Diastereoselective One-Pot Synthesis of Succinimides Bearing a Chromone Unit

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Abstract A diastereoselective synthesis of highly substituted succinimide derivatives with chromone and carboxylic ester functionalities from 3-formylchromones, Meldrum’s acid, and alkyl isocyanides in the presence of alcohols in moderate to good yields is described.

Key words formylchromone, isocyanide, Meldrum’s acid, succinimide

Succinimides represent a privileged scaffold in medicinal chemistry, and this structural motif can be found in many natural products such as moiramide B, andrimid, hirsutellone A, and haterumaimide A (Figure 1).1

Succinimide-substructure-containing compounds show great pharmacological potential acting as enzyme inhibitors, analgesics, antimicrobial agents, anxiolytics, cytotoxic, anticonvulsants, antitumor drugs, and anti-Parkinson’s agents.2 On the other hand, chromones are an important moiety, forming the nucleus of a class of heterocyclic natural products called flavanoids that occur naturally in fruits, vegetables, nuts, seeds, flowers, and bark.3 They are an integral part of the human diet and have been reported to exhibit a wide range of biological effects.4 They display not only spasmolytic, diuretic, clotting, antibacterial, antiviral, antitumoral, anti-inflammatory, and anti-anaphylactic activity, but can also be used as antioxidants, pigments, phototoxic materials, and biodegradable agrochemicals.5

Meldrum’s acid and its 5-arylidene or 5-alkylidene derivatives (which are readily accessible from the reactions of Meldrum’s acid and aldehydes or ketones) have acquired considerable interest as highly reactive electron-deficient heterodienes in isocyanide-based multicomponent reactions. In our earlier publications,6 we have described four relatively facile routes to amidodiesters and triamides by taking advantage of Meldrum’s acid derivatives. These compounds were obtained by treatment of Meldrum’s acids with aldehydes (5-alkylidene or 5-arylmethylidene Meldrum’s acids) and isocyanides in the presence of such nucleophiles as alcohols,6a–c phenols,6c and primary amines6d in dichloromethane. Based on these efficient and useful multicomponent reactions, more efforts were made to investigate the reactions of Meldrum’s acid derivatives and isocyanides with other nucleophiles such as water,7 diols,8 arylhydroxylamines,9 aryl hydrazines,10 2-hydroxy benzaldehydes,11 sugar hydroxyaldehydes,12 and urea,13 which produced 4-oxobutanoic acids, 2-arylisoxazolidine-3,5-diones, 1,4-dioxepane-5,7-diones, 1-arylpseudazolidine-3,5-diones, 3,4-dihydrocoumarins, 5-oxo-perhydrofurans, 3,2-b]pyrans, and barbituric acid derivatives, respectively.
Recently, we reported the pseudo-five-component tandem reaction of 3-formylchromones, Meldrum’s acid, and isocyanides with primary aryl amines, which offers an efficient route to construct chromone-containing tripeptides under mild conditions with high efficiency. However, when the substrate combination was switched from primary aryl amines to alcohols, to our surprise, none of the expected products were obtained. We now disclose a new multicomponent cascade reaction of 3-formylchromones with Meldrum’s acid, isocyanides, and alcohols dia stereoselectively providing polyfunctionalized succinimide derivatives (Scheme 1).

In an initial experiment, a solution of equimolar amounts of 6-methyl-3-formylchromone, Meldrum’s acid, benzyl isocyanide, and 2-adamantol in dry dichloromethane was stirred at room temperature for 24 hours to afford benzyl isocyanide, 2-adamantol in dry dichloromethane to produce the corresponding succinimide derivatives in good yields. Furthermore, it was observed that the nature of the substituents at C-6 and C-8 of the chromone ring affects the reaction significantly. Under similar reaction conditions, starting with Meldrum’s acid, cyclohexyl isocyanide, ethanol, and chlorinated 3-formylchromones, such as 6-chloro-3-formylchromone or 6,8-dichloro-3-formylchromone, the corresponding known products were isolated, respectively, without the participation of Meldrum’s acid and ethanol, which did not enter into these reactions.

