Sequential Knoevenagel Condensation/Cyclization for the Synthesis of Indene and Benzofulvene Derivatives

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ABSTRACT: Sequential Knoevenagel condensation/cyclization leading to indene and benzofulvene derivatives has been developed. The reaction of 2-(1-phenylvinyl)benzaldehyde with malonates gave benzylidene malonates, cyclized indenes, and dehydrogenated benzofulvenes. The product selectivity depends on the reaction conditions. The reaction with piperidine, AcOH in benzene at 80 °C for 1.5 h gave a benzylidene malonate in 75% yield as a major product. The reactions with piperidine, AcOH in benzene at 80 °C for 17 h and with TiCl4-pyridine at room temperature gave an indene derivative in 56 and 79% yields, respectively, as a major product. The reaction with TiCl4-Et3N gave a benzofulvene in 40% yield selectively. Indene was transformed to a benzofulvene derivative using the reagents TiCl4-Et3N and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The reaction of variously substituted aryl derivatives with dimethyl malonate gave indene and benzofulvene derivatives. The reactions of 2-(1-phenylvinyl)benzaldehyde with Meldrum’s acid or malononitrile also gave cyclized compounds in the suitable sequential or stepwise conditions. Furthermore, the reaction of 2-arylbenzaldehydes has been investigated. The limitation and scope have been described. The reaction mechanism of the cyclization steps has been examined by DFT calculations.

INTRODUCTION

Indenes and benzofulvenes are important core structures in organic chemistry due to their presence in many biologically active compounds and functional materials. Various methods to construct indene rings have been developed. For example, Lewis and Brønsted acid-catalyzed reactions such as Nazarov-type 4π-electrocyclization, Friedel–Crafts cyclization, and reaction of styrylmalonates with aromatic aldehydes have been reported recently. Among the methods developed, cyclization reactions of ortho-substituted arenes to provide functionalized indenes have been utilized efficiently. Transition-metal-catalyzed cyclization of ortho-substituted arenes has been investigated. Iodine-promoted and base-promoted cyclization reactions have been reported. Lewis and Brønsted acid-catalyzed reactions of alkene conjugate addition have been studied. It is desirable to find new efficient methods to construct variously functionalized indene derivatives.

Sequential reactions are considered to be efficient and favorable for the sustainable concepts. The Knoevenagel condensation is the reactions of aldehydes and ketones with active methylene compounds to give alkylidene- or benzylidene-dicarbonyls or analogous compounds, for example, in the presence of amines, ammonium salts, and Lewis acids with amines. Since Knoevenagel products are highly reactive compounds, several sequential reactions involving Knoevenagel condensation have been reported.

For example, originally, Knoevenagel reported formation of bis-adducts. Various sequential reactions under the condensation conditions to give intermolecular Michael adducts including the reaction with two kinds of active methylene compounds and further transformation of the adducts and intermolecular hetero-Diels-Alder cycloadducts (Scheme 1A). Sequential intramolecular hetero-Diels-Alder and 1,5-hydride shift/cyclization reactions were also reported as efficient methods (Scheme 1B). The initial alkylidene or benzylidene compounds are directly transformed by the subsequent step under the reaction conditions. It is of interest to find new sequential reactions involving Knoevenagel condensation.

In this work, a highly reactive diphenylethene moiety in ortho-substitution of arenaldehydes has been used to cause
sequential Knoevenagel condensation/cyclization reactions (Scheme 1C). The reaction mechanism has been examined by DFT calculations.

**RESULTS AND DISCUSSION**

The reaction of 2-(1-phenylvinyl)benzaldehyde 1a with methyl malonate 2a under the various Knoevenagel reaction conditions has been examined first.

The reaction of 1a and 2a with piperidine, AcOH in benzene at 80 °C for 1.5 h gave the benzylidene malonate 3a in 75% yield as a major product (Scheme 2). The same reaction conditions for 17 h gave an indene derivative 4a in 56% yield. The reaction with TiCl₄-pyridine (1:4 equiv) in CH₂Cl₂ at room temperature gave an indene derivative 4a in 79% yield (Scheme 3, Table 1, entry 1). The reaction of variously substituted aryl derivatives 1 with dimethyl malonate 2a also gave indene derivatives 4 (Table 1).

Transformation of 3a to 4a was also achieved by the reaction with catalytic amounts of Sc(OTf)₃ in dichloromethane at 40 °C in 74% yield (Scheme 2).

Next, the reaction of 1a and 2a with TiCl₄-Et₃N (1:4 equiv ratio) was examined. The reaction gave a 1:1 mixture of 4a and 5a in 61% yield. After examining various ratios of TiCl₄-Et₃N, it was found that the reaction with TiCl₄-Et₃N (2:8 equiv) in CH₂Cl₂ at room temperature for 17 h gave a benzofulvene 5a in 40% yield selectively (Scheme 4, Table 2, entry 1). The reaction of variously substituted aryl derivatives 1 and 2a with TiCl₄-Et₃N also gave benzofulvene derivatives 5 as orange crystals (Table 2). The structure of 5e was determined by X-ray analysis (Figure S1 in the Supporting Information, CCDC 2105106). The reaction of 1a with diethyl malonate 2b gave the corresponding indene 4h and benzofulvene 5h (Tables 1 and 2). The reaction of naphthyl derivative 1i and 2a with TiCl₄-Et₃N (2:8) also gave 5i as a major product in 41% yield.

