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Diastereoselective One-Pot Synthesis of Succinimides Bearing a Chromone Unit

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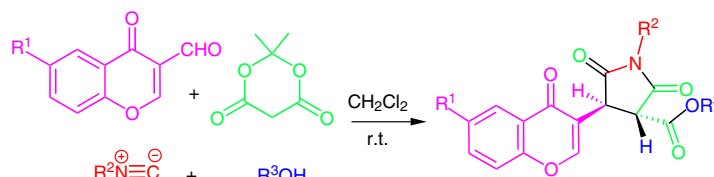Maryam Moayedi[b]
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Abstract A diastereoselective synthesis of highly substituted succinimide derivatives with chromone and carboxylic ester functionalities from 3-formylchromones, Meldrum's acid, and alkyl isocyanides in the presence of alcohols in 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]
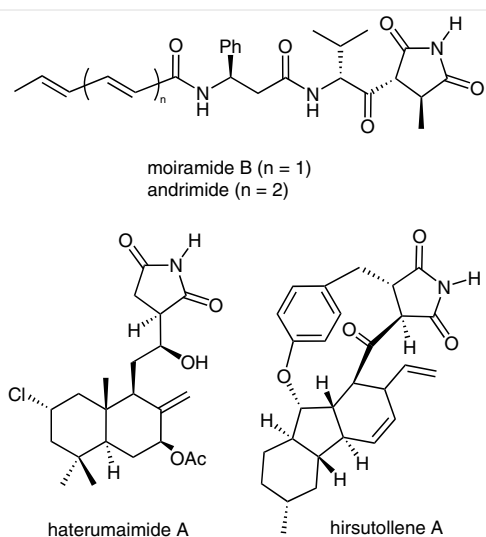

Figure 1 Examples of biologically active succinimide-containing natural products

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, photoactive 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 amines[6d] 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-arylpyrazolidine-3,5-diones, 3,4-dihydrocoumarins, 5-oxo-perhydrofuro-[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.[14] However, when the substrate combination was switched from primary aryl amines to alcohols, to our surprise, none of the expected products **5** were obtained. We now disclose a new multicomponent cascade reaction of 3-formylchromones **1** with Meldrum's acid (**2**), isocyanides **3**, and alcohols **4** diastereoselectively providing polyfunctionalized succinimide derivatives **6** (Scheme 1).

Scheme 1 Synthesis of chromone-bound succinimides **6**
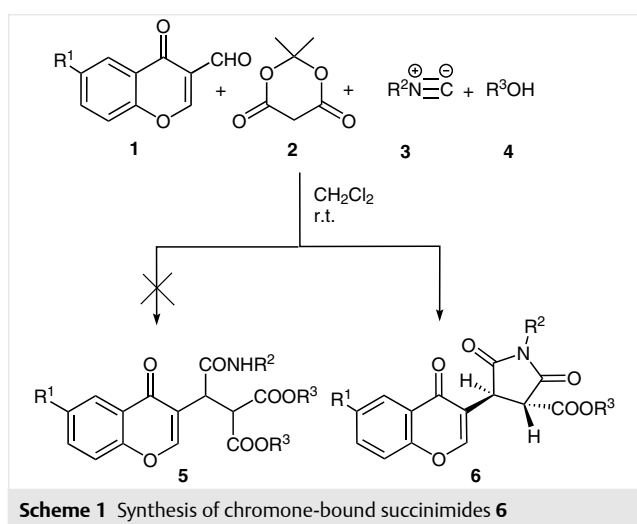
In an initial experiment, a solution of equimolar amounts 6-methyl-3-formylchromone, Meldrum's acid, benzyl isocyanide, and 2-adamantol in dry dichloromethane was stirred at room temperature for 24 hours to afford 2-adamantyl 1-benzyl-4-(6-methyl-4-oxo-4H-chromen-3-yl)-2,5-dioxopyrrolidine-3-carboxylate (**6i**) in 85% yield (Table 1, entry 9). To evaluate the use of this interesting approach, a variety of 3-formylchromones, alkyl isocyanides, and various alcohols was examined. Notably, the reaction was straightforward and proceeded cleanly at room temperature in dry dichloromethane to produce the corresponding products **6a**–**k** in moderate to good yields, and no undesirable side reactions were observed. The structures of the new products **6a**–**k** were established by their satisfactory elemental analyses and spectroscopic (^{1}H, ^{13}C NMR, and IR) studies.[15]

