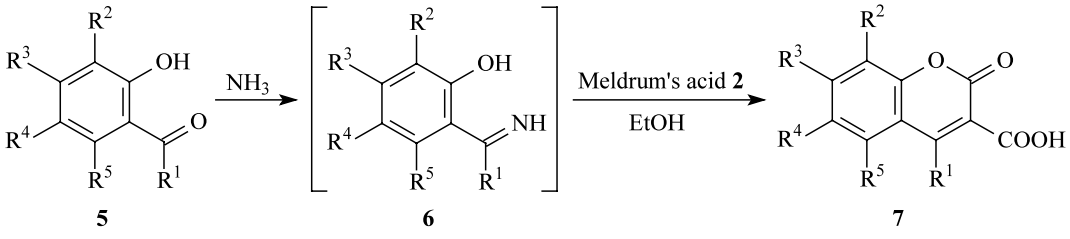

Figure 2. Synthesis of 4-alkylcoumarin-3-carboxylic acids via a ketimine intermediate.

Table 2. Synthesis of 4-alkylcoumarin-3-carboxylic acids (Fig. 2)

Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)	mp (°C)
a	Me	H	H	H	H	57	161–162
b[a]	Me	H	F	H	H	66	205–206
c	Me	H	H	Cl	H	62	151–152
d	Me	H	MeO	H	H	60	184–185
e	Et	H	H	H	H	51	165–166
f	*n*-Pr	H	H	H	H	54	144–146
g[a]	2-PhEt	H	H	H	H	53	160–161
h[a]	Me	H	H	CH–CH=CH–CH		12	190–192

[a] New compounds.[23]

yields using this method. Since the isolation and the purification of intermediates were eliminated, the synthesis is straightforward despite involving two steps.

In summary, we have developed a convenient method for the synthesis of coumarin-3-carboxylic acids from *ortho*-hydroxyaryl aldehydes and Meldrum's acid. The reaction is rapid and clean. This method has been successfully modified to prepare their 4-alkyl substituted derivatives from the less reactive *ortho*-hydroxyaryl ketones.

Acknowledgements

This work was supported by NIH R33CA-86364. The 500 MHz NMR spectrometer was purchased in part with a grant from the National Sciences Foundation, NSF 9724412.

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17. A mixture of *ortho*-hydroxyaryl aldehyde (20 mmol), Meldrum's acid (2.89 g, 20 mmol), piperidinium acetate (58 mg, 0.4 mmol) and ethanol (10 mL) was stirred at room temperature for 20 min, and then refluxed for 2 h. The reaction mixture was allowed to cool down to room temperature, followed by chilling in an ice bath for 1 h. The crystallized product was filtered, washed three times with ethanol, and dried in vacuo.
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22. *ortho*-Hydroxyaryl ketone (20 mmol) was shaken with 7 M ammonia solution in methanol (15 mL) at room temperature overnight. The mixture was concentrated in vacuo to dryness. Meldrum's acid (3.46 g, 24 mmol) and ethanol (10 mL) were added to the residue. The mixture was refluxed for 5 h, and then allowed to cool to room temperature. After complete precipitation, the product was filtered and recrystallized from aqueous acetone. For the products highly soluble in ethanol (**7g** and **7h**), the solvent was removed in vacuo after the reaction. The residue was proportioned between 5% aqueous sodium carbonate solution (20 mL) and ethyl acetate (10 mL). The aqueous phase was acidified with 1 M HCl to pH 2, followed by extraction with ethyl acetate (10 mL×3). The organic phase was combined, washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to dryness. The residue was recrystallized from aqueous acetone.
23. Spectral data for new compounds. 7-Fluoro-4-methyl-2-oxo-2*H*-benzopyran-3-carboxylic acids (**7b**). ^{1}H NMR (DMSO-d_6) δ 13.6 (s, broad, 1H), 7.84 (m, 1H), 7.34 (m, 1H), 7.26 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 166.3, 163.3 (d, $^1J_{CF}=249.5$ Hz), 157.8, 153.0 (d, $^3J_{CF}=7.3$

Hz), 144.0, 127.8 (d, $^3J_{CF}=11.1$ Hz), 116.8, 113.3, 112.1 (d, $^2J_{CF}=22.0$ Hz), 103.9 (d, $^2J_{CF}=25.9$ Hz), 15.9. ESI-MS m/z 223.1 (MH^+). 4-(2-Phenylethyl)-2-oxo-2*H*-benzopyran-3-carboxylic acids (**7g**). ^{1}H NMR (DMSO-d_6) δ 13.7 (s, broad, 1H), 7.81 (d, $J=8.0$ Hz, 1H), 7.52 (t, $J=7.4$ Hz, 1H), 7.44 (m, 1H), 7.34 (m, 5H), 7.20 (t, $J=7.4$ Hz, 1H), 3.02 (t, $J=8.1$ Hz, 2H), 2.88 (t, $J=8.1$ Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 166.8, 158.8, 152.1, 143.6, 141.5, 130.3, 128.4, 128.3, 126.1, 125.1, 124.3, 119.4, 116.3, 34.9, 31.5. ESI-MS m/z 295.1 (MH^+). 1-Methyl-3-oxo-3*H*-naphtho[2,1-*b*]pyran-2-carboxylic acid (**7h**). ^{1}H NMR (DMSO-d_6) δ 13.6 (s, broad, 1H), 8.65 (d, $J=9.0$ Hz, 1H), 8.26 (d, $J=9.0$ Hz, 1H), 8.11 (d, $J=8.5$ Hz, 1H), 7.73 (t, $J=7.6$ Hz, 1H), 7.65 (t, $J=7.6$ Hz, 1H), 7.59 (d, $J=8.5$ Hz, 1H), 2.89 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 166.3, 156.9, 153.3, 150.2, 134.8, 131.3, 129.8, 129.6, 128.3, 125.9, 125.7, 122.9, 117.2, 113.6, 22.7. ESI-MS m/z 255.1 (MH^+).