**Table 1. Reaction of 1 and 2a,b with TiCl₄-Pyridine (1:4)**

| entry | R¹ | R² | R³ | 2 R⁴ | 4 | yield (%) |
|-------|----|----|----|------|---|-----------|
| 1     | 1a | H  | H  | H    | 2a | Me        | 4a | 79 |
| 2     | 1b | Me | H  | H    | 2a | Me        | 4b | 46 |
| 3     | 1c | Cl | H  | H    | 2a | Me        | 4c | 54 |
| 4     | 1d | H  | Me | H    | 2a | Me        | 4d | 55 |
| 5     | 1e | H  | Cl | H    | 2a | Me        | 4e | 57 |
| 6     | 1f | H  | H  | Cl   | 2a | Me        | 4f | 66 |
| 7     | 1g | H  | F  | H    | 2a | Me        | 4g | 50 |
| 8     | 1a | H  | H  | H    | 2b | Et        | 4h | 50 |

*aAn inseparable mixture of possible 4g and 3g.

Scheme 1. (A) Sequential Intermolecular Reactions under Condensation Conditions to Give Michael Adducts and Hetero-Diels-Alder Adducts, (B) Sequential Intramolecular Hetero-Diels-Alder and 1,5-Hydride Shift/Cyclization Reactions, and (C) Sequential Knoevenagel Condensation/Cyclization

Scheme 2. Reaction of 1a and 2a with Piperidine, AcOH in Benzene

Scheme 3. Reaction of 1a–h and 2a,b with TiCl₄-Pyridine (1:4 equiv) in CH₂Cl₂

Scheme 4. Reaction of 1a with Sc(OTf)₃ in Dichloromethane at 40 °C
The indenes 4a,h were transformed to benzofulvene derivatives 5a,h using the reagents TiCl\textsubscript{4}-Et\textsubscript{3}N or DDQ in 67−98% yields (Scheme 5).

Scheme 5. 4a,h Transformation to Benzofulvene Derivatives 5a,h

In order to examine the effect of phenyl on vinyl group of 1a, the reaction of 6 with 2a in the presence of TiCl\textsubscript{4}-pyridine/Et\textsubscript{3}N was carried out. The reaction under the examined conditions gave the Knoevenagel product 7 as an isolable product in 23−64% yield (Scheme 6).

The reactions of 2-(1-phenylvinyl)benzaldehydes 1 with other active methylene compounds were examined next. The reaction of 1a and Meldrum’s acid 8 in the presence of TiCl\textsubscript{4}-pyridine or TiCl\textsubscript{4}-Et\textsubscript{3}N gave a complex mixture. However, the reaction in the presence of piperidine (0.2 equiv) in benzene at room temperature gave cyclized product 9 in 80% yield (Scheme 7). The reaction with piperidine (0.2 equiv) and acetic acid (1 equiv) in benzene at room temperature gave 9 as an isolable product in lower yield (42%). The corresponding Knoevenagel adduct was not isolated under the examined conditions.

Since the properties of conjugated systems are of interest, dehydrogenation of indene products was examined. 18,6b,c Dehydrogenation of 9 proceeded by the reaction with DDQ (1 equiv) in benzene at room temperature to give benzofulvene 10 in 94% yield (Scheme 7).

The reaction of 1a and malononitrile 11 with TiCl\textsubscript{4}-pyridine or TiCl\textsubscript{4}-Et\textsubscript{3}N (1:4) gave Knoevenagel adduct 12a in 50−39% yields. The reaction with TiCl\textsubscript{4}-Et\textsubscript{3}N (2:8 ratio) gave a mixture of 12a and 13a in 17 and 11% yields, respectively. The reaction in the presence of piperidine (0.2 equiv) in benzene at room temperature gave adduct 12a in 82% yield (Scheme 8, Table 3). The reaction of 12a with catalytic amounts of Sc(OTf)\textsubscript{3} in dichloromethane at room temperature gave 13a in 99% yield. Dehydrogenation of 13a with DDQ (1 equiv) in CH\textsubscript{2}Cl\textsubscript{2} at room temperature provided 14a in 61% yield. Thus, the effective reaction conditions to give cyclized product sequentially could not be found. The reaction of the Me and Cl substituted derivatives 1b,c with malononitrile followed by cyclization and dehydration also proceeded stepwise to give 13b,c and 14b,c.

The electrophilicity parameters are reported as ethyl benzylidenemalonate (−20.55) < benzylidenemalononitrile...
because the cyclization may be accelerated by Lewis acid or H+ these cyclization reactions may not be easy to compare, partly because the cyclization may be accelerated by Lewis acid or H+ coordination to O or N. In addition, some intermediates seem to be unstable under the Lewis acid conditions.

Furthermore, to extend the scope of sequential Knoevenagel condensation/cyclization reaction, the reactions of 2-arylbenzaldehydes 15a-c with an active methylene compound have been investigated (Scheme 9, Table 4). However, the reaction of 2-phenoxybenzaldehyde 19 and methyl malonate 2a with TiCl4/Et3N or TiCl4/pyridine gave only Knoevenagel adduct 20. The stepwise reaction of 20 to the xanthene derivative 21 with Sc(OTf)3 and subsequent treatment of 21 with DDQ gave 22 (Scheme 11).