The elucidation of the structure of **6** using ^{1}H NMR and ^{13}C NMR spectroscopic data is discussed with **6i** as an example. The ^{1}H NMR spectrum of **6i** consisted of multiplet signals for the adamantyl rings (δ_H = 1.49–2.06 ppm) and the OCH resonance (δ_H = 5.00–5.04 ppm), a sharp singlet for the methyl (δ_H = 2.45 ppm) hydrogens, and two AB systems

for the two methine (δ_H = 4.02 and 4.08 ppm, $^3J_{HH}$ = 6.1 Hz) protons of the succinimide moiety and methylene protons (δ_H = 4.75 and 4.86 ppm, $^2J_{HH}$ = 14.4 Hz). The aromatic protons gave rise to multiplets and a doublet in the aromatic region of the spectrum (δ_H = 7.26–7.94 and δ_H = 7.95 ppm, $^3J_{HH}$ = 5.9 Hz). The vinylic methine occurred as a sharp singlet (δ_H = 7.96 ppm).

The ^{1}H-decoupled ^{13}C NMR spectrum of **6i** showed 30 distinct resonances in agreement with the suggested structure.
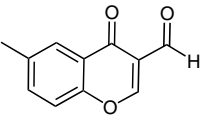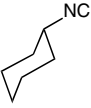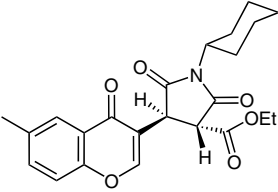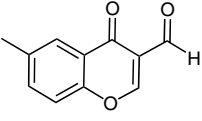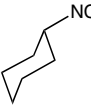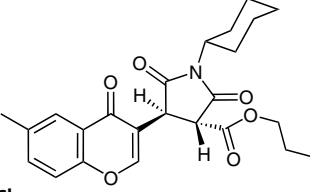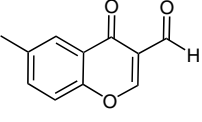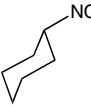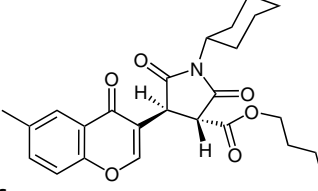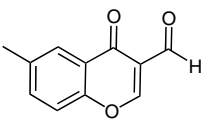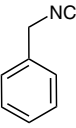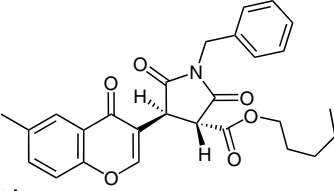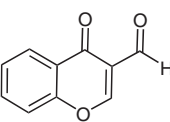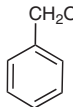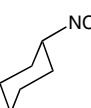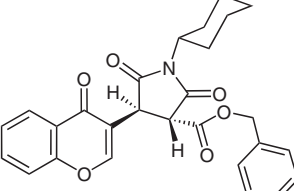
Encouraged by the results obtained with the above reaction conditions, and in order to show the generality and scope of this new protocol, we turned our attention to various 3-formylchromones, isocyanides, and alcohols. Four 3-formylchromones, six alkyl or aryl isocyanides, and eleven alcohols were examined. Two 3-formylchromone derivatives (3-formylchromone and 3-formyl-6-methyl-chromone) afforded chromone-bound succinimides in moderate to 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[16] (1Z)-7-chloro-1-[(6-chloro-4-oxo-4H-chromen-3-yl)methylene]-3-(cyclohexylimino)-1,3-dihydro-9H-furo[3,4-b]-chromen-9-one (**7a**) and (1Z)-5,7-dichloro-3-(cyclohexylimino)-1-[(6,8-dichloro-4-oxo-4H-chromen-3-yl)methylene]-1,3-dihydro-9H-furo[3,4-b]chromen-9-one (**7b**) were isolated, respectively, without the participation of Meldrum's acid and ethanol, which did not enter into these reactions.