In addition, we found that the reactions proceeded very efficiently with alkyl isocyanides (cyclohexyl isocyanide, benzyl isocyanide, 1,1,3,3-tetramethylbutyl isocyanide, and 2-morpholinooethyl isocyanide), but failed to furnish the expected chromone-bound succinimide derivatives with aryl isocyanides (2,6-dimethylphenyl isocyanide and 2-naphthyl isocyanide).

A variety of structurally diverse alcohols underwent the one-pot reaction smoothly without need for a catalyst to afford the corresponding succinimide derivatives in good yields. As shown in Table 1, primary alcohols (ethanol, 1-propanol, 1-butanol, and 1-pentanol) benzylic alcohols (benzyl- and 4-chlorobenzyl alcohol), heterocyclic alcohol (2-furylmethanol), hindered and unhindered secondary and tertiary alcohols (2-adamantol, cyclohexanol, and tert-amyl alcohol) were used in this protocol with good results.

In the case of the sterically unhindered methanol, the amido diester fragments were formed instead of the expected formation of succinimide moieties (Table 1, entries 12 and 13).
### Table 1  Structure of Compounds 6a–k and 5a–b

<table>
<thead>
<tr>
<th>Entry</th>
<th>3-Formylchromone</th>
<th>Alcohol</th>
<th>Isocyanide</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>EtOH</td>
<td>NC</td>
<td><img src="image2.png" alt="Product" /></td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>CH3OH</td>
<td>NC</td>
<td><img src="image4.png" alt="Product" /></td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>CH3OH</td>
<td>NC</td>
<td><img src="image6.png" alt="Product" /></td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>CH3OH</td>
<td>NC</td>
<td><img src="image8.png" alt="Product" /></td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Structure" /></td>
<td>phenyl</td>
<td>NC</td>
<td><img src="image10.png" alt="Product" /></td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Structure" /></td>
<td>CH3OH</td>
<td>NC</td>
<td><img src="image12.png" alt="Product" /></td>
<td>70</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield calculated using HPLC analysis.
O

\[\text{O} \text{OH} \] \[\text{O} \text{NO} \]

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A plausible mechanism for the formation of the fully functionalized succinimides 6 is proposed in Scheme 2. The reaction may be rationalized by initial formation of the conjugated electron-deficient heterodiene by Knoevenagel condensation of the 3-formylchromone 1 and Meldrum’s acid (2), followed by a [4+1]-cycloaddition reaction with isocyanide 3 to afford an iminolactone intermediate 9. Conjugate addition of the alcohol on the enone moiety of 9, followed by cleavage of the five-membered iminolactone ring gives 10 and hence the α-oxoketene 11 by well precedent17 electrocyclic ring opening of O-alkylated Meldrum’s acids. The α-oxoketene 11 can then undergo intramolecular reaction between the amide and ketene moieties to give stable carbanion intermediate 12. The resulting enolate 12 undergoes stereoselective reprotonation to yield the thermodynamically favorable isomer of the product 6. Among the alcohols studied, only methanol, as the least sterically hindered alcohol, can compete with the adjacent amide nitrogen atom in attacking the ketene moiety to produce the dimethyl malonate derivative 5.

It is important to note that compound 6 has two stereogenic centers, and therefore, two pairs of diastereoisomers are expected. The $^1$H NMR and $^{13}$C NMR spectra of the crude reaction mixture obtained from products were consistent with the presence of only one diastereomer. All measured coupling constants for the protons H3 and H4 in compounds 6a–k are in the range of 6.0–6.8 Hz which suggests a trans arrangement for these two hydrogen atoms. The relative configuration was determined by X-ray crystal-structure analysis in the case of 6i (Figure 2).
In summary, we have developed a four-component tandem reaction for the formation of biologically interesting chromone-bound succinimides. The merit of this diastereoselective cascade reaction is highlighted by its mild reaction conditions, easy workup, acceptable yields, high bond efficiency of producing five new bonds (two C–C and three C–heteroatom), and two stereocenters in a single operation.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378926.