The probable reaction mechanism to give products sequentially is shown in Scheme 12. First, Knoevenagel condensation of the active methylene compound such as 2a gives Lewis acid coordinated or protonated intermediate A, according to the reported mechanism.10,20 Intramolecular alkene addition affords the carbocation intermediate B, which is stabilized by two aryl groups. Intermediate B undergoes deprotonation to afford C. Protonation of the α-carbon of C may lead to indene 4a. Furthermore, dehydrogenation occurred to afford benzofulvene 5a in the presence of 2 equiv of TiCl4 and 8 equiv of Et3N in one pot.

The oxidative reactions using titanium tetrachloride and a tertiary amine have been reported previously.21 Based on the reports, the intermediate C can be dehydrogenated to give Ti-complex D, which leads to 5a.

The reaction mechanism of the cyclization step in Scheme 12 has been examined by the DFT calculations in order to compare the observed reactivities of various substrates.

The calculations were performed by the B3LYP/6-31G* level including the PCM solvent effect (solvent = CH2Cl2 or benzene). TS geometry was characterized by vibrational analysis, which checked whether the obtained geometry has

| Table 4. Stepwise Reaction of 15a–c and 2a to 16a–c, 17a–c, and 18a–c |
|---|
| entry | 15 | R | 16 | yield (%) | 17 | yield (%) | 18 | yield (%) |
| 1 | 15a | H | 16a | 78a | 17a | 94 | 18a | 69b |
| 2 | 15b | Me | 16b | 86 | 17b | 88 | 18b | 86c |
| 3 | 15c | Cl | 16c | 82 | 17c | 81 | 18c | 40d |

The reaction of 15a and 2a with TiCl4/Et3N (2:8) gave 16a in 81% yield. At 40 °C in CH2Cl2. At 80 °C in 1,2-dichloroethane. At 110 °C in toluene.

The reaction of 17d with DDQ at room temperature gave 18d in 92% yield.

| Table 3. Stepwise Reaction of 1a–c and 11 to 12a–c, 13a–c, and 14a–c |
|---|
| entry | 1 | R1 | 12 | yield (%) | 13 | yield (%) | 14 | yield (%) |
| 1 | 1a | H | 12a | 82a | 13a | 99 | 14a | 61c |
| 2 | 1b | Me | 12b | 73a | 13b | 91 | 14b | 89b |
| 3 | 1c | Cl | 12c | 70a | 13c | 95 | 14c | 74b |

The reaction with piperidine (0.2 equiv) in benzene at r.t. the reaction with piperidine (0.2 equiv) and acetic acid (1.0 equiv) in benzene at 80 °C. The reaction with DDQ at r.t. in dichloromethane.

The reaction with DDQ at 80 °C in 1,2-dichloroethane.

< benzylidene Meldrum’s acid (−9.15).19 However, these cyclization reactions may not be easy to compare, partly because the cyclization may be accelerated by Lewis acid or H+ coordination to O or N. In addition, some intermediates seem to be unstable under the Lewis acid conditions.

Furthermore, to extend the scope of sequential Knoevenagel condensation/cyclization reaction, the reactions of 2-arylbenzaldehydes 15a–c with an active methylene compound have been investigated (Scheme 9, Table 4). However, the reaction of 2-phenoxybenzaldehyde 19 and methyl malonate 2a with TiCl4/Et3N or TiCl4/pyridine gave only Knoevenagel adduct 20. The stepwise reaction of 20 to the xanthene derivative 21 with Sc(OTf)3 and subsequent treatment of 21 with DDQ gave 22 (Scheme 11).

The probable reaction mechanism to give products sequentially is shown in Scheme 12. First, Knoevenagel condensation of the active methylene compound such as 2a gives Lewis acid coordinated or protonated intermediate A, according to the reported mechanism.10,20 Intramolecular alkene addition affords the carbocation intermediate B, which is stabilized by two aryl groups. Intermediate B undergoes deprotonation to afford C. Protonation of the α-carbon of C may lead to indene 4a. Furthermore, dehydrogenation occurred to afford benzofulvene 5a in the presence of 2 equiv of TiCl4 and 8 equiv of Et3N in one pot.

The oxidative reactions using titanium tetrachloride and a tertiary amine have been reported previously.21 Based on the reports, the intermediate C can be dehydrogenated to give Ti-complex D, which leads to 5a.

The reaction mechanism of the cyclization step in Scheme 12 has been examined by the DFT calculations in order to compare the observed reactivities of various substrates.

The calculations were performed by the B3LYP/6-31G* level including the PCM solvent effect (solvent = CH2Cl2 or benzene). TS geometry was characterized by vibrational analysis, which checked whether the obtained geometry has
single imaginary frequencies ($\nu^\ddagger$). From TSs, reaction paths were traced by the intrinsic reaction coordinate (IRC) method\textsuperscript{25} to obtain the energy-minimum geometries. Relative Gibbs free energies in kcal/mol ($T = 298.15$ K, $P = 1$ atm) were refined by single-point calculations of RB3LYP/6-311+G(d,p) SCRF = (PCM, solvent = CH$_2$Cl$_2$ or benzene).