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

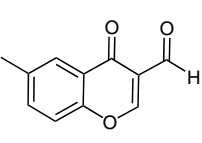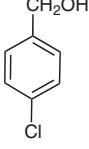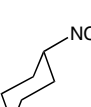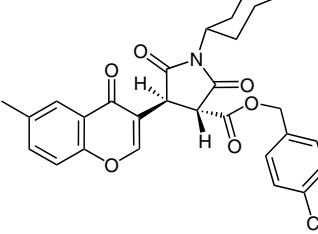A variety of structurally diverse alcohols underwent the one-pot reaction smoothly without need for a catalyst to afford the corresponding succinimide derivatives in good yields. As shown in Table 1, primary alcohols (ethanol, 1-propanol, 1-butanol, and 1-pentanol) benzylic alcohols (benzyl- and 4-chlorobenzyl 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).

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Table 1 Structure of Compounds **6a–k** and **5a–b**

Entry	3-Formylchromone	Alcohol	Isocyanide	Product	Yield (%)[a]
1		EtOH		**6a**	69
2		CH₂OH		**6b**	65
3		CH₂OH		**6c**	67
4		CH₂OH		**6d**	60
5		CH₂OH		**6e**	60
6		CH₂OH		**6f**	70

| 7 | | CH₂OH | NC | 6g | 55 |

CH$_2$OH

6g

| 8 | | OH | NC | **6h** | 62 |

| 9 | | OH | NC | **6i** | 85 |

| 10 | | OH | NC | **6j** | 55 |

| 11 | | OH | NC | **6k** | 50 |

| 12 | | MeOH | NC | **5s** | 70 |

| 13 | | MeOH | NC | **5b** | 65 |

ᵃ Yield of pure isolated product.

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 precedented[17] 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 thermody-