References and Notes

(15) General Procedure for the Synthesis of Alkyl-1-alkyl-4-(4-oxo-4H-chromen-3-yl)-2,5-dioxopyrrolidine-3-carboxylates 6

A mixture of the appropriate 3-formylchromone 1 (1 mmol) and Meldrum’s acid (2, 1 mmol) was stirred in anhydrous CH2Cl2 (10 mL) for 3 h at r.t., and then alcohol 4 (1 mmol) followed by alkyl isocyanide 3 (1 mmol) was added at rt. After complete conversion, as monitored by TLC using EtOAc–hexane (1:1) as eluent, the mixture was concentrated in vacuo, and the solid residue was washed with EtO and crystallized from CHCl3–hexane (1:3) to afford pure product 6.

rac-2-Adamantyl (3R,4S)-1-Benzyl-4-(6-methyl-4-oxo-4H-chromen-3-yl)-2,5-dioxopyrrolidine-3-carboxylate (6i)

White powder; mp 195–196 °C (melt.). IR (KBr): νmax = 1783, 1709, 1646 (C=O), 1616 (C=C) cm–1. 1H NMR (300.1 MHz, CDCl3): δ = 1.49–2.06 (14 H, m, adamantyl), 2.45 (3 H, s, CH3), 4.02 and 4.08 (2 H, AB-ν system, JHH = 6.1 Hz, CHCH), 4.75 and 4.86 (2 H, AB-ν system, JHH = 14.4 Hz, PhCH2). 13C NMR (75.5 MHz, CDCl3): δ = 176.6, 174.9, 170.8, 166.8, 154.6, 153.8, 153.5, 153.3, 128.6, 128.2, 127.8, 125.0, 123.4, 119.2, 79.8, 52.0, 44.0, 37.2, 36.3, 36.2, 31.8, 31.6, 31.5, 31.4, 27.0, 26.8, 21.0. Anal. Calcd (%): C, 73.13; H, 7.20; N, 2.66. Found: C, 72.81; H, 5.97; N, 2.70.

X-ray Data for 6i

C25H31N1O6, M = 525.58 g·mol–1, orthorhombic system, space group P212121, a = 10.889(19), b = 11.934(19), c = 22.490(3) Å, V = 2707.9(8) Å3, Z = 4, Dcalc = 1.289 g cm–3, μ(Mo Kα) = 0.898 mm–1, crystal dimension of 0.50 × 0.30 × 0.25 mm. The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL of the X-Step32 suite of programs. Crystallographic data for 6i have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 1019444, Union Road, Cambridge CB2 1EZ, UK. Fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk.

rac-Dimethyl [1-(6-methyl-4-oxo-4H-chromen-3-yl)-2-oxo-2,1,3-tetramethylbutyl]amino[4-ethyl]malonate (5a)

White powder; mp 198–201 °C (dec.). IR (KBr): νmax = 3330 (NH), 1730, 1681, 1649 (C=O), 1621 (C=C) cm–1. 1H NMR (300.1 MHz, CDCl3): δ = 0.83 (9 H, s, CMe3), 1.29 (6 H, br s, CMe3), 1.49 and 1.73 (2 H, AB-ν system, JHH = 14.8 Hz, CH2), 2.43 (3 H,
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s,CH\textsubscript{3}), 3.55 and 3.74 (6 H, 2 s, 2 OCH\textsubscript{3}), 4.25 (1 H, d, \(J_{HH} = 12.4\) Hz, CH) 4.58 (1 H, d, \(J_{HH} = 12.4\) Hz, CH), 6.40 (1 H, s, NH), 7.34 (1 H, d, \(J_{HH} = 8.8\) Hz, CH\textsubscript{3}C=CHCH\textsubscript{3}), 7.48 (1 H, dd, \(J_{HH} = 8.8\) Hz, \(J_{HH} = 1.6\) Hz, CH\textsubscript{3}C=CHCH\textsubscript{3}), 7.97 (1 H, s, C=CHO), 7.98 (1 H, s, CH\textsubscript{3}C=CHC), \(\delta\) = 177.0, 168.6, 167.9, 167.8, 154.3, 153.6, 153.5, 135.4, 125.2, 123.0, 119.6, 118.0, 55.2, 52.9, 52.9, 52.0, 51.4, 41.4, 31.4, 31.2, 29.1, 28.7, 20.9. Anal. Calcd (%) for C\textsubscript{25}H\textsubscript{33}NO\textsubscript{7} (459.53): C, 65.34; H, 7.24; N, 3.05. Found: C, 65.50; H, 7.24; N, 3.08.