Based on the previous theoretical study by Marrone et al.,\textsuperscript{20a,b} the TiCl$_4$-promoted Knoevenagel condensation of dimethyl malonate and aldehydes may give titanyl (TiOCl$_2$) complex in situ. In this study, the reaction mechanism starting from the Knoevenagel adduct $A$ (in Scheme 12) in situ was calculated by the use of the titanyl (TiOCl$_2$) complex models.

Intramolecular addition of an alkene to the Knoevenagel adduct--TiOCl$_2$ complex $AN$ with Me$_3$N, leading to the formation of intermediate $BN$, deprotonation of $BN$ by Me$_3$N (as a model for an amine) to form an alkene, and generation of the intermediate CN.

The steps $AN \rightarrow BN \rightarrow CN$ were calculated (Scheme 13). The energy of transition state of cyclization, TSAN ($\Delta G^\ddagger = +11.27$ kcal/mol), is higher than that of deprotonation by Me$_3$N, TSNB ($\Delta G^\ddagger = +7.35$ kcal/mol).

Since TSAN is higher than TSNB, cyclization steps for various TiOCl$_2$-coordinate substrate models without Me$_3$N have been calculated and compared (Scheme 14). The activation energy of TSA1 is similar to that of TSAN of the model with Me$_3$N. The transition state (TSA1) of cyclization for TiOCl$_2$-coordinate 2-{1-phenylvinyl} derivative $3a$, $A1$ to $B1$, is more stable than TSA2 for TiOCl$_2$-coordinate 2-vinyl derivative $7$, $A2$ to $B2$. The intermediate $B1$ is highly stabilized by two aryl groups. Furthermore, the reaction models $A3$ and $A4$ for Knoevenagel adducts $16a$,$d$ from 2-aryldonaldehydes $15a$,$d$ have been calculated. The activation energy of TS$3A$ (+21.94 kcal/mol) is much higher than that of TSA1 due to destruction of the aromatic ring. However, the activation energy of TSA4 for the di-MeO derivative is +11.64 kcal/mol and comparable to the TSA1 because two electron-donating groups stabilize the cation intermediate. On the other hand, the activation energy of TSA5 for the oxygen-substituted derivative $20$ is higher (+22.68 kcal/mol). This is probably

Scheme 12. Probable Reaction Mechanism from $1a$ to Give Products $4a$ and $5a$ Sequentially

Scheme 13. Transition of $AN$ to $BN$ and then to $CN$

Scheme 14. Cyclization Steps for Various TiOCl$_2$-Coordinate Substrate Models
because of both the electronic effect and the steric reason by the six-membered ring formation. Those calculations are in agreement with the experimental results.

Next, the reactivity between dimethyl malonate and Meldrum’s acid with dimethylammonium ion as a model of the piperidine-catalyzed reaction was compared (Scheme 15). TSA7 is more stable than TSA6. This is in agreement with the experimental results. Those calculations are in agreement with the electrophilicity of benzylidemalonomalate and benzylidene Meldrum’s acid, as described above.

Scheme 15. Reactivity between Dimethyl Malonate and Meldrum’s Acid with the Dimethylammonium Ion

Dehydrogenation step C to D in Scheme 16 was also examined. Hall et al. suggested formation of the iminium ion by the redox reaction between TiCl4 and Et3N. Therefore, hydride transfer of C1 with the iminium ion, formed in situ from TiCl4 and Me3N (as a model of Et3N), is considered. The removal of a hydride from the indene ring gives intermediate D1. Although the full mechanism of dehydrogenation by TiCl4-Et3N is not clear, the hydride transfer path by the iminium ion may be possible as shown by the model calculations. Dehydrogenation by DDQ may also involve the hydride transfer step.

Scheme 16. Dehydrogenation Step C to D

In summary, sequential Knoevenagel condensation/cyclization leading to indene and benzofulvene derivatives has been developed. The reaction of 2-(1-phenylvinyl)benzaldehyde with malonates gave benzylidene malonates, cyclized indenes, and dehydrogenated benzofulvenes. The product selectivity depends on the reaction conditions. Reaction of variously substituted aryl derivatives with dimethyl malonate gave indene and benzofulvene derivatives. The reactions of 2-(1-phenylvinyl)benzaldehyde with Meldrum’s acid or malonitrile also gave cyclized compounds in the suitable sequential or stepwise conditions. Furthermore, the reaction of 2-arylbenzaldehydes has been investigated. The limitation and scope have been described. The reaction mechanism of the cyclization steps has been examined by the DFT calculations.

Further study on the transformation and the utility of the products is under investigation.

EXPERIMENTAL SECTION

General Methods. 1H chemical shifts are reported in ppm relative to MeSi. 13C chemical shifts are reported in ppm relative to CDCl3 (77.1 ppm). 19F chemical shifts are reported in ppm relative to CFC13. 13C multiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI or CI. The mass analyzer type used for EI and CI is double-focusing. All reactions were carried out under a nitrogen atmosphere. Column chromatography was performed on silica gel (75–150 μm).