namically 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).
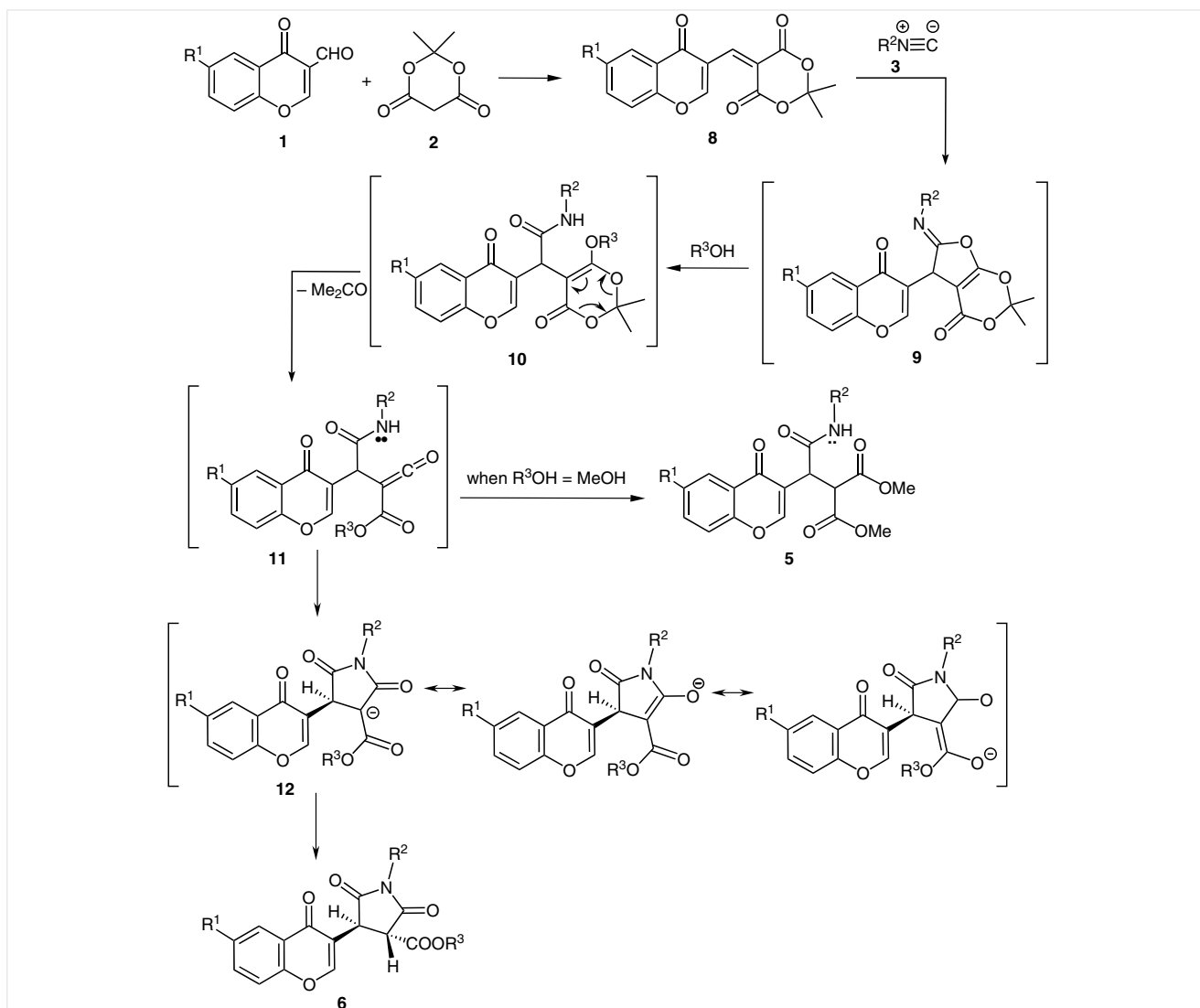
Scheme 2 Possible mechanisms for the formation of products **5** and **6**
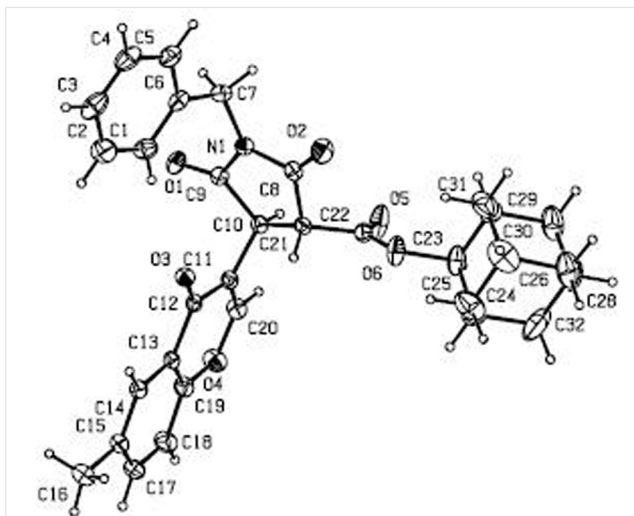
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Figure 2 X-ray crystal structure of (3*R*,4*S*)-**6i**

