Multicomponent protocol for the synthesis of substituted methyl 3-(3-hydroxy-4-oxo-4H-chromen-2-yl)propanoates from 3-hydroxy-4H-chromen-4-one

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ABSTRACT
An efficient one-stage method for the preparation of substituted methyl 3-(3-hydroxy-4-oxo-4H-chromen-2-yl)propanoates was developed. The suggested approach based on multicomponent reaction of 3-hydroxy-4H-chromen-4-one with carbonyl compounds and Meldrum’s acid. The advantages of this synthesis are readily accessible starting materials, mild reaction conditions, atom economy and easy workup procedure, which can avoid chromatographic purifications. The structures of the obtained compounds were established by 1H, 13C-NMR spectroscopy and high-resolution mass spectrometry.

GRAPHICAL ABSTRACT

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Introduction
3-Hydroxy-4H-chromen-4-one derivatives are an important class of heterocyclic compounds. 3-Hydroxy-4H-chromen-4-one core is part of a variety of natural compounds with a wide range of biological activity.[1−3] Numerous representatives of products of this type are widely used in medicine, wherein 2-aryl-3-hydroxy-4H-chromen-4-ones are utilized for this purpose. For example, the well-known plant flavanol quercetin belonging to this class is one of the leaders in terms of the variety of described biological properties.[4−8] Other well-studied flavanols of natural origin are fisetin, morin, gossypetin and myricetin which are also widely employed in medicinal chemistry.[9−15] At the same time, the biological activity of 3-hydroxy-4H-chromen-4-ones containing other substituents in position 2 have been poorly studied.[16]
Another important application of 3-hydroxy-4\textsubscript{H}-chromen-4-one derivatives is based on the interesting spectral properties of these products. The promising fluorescent properties of these compounds are mainly associated with the excited state intramolecular proton transfer (ESIPT) process. So, the employment of compounds of this class as fluorescence labels and sensors has been proposed in the literature.\textsuperscript{[17–21]} In addition, a report\textsuperscript{[22]} describes the use of substituted 3-hydroxy-4\textsubscript{H}-chromen-4-one as the longest wavelength fluorescent dyes. Another important aspect of the application of 3-hydroxy-4\textsubscript{H}-chromen-4-ones is the ability to complex formation.\textsuperscript{[23,24]} Thus, products containing a 3-hydroxy-4\textsubscript{H}-chromen-4-one fragment are of considerable interest in various fields of science and technology. In this regard, actual task is elaboration of synthetic approaches that allows one to obtain a wide range of products of this type without using a complex sequence of multistage syntheses. To implement this goal the methodology of multicomponent reactions using unsubstituted 3-hydroxy-4\textsubscript{H}-chromen-4-one can be applied.

Previously, we proposed a convenient method for the synthesis of methylpropanoates 1 containing 5-hydroxy-2-methyl-4\textsubscript{H}-pyran-4-one fragment based on the multicomponent reaction of allomaltol 2 with carbonyl compounds 3 and Meldrum’s acid 4 (Scheme 1A).\textsuperscript{[25]} At the same time, the method of enantioselective C2-functionalization of 3-hydroxy-4\textsubscript{H}-chromen-4-one 5 promoted by N-heterocyclic carbenes leading to 3-(3-hydroxy-4-oxo-4\textsubscript{H}-chromen-2-yl)propanoates 6 is described in the literature. (Scheme 1B).\textsuperscript{[26]}

As part of ongoing research in our group toward the multicomponent reactions using Meldrum’s acid\textsuperscript{[25,27–31]} herein we describe a highly efficient method for the synthesis of 3-hydroxy-4\textsubscript{H}-chromen-4\textsubscript{H}-one derivatives 8 (Scheme 1C).

Scheme 1. Synthesis of methylpropanoates.

![Scheme 1](image-url)
Results and discussion

In the present communication we have shown that a multicomponent condensation of 3-hydroxy-4H-chromen-4-one 9, carbonyl compounds 10 and Meldrum’s acid 4 leads to previously unknown substituted methyl 3-(3-hydroxy-4-oxo-4H-chromen-2-yl)propanoates 8 (Scheme 1C). It should be noted that the formation of a methyl ester fragment in the structure of the target compounds 8 is due to the use of methanol as a solvent.

We started the considered investigation employing aldehydes as a carbonyl component. Initially, we have chosen the model reaction of 3-hydroxy-4H-chromen-4-one 9, 4-methoxybenzaldehyde 10a and Meldrum’s acid 4 in MeOH and the results are summarized in Table 1. In order to achieve the best results, we varied the time and temperature of the reaction, as well as the basic reagents.

The optimal results were obtained using Et3N as a base, the best yield was achieved at reflux for 2 h (Table 1, entry 2). A further increase of the process time did not affect the yield of product 8a (Table 1, entry 3). At the same time the target 3-(3-hydroxy-4-oxo-4H-chromen-2-yl)propanoate 8a is formed only in 22% yield upon 2 h stirring of the reaction mixture at room temperature (Table 1, entry 4). Wherein, prolonged stirring under these conditions increases the yield only up to 41%. (Table 1, entries 5 and 6). We also tested the use of various bases in the studied multicomponent process (Table 1, entries 8–11). Thus, it was demonstrated that the employment of triethylamine is preferable for the considered reaction (Table 1, entry 2). At the same time, the application of other bases (DABCO, DIPEA, DBU, K2CO3) decreased the yield of the target product 8a (Table 1, entries 8–11). Whereby it is important to emphasize that the use of base is a necessary condition for the studied process (Table 1, entry 7).