1a–i and 6 were prepared according to the literature. 15b,15d were prepared according to the literature. 15c was prepared according to the literature method.

Procedures for Preparation of 3a. To a solution of 1a (491 mg, 2.3 mmol) in benzene (20 mL) were successively added dimethyl malonate 2a (0.32 g, 0.27 mL, 2.5 mmol), piperidine (0.20 g, 0.23 mL, 2.3 mmol), and AcOH (0.15 g, 0.14 mL, 2.5 mmol) at 0 °C and then heated at reflux. After heating for 1.5 h, the crude products were concentrated in vacuo, and the residue was purified by column chromatography over silica gel eluting with hexane-EtOAc to give 3a (586 mg, 75%).

3a: R = 0.1 (hexane-EtOAc = 10:1); pale yellow oil; 1H NMR (400 MHz, CDCl3) δ (ppm) 7.36–7.39 (m, 2H), 7.45–7.51 (m, 5H), 7.98 (dd, J = 8.1, 0.6 Hz, 1H), 9.92 (d, J = 0.6 Hz, 1H); 13C NMR (100.6 MHz, CDCl3) δ (ppm) 128.24 (CH), 128.70 (CH), 128.74 (CH), 129.24 (CH), 130.00 (CH), 130.78 (CH), 132.12 (C), 136.44 (C), 139.91 (C), 147.44 (C), 191.26 (CH); IR (KBr) 2875, 1684, 1588, 1392, 1253, 127.79 (CH), 127.99 (C), 128.01 (CH), 128.02 (CH), 128.40 (CH), 129.52, 129.62, 129.67 (CH), 130.48 (CH), 130.75 (CH), 134.44 (C), 134.78 (CH), 134.93 (C), 143.78 (CH), 145.02 (C), 145.12 (C), 149.03 (C), 150.22 (C), 153.45 (C), 160.04 (C), 164.15 (C), 166.34 (C), 166.91 (C); MS (EI) m/z 219 ([M + H]+, 30), 217 ([M + H]+, 100%); HRMS (EI) m/z 217.0414, 219.0401 (calcd for C10H10ClO [M + H]+ 217.0420, 219.0408).

Procedures for Preparation of 4a. To a solution of 1a (1.05 g, 5.0 mmol) in CH2Cl2 (20 mL) was added dimethyl malonate 2a (491 mg, 2.3 mmol), piperidine (0.20 g, 0.23 mL, 2.3 mmol), and AcOH (0.15 g, 0.14 mL, 2.5 mmol) at 0 °C and then heated at reflux. After heating for 1.5 h, the crude products were concentrated in vacuo, and the residue was purified by column chromatography over silica gel eluting with hexane-EtOAc to give 4a (1.27 g, 79%).

4a: R = 0.4 (hexane-EtOAc = 10:1); pale yellow oil; 1H NMR (400 MHz, CDCl3) δ (ppm) 3.57 (d, J = 8.6 Hz, 1H),...
3.69 (s, 3H), 3.83 (s, 3H), 4.28 (dd, dJ = 8.6, 2.1 Hz, 1H), 6.53 (d, dJ = 2.1 Hz, 1H), 7.24 (ddd, dJ = 7.4, 7.4, 1.0 Hz, 1H), 7.33 (ddd, dJ = 7.4, 0.7 Hz, 1H), 7.36–7.40 (m, 2H), 7.42–7.47 (m, 2H), 7.54 (d, dJ = 7.6 Hz, 1H), 7.56–7.59 (m, 2H); 13C NMR (100.6 MHz, CDCl3) δ (ppm) 47.34 (CH), 52.76 (CH2), 52.84 (CH2), 53.31 (CH), 121.14 (CH), 124.81 (CH), 125.53 (CH), 127.70 (CH), 128.31 (CH), 128.81 (CH), 133.64 (C), 134.25 (CH), 134.68 (C), 142.88 (C), 145.04 (C), 145.51 (C), 168.13 (C), 168.74 (C); IR (neat) 2953, 1754, 1730, 1598, 1565, 1491, 1435, 1156, 1072, 1029 cm–1; MS (EI) m/z 356 (M+•, 47), 296 (100), 202 (64%); HRMS (EI) m/z 356.0810, 358.0793 (calcld for C20H17ClO4 356.0815, 358.0786).