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

Supporting Information

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

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(15) **General Procedure for the Synthesis of Alkyl-1-alkyl-4-(4-oxo-4*H*-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 CH_2Cl_2 (10 mL) for 3 h at r.t., and then alcohol **4** (1 mmol) followed by alkyl isocyanide **3** (1 mmol) was added at r.t. 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 Et_2O and crystallized from CH_2Cl_2–hexane (1:3) to afford pure product **6**.
***rac*-2-Adamantyl (3*R*,4*S*)-1-Benzyl-4-(6-methyl-4-oxo-4*H*-chromen-3-yl)-2,5-dioxopyrrolidine-3-carboxylate (6i)**
White powder; mp 195–196 °C (melt.). IR (KBr): ν_{max} = 1783, 1709, 1646 (C=O), 1616 (C=C) cm^{-1}.^{1}H NMR (300.1 MHz, CDCl$_3$): δ = 1.49–2.06 (14 H, m, adamantyl), 2.45 (3 H, s, CH$_3$), 4.02 and 4.08 (2 H, AB-*q* system, $^3J_{HH}$ = 6.1 Hz, C*H*C*H*), 4.75 and 4.86 (2 H, AB-*q* system, $^2J_{HH}$ = 14.4 Hz, PhC*H$_2$*), 5.00 (1 H, m, OC*H*), 7.26–7.94 (7 H, m, arom. H), 7.95 (1 H, d, $^3J_{HH}$ = 5.9 Hz, arom. H.), 7.96 (1 H, s, C=C*H*O). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 176.6, 174.9, 170.8, 166.8, 154.8, 154.6, 135.8, 135.6, 135.3, 128.6, 128.2, 127.8, 125.0, 123.4, 119.2, 118.0, 79.5, 52.0, 44.0, 43.2, 37.2, 36.3, 36.2, 31.8, 31.6, 31.5, 31.4, 27.0, 26.8, 21.0. Anal. Calcd (%) for C$_{32}$H$_{31}$NO$_6$ (525.59): C, 73.13; H, 5.94; N, 2.66. Found: C, 72.81; H, 5.97; N, 2.70.
X-ray Data for 6i
C$_{32}$H$_{31}$N$_1$O$_6$, M = 525.58 g·mol^{-1}, orthorhombic system, space group $P2_12_12_1$, a =10.0889(19), b = 11.9344(19), c = 22.490(3) Å, V = 2707.9(8) Å^3, Z = 4, D_{calcd}= 1.289 g cm^{-3}, μ(Mo Kα)= 0.089 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.[18] 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-4*H*-chromen-3-yl)-2-oxo-2-[(1,1,3,3-tetramethylbutyl)amino]ethyl}malonate (5a)**
White powder; mp 198–201 °C (dec.). IR (KBr): ν_{max} = 3330 (NH), 1730, 1681, 1649 (C=O), 1621 (C=C) cm^{-1}. ^{1}H NMR (300.1 MHz, CDCl$_3$): δ = 0.83 (9 H, s, CMe$_3$), 1.29 (6 H, br s, CMe$_2$), 1.49 and 1.73 (2 H, AB-*q* system, $^2J_{HH}$ = 14.8 Hz, CH$_2$), 2.43 (3 H,

s,CH$_3$), 3.55 and 3.74 (6 H, 2 s, 2 OCH_3), 4.25 (1 H, d, $^3J_{HH}$ = 12.4 Hz, CH) 4.58 (1 H, d, $^3J_{HH}$ = 12.4 Hz, CH), 6.40 (1 H, s, NH), 7.34 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH$_3$C=CHCH), 7.48 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 1.6 Hz, CH$_3$C=CHCH), 7.97 (1 H, s, C=CHO), 7.98 (1 H, s, CH$_3$C=CHC). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 177.0, 168.6, 167.9, 167.8, 154.3, 153.6, 135.5, 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$_{25}$H$_{33}$NO$_7$ (459.53): C, 65.34; H, 7.24; N, 3.05. Found: C, 65.50; H, 7.24; N, 3.08.

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