Applying the above conditions, we have obtained a wide range of substituted methyl 3-(3-hydroxy-4-oxo-4H-chromen-2-yl)propanoates 8a–m using various aldehydes as
Note that the proposed method is of a general nature and allows one to obtain target compounds \(8a-m\) containing aromatic, heterocyclic or aliphatic substituents in high yields. The type of aldehyde \(10a-m\) does not significantly influence the studied process.

The synthesized products \(8a-m\) are solid crystalline compounds, whose structure was confirmed by \(^1\)H, \(^{13}\)C-NMR spectroscopy and high-resolution mass spectrometry. \(^1\)H NMR spectra of the products exhibit characteristic signals of the protons of the methine fragment in the region \(\delta 4.7–5.2\) ppm and of the protons of the methylene group in the region \(\delta 2.9–3.32\) ppm. The remaining signals are also in good agreement with the presented structures.

Table 2. Synthesis of methyl 3-(3-hydroxy-4-oxo-4\(H\)-chromen-2-yl)propanoates \(8a-m\).\(^a\)

| \(8a\) | \(8b\) | \(8c\) | \(8d\) | \(8e\) | \(8f\) | \(8g\) | \(8h\) | \(8i\) | \(8j\) | \(8k\) | \(8l\) | \(8m\) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 84% | 79% | 76% | 86% | 82% | 84% | 83% | 90% | 92% | 91% | 79% | 70% | 70% |

\(^a\)Reaction conditions: \(9\) (3 mmol, 0.49 g), \(10\) (3.3 mmol), \(4\) (3.6 mmol, 0.52 g), Et\(_3\)N (3.3 mmol, 0.34 g), MeOH (8 mL), reflux, 2 h.

The carbonyl component (Table 2). Note that the proposed method is of a general nature and allows one to obtain target compounds \(8a-m\) containing aromatic, heterocyclic or aliphatic substituents in high yields. The type of aldehyde \(10a-m\) does not significantly influence the studied process.

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After having established a general synthetic pathway to target compounds \(8a-m\), we tested the studied multicomponent approach using ketones \(10n-q\) as the carbonyl component. It was shown that condensation of 3-hydroxy-4\(H\)-chromen-4-one \(9\), various ketones \(10n-q\) and Meldrum’s acid \(4\) in refluxing MeOH for 2 h leads to methyl esters \(8n-q\) (Table 3). Wherein, Et\(_3\)N also was used as basic reagent similar to the example described above for the aldehydes \(10n-q\).
acid moiety accompanied by elimination of CO$_2$ and acetone produced lactone D. Finally, intermediate D is transformed to the target methyl ester 8 via nucleophilic opening of lactone ring under the action of methanol.

**Conclusion**

In summary, convenient one pot approach for the synthesis of substituted methyl 3-(3-hydroxy-4-oxo-4H-chromen-2-yl)propanoates was elaborated. The suggested protocol is based upon the multicomponent reaction of 3-hydroxy-4H-chromen-4-one with carbonyl compounds and Meldrum’s acid. The proposed method is of a general nature and allows one to use various aldehydes and ketones, wherein the target 3-hydroxy-4H-chromen-4-one containing methyl propanoates were obtained in high yields.
The advantages of this synthesis are easily available starting compounds, mild reaction conditions, atom economy and simple workup procedure without chromatographic purifications. The structures of the obtained compounds were established by $^1$H, $^{13}$C-NMR spectroscopy and high-resolution mass spectrometry.

**Experimental**

Unless otherwise stated, all starting chemicals were commercially available and were used as received. NMR spectra were recorded with Bruker AM 300 (300 MHz) spectrometers in DMSO-d$_6$. Chemical shifts (ppm) are given relative to solvent signals (2.50 ppm for $^1$H NMR and 39.52 ppm for $^{13}$C NMR). High-resolution mass spectra (HRMS) were obtained on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The melting points were determined on a Kofler hot stage.

**General procedure for the synthesis of methyl 3-(3-hydroxy-4-oxo-4H-chromen-2-yl)propanoates 8**

A mixture of 3-hydroxy-4H-chromen-4-one 9 (3 mmol, 0.49 g), corresponding aldehyde or ketone 10 (3.3 mmol), Meldrum’s acid 4 (3.6 mmol, 0.52 g) and Et$_3$N (3.3 mmol, 0.34 g) in MeOH (8 mL) was refluxed for 2 h. The resulting solution was cooled to room temperature. The precipitate formed was filtered off and washed with MeOH (3 x 5 mL).

Full experimental details, copies of $^1$H and $^{13}$C NMR spectra can be found via the ‘Supplemental material’ section of this article’s webpage.

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