4f: 1 mmol scale, 235 mg, 66%; Rf = 0.5 (hexane-ETOAc = 1:1); yellow oil; 1H NMR (400 MHz, CDCl3) δ (ppm) 3.58 (d, dJ = 8.6 Hz, 1H), 3.71 (s, 3H), 3.83 (s, 3H), 4.26 (dd, dJ = 8.6, 2.0 Hz, 1H), 6.52 (d, dJ = 2.0 Hz, 1H), 7.30 (d, dJ = 8.0, 2.0 Hz, 1H), 7.37–7.47 (m, 2H), 7.51–7.55 (m, 2H); 13C NMR (100.6 MHz, CDCl3) δ (ppm) 52.28 (CH2), 57.29 (CH3), 61.48 (CH2), 120.67 (CH), 126.13 (CH), 133.06 (CH), 133.49 (C), 168.70 (C); IR max (CH3CN) 250 (ε 22,700), 3084 (ε 30,500), 3180 (ε 22,700), 3164 (ε 22,700), 3048 (ε 22,700), 2920 (ε 22,700), 2363 (ε 22,700), 2240 (ε 22,700), 2100 (ε 22,700), 1900 (ε 22,700), 1800 (ε 22,700), 1700 (ε 22,700), 1600 (ε 22,700), 1500 (ε 22,700), 1400 (ε 22,700), 1300 (ε 22,700), 1200 (ε 22,700), 1100 (ε 22,700), 1000 (ε 22,700), 900 (ε 22,700), 800 (ε 22,700), 700 (ε 22,700), 600 (ε 22,700), 500 (ε 22,700), 400 (ε 22,700), 300 (ε 22,700), 200 (ε 22,700), 100 (ε 22,700); HRMS (EI) m/z 356.0814, 358.0791 (calcld for C20H17ClO4 356.0815, 358.0786).

Procedures for Preparation of 5a. To a solution of 1a (209.9 mg, 1.0 mmol) in CH2Cl2 (6 mL) were added dimethyl malonate 2a (132.1 mg, 0.11 mL, 1.0 mmol) and Et3N (809.5 mg, 1.12 mL, 8.0 mmol). After cooling to 0°C, TiCl4 (379.4 mg, 2.0 mmol) in CH2Cl2 (1 mL) was slowly added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred for 17 h. The mixture was quenched with 1 M HCl solution and extracted with CH2Cl2.

The organic layer was washed with saturated aqueous NaHCO3, dried over Na2SO4, and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-ETOAc to give 5a (135 mg, 40%).

5a: Rf = 0.4 (hexane-ETOAc = 15: 1); orange crystals; mp 108–109°C (hexane); 1H NMR (400 MHz, CDCl3) δ (ppm) 3.88 (s, 3H), 4.00 (s, 3H), 7.18 (ddd, dJ = 7.6, 7.6, 1.0 Hz, 1H), 7.31 (ddd, dJ = 7.6, 7.4, 1.0 Hz, 1H), 7.40 (d, dJ = 7.6 Hz, 1H), 7.42–7.50 (m, 5H), 7.65–7.68 (m, 2H); 13C NMR (100.6 MHz, CDCl3) δ (ppm) 35.18 (CH2), 52.13 (CH2), 137.45 (C), 150.96 (C), 164.57 (C), 169.34 (C), 142.16 (C), 145.08 (C), 145.51 (C), 167.90 (C), 168.56 (C); IR (neat) 2981, 1749, 1732, 1598, 1468, 1346, 1153, 1035 cm–1; MS (EI) m/z 350 (M+•, 51), 276 (100%); HRMS (EI) m/z 350.1519 (calcld for C19H14O4 350.1518).

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Sb: 1 mmol scale, 151 mg; Rf = 0.3 (hexane-EtOAc = 10:1); red-orange crystals; mp 108–110 °C; 1H NMR (400 MHz, CDCl₃) δ (ppm) 2.42 (s, 3H), 3.87 (s, 3H), 3.99 (s, 3H), 7.18 (dd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.6, 1.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.45 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.57 (d-like, J = 8.0 Hz, 2H); 13C NMR (100.6 MHz, CDCl₃) δ (ppm) 21.53 (CH₃), 52.70 (CH₃), 53.13 (CH₃), 120.64 (C), 121.57 (CH), 124.01 (CH), 124.17 (CH), 126.99 (CH), 127.67 (CH), 129.50 (CH), 130.25 (CH), 131.36 (CH), 133.54 (C), 139.53 (C), 143.20 (C), 149.38 (C), 151.93 (C), 164.35 (C), 167.01 (C); IR (KBr) 2951, 1723, 1617, 1422, 1253, 1216, 1044 cm⁻¹; δ_max (CH3CN) 256 (ε 12,700), 316 (7400), 430 (1100) nm; MS (EI) m/z 356 (M⁺, 35), 354 (M⁺, 100), 323 (20), 189 (29%); HRMS (EI) m/z 354.0652, 356.0652 (calcd for C₂H₂₆O₅F: 354.0659, 356.0629); anal. calcd for C₂H₂₆O₅F: C, 67.71; H, 4.26. Found: C, 67.70; H, 4.02.

Sg: 1 mmol scale, 178 mg; Rf = 0.5 (hexane-ether = 1:1); orange crystals; mp 100–101 °C (hexane-EtOAc); 1H NMR (400 MHz, CDCl₃) δ (ppm) 3.88 (s, 3H), 4.01 (s, 3H), 7.29 (d, J = 8.0, 1.9 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 1.9 Hz, 1H), 7.42–7.50 (m, 3H), 7.44 (s, 1H), 7.61–7.64 (m, 2H); 13C NMR (100.6 MHz, CDCl₃) δ (ppm) 52.90 (CH₃), 53.26 (CH₃), 122.12 (CH), 124.90 (CH), 124.94 (CH), 127.70 (CH), 128.92 (CH), 129.59 (CH), 129.84 (CH), 133.16 (C), 133.84 (C), 136.90 (C), 141.42 (C), 148.05 (C), 151.26 (C), 164.10 (C), 166.40 (C); IR (KBr) 2952, 1723, 1617, 1422, 1253, 1216, 1044 cm⁻¹; δ_max (CH3CN) 256 (ε 12,700), 316 (7400), 430 (1100) nm; MS (EI) m/z 356 (M⁺, 35), 354 (M⁺, 100), 323 (20), 189 (29%); HRMS (EI) m/z 354.0652, 356.0652 (calcd for C₂H₂₆O₅F: 354.0659, 356.0629); anal. calcd for C₂H₂₆O₅F: C, 67.71; H, 4.26. Found: C, 67.70; H, 4.02.

Sv: 1 mmol scale, 186 mg; Rf = 0.5 (hexane-ether = 1:1); orange crystals; mp 99–100 °C (hexane-EtOAc); 1H NMR (400 MHz, CDCl₃) δ (ppm) 3.88 (s, 3H), 4.01 (s, 3H), 53.21 (CH₂), 121.87 (CH), 122.06 (CH), 125.00 (CH), 126.09 (CH), 126.67 (CH), 127.69 (CH), 128.98 (CH), 129.59 (CH), 133.36 (C), 133.68 (C), 136.52 (C), 145.01 (C), 147.96 (C), 150.81 (C), 164.16 (C), 166.55 (C); IR (KBr) 2951, 1735, 1723, 1617, 1444, 1249, 1216, 1046 cm⁻¹; MS (EI) m/z 356 (M⁺, 59), 354 (M⁺, 100), 296 (49%); δ_max (CH₃CN) 257 (ε 25,700), 334 (11,300), 413 (1930) nm; HRMS (EI) m/z 354.0659, 356.0648 (calcd for C₂H₂₆O₅F: 354.0659, 356.0629); anal. calcd for C₂H₂₆O₅F: C, 75.84; H, 5.79. Found: C, 75.49; H, 5.93.

Sv: 0.89 mmol scale, 136 mg; Rf = 0.5 (hexane-ether = 1:1); dark red crystals; mp 124–125 °C (hexane-EtOAc); 1H NMR (400 MHz, CDCl₃) δ (ppm) 3.88 (s, 3H), 4.04 (s, 3H), 7.18 (d, J = 8.6, 6.7, 1.2 Hz, 1H), 7.26 (s, 1H), 7.63 (d, J = 8.1, 6.7, 1.2 Hz, 1H), 7.46–7.53 (m, 6H), 7.59 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H); 13C NMR (100.6 MHz, CDCl₃) δ (ppm) 52.90 (CH₃), 53.29 (CH₂), 120.67 (CH), 123.08 (C), 125.15 (CH), 126.14 (CH), 126.54 (CH), 127.01 (CH), 127.57 (CH), 128.06 (C), 128.37 (CH), 128.45 (CH), 128.58 (CH), 128.69 (CH), 130.32 (C), 132.73 (C), 137.31 (C), 140.15 (C), 148.98 (C), 153.76 (C), 164.15 (C), 166.87 (C); IR (KBr) 2951, 1720, 1617, 1432, 1245, 1208, 1125, 1048 cm⁻¹; δ_max (CH₃CN) 221 (ε 21,200), 291 (17,100), 334 (5410) nm; MS (EI) m/z 370 (M⁺, 100), 370/371. Article

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5a was also obtained by treatment of 4a (182 mg, 0.56 mmol) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (127 mg, 0.56 mmol) in CH₂Cl₂ (2.0 mL) at room temperature for 17 h. Chromatography over silica gel eluting with hexane-EtOAc gave 5a (175 mg, 98%).

To a solution of 1a (833 mg, 4.0 mmol) in benzene (6 mL) were added Meldrum acid (18), 248 (100), 232 (95%); HRMS (EI) m/z 256.0999 (calcld for C₁₅H₂₀N₂ 256.1000).

12b: piperidine (0.2 equiv), 5.5 mmol scale, 1.08 g, 73%; R₉ = 0.3 (hexane-CH₂Cl₂ = 2:1); yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 2.35 (3H, s), 1.53 (3H, s), 1.94 (s, 1H), 7.09 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.38 (dd, J = 7.6, 1.2 Hz, 1H), 7.51 (dd, J = 7.6, 7.4, 1.2 Hz, 1H), 7.59 (dd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.88 (s, 1H), 8.18 (d, J = 7.4 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 21.21 (CH₃), 83.38 (C), 112.51 (C), 113.61 (C), 118.26 (CH₂), 126.91 (CH), 128.30 (CH), 128.51 (CH), 129.55 (CH), 129.78 (C), 130.92 (CH), 133.66 (CH), 137.03 (C), 138.82 (C), 145.08 (C), 146.23 (C), 159.72 (CH); IR (neat) 3029, 2229, 1518, 1510, 1214 cm⁻¹; MS (EI) m/z 270 (M⁺, 100), 255 (62), 205 (88%); HRMS (EI) m/z 270.1159 (calcld for C₁₅H₂₂N₂ 270.1157).

12c: piperidine (0.2 equiv), acetic acid (1.0 equiv) at 80 °C, 1.0 mmol scale, 204 mg, 70%; R₆ = 0.3 (hexane-CH₂Cl₂ = 1:1); colorless oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 5.21 (s, 1H), 5.98 (s, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.36 (dd, J = 7.6, 1.4 Hz, 1H), 7.54 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.61 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.86 (s, 1H), 8.20 (dd, J = 7.8, 0.7 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 83.93 (C), 112.41 (C), 113.54 (C), 119.76 (CH₂), 128.32 (CH), 128.54 (CH), 128.89 (CH), 129.11 (CH), 129.76 (C), 130.94 (CH), 133.84 (CH), 134.87 (C), 138.21 (C), 144.26 (C), 145.28 (C), 159.32 (CH); IR (KBr) 3037, 2236, 1588, 1487, 1089, 1010 cm⁻¹; MS (EI) m/z 292 (M⁺, 22), 290 (M⁺, 64), 255 (100), 225 (90%); HRMS (EI) m/z 290.0615, 292.0595 (calcld for C₁₅H₁₁Cl₂N, 290.0615, 292.0581).

Procedure for Preparation of 13a. To a solution of 12a (267 g, 1.0 mmol) in CH₂Cl₂ (3 mL) was added Sc(OTf)₃ (104 mg, 0.2 mmol). The reaction mixture was stirred for 17 h. Saturated aqueous NaHCO₃ was added to the mixture. The residue was extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated in vacuo to give 13a (265 mg, 99%).

13a: yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 4.01 (d, J = 6.8 Hz, 1H), 4.06 (dd, J = 6.8, 2.1 Hz, 1H), 6.47 (d, J = 2.1 Hz, 1H), 7.37 (ddd, J = 7.4, 7.4, 1.1 Hz, 1H), 7.41–7.50 (m, 4H), 7.58–7.61 (m, 3H), 7.74 (d, J = 7.4 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 25.83 (CH), 47.44 (CH), 111.59 (C), 111.82 (C), 121.88 (CH), 123.91 (CH), 126.93 (CH), 127.48 (CH), 127.80 (CH), 128.98 (CH), 129.19 (CH), 133.94 (C), 141.23 (C), 143.50 (C), 149.59 (C); IR (KBr) 3049, 2922, 2588, 1489, 1443, 1531, 1071, 1099 cm⁻¹; MS (EI) m/z 256 (M⁺, 20), 191 (100%); HRMS (EI) m/z 256.0997 (calcld for C₁₅H₁₃N₂O₂ 256.1000).

13b: 1 mmol scale, 247 mg, 91%; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 2.41 (s, 3H, 3.97 (d, J = 6.8 Hz, 1H), 4.01 (dd, J = 6.8, 2.1 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.34 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 7.42 (ddd, J = 7.6, 7.4, 0.9 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H),...
The reaction mixture was allowed to warm to room temperature and stirred for 17 h. The mixture was quenched with water and extracted with CH₂Cl₂. The organic layer was washed with saturated aqueous NaHCO₃ dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-EtOAc to give 16a (230 mg, 78%).

16a: Rₛ = 0.4 (hexane-EtOAc = 10:1); colorless oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 3.77 (3H, 1H), 3.78 (s, 3H), 7.12–7.47 (m, 9H), 7.70 (s, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 125.58 (CH), 127.49 (CH), 127.92 (CH), 128.31 (CH), 128.41 (CH), 129.78 (CH), 130.17 (CH), 130.20 (CH), 131.94 (C), 139.68 (C), 142.70 (C), 144.33 (Cl), 163.42 (C), 167.04 (C); IR (neat) 2976, 2868, 1377, 1626, 1437, 1116, 1069 cm⁻¹; MS (EI) m/z 296 (M⁺, 92), 264 (94), 204 (100%); HRMS (EI) m/z 296.1042 (calcd for C₁₈H₁₆O₅ 296.1049).

16b: 2.7 mmol scale, 726 mg, 86%; Rₛ = 0.1 (hexane-EtOAc = 10:1); pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 2.40 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 7.15 (dike, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.31–7.44 (m, 6H), 7.68 (s, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 24.17 (CH₃), 52.53 (CH₂), 52.60 (CH₂), 125.59 (C), 127.84 (CH), 128.26 (CH), 128.32 (CH), 128.35 (CH), 129.01 (C), 129.77 (C), 130.97 (C), 139.75 (C), 140.62 (C), 144.22 (C), 164.48 (C), 166.34 (C); IR (neat) 2952, 1735, 1626, 1607, 1436, 1326, 1070 cm⁻¹; MS (EI) m/z 310 (M⁺, 11), 278 (80), 250 (52), 219 (100%); HRMS (EI) m/z 310.1204 (calcd for C₁₈H₁₆O₅ 310.1208).

16c: 0.5 mmol scale, 137 mg, 82%; Rₛ = 0.2 (hexane-EtOAc = 10:1); colorless oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 3.79 (s, 3H), 3.80 (s, 3H), 7.30–7.43 (m, 3H), 7.37–7.47 (m, 5H), 7.60 (s, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 52.71 (CH₂), 52.76 (CH₂), 127.02 (C), 127.64 (CH), 128.50 (CH), 128.60 (CH), 129.63 (CH), 130.18 (CH), 134.00 (C), 136.06 (C), 138.37 (C), 143.00 (CH), 144.28 (C), 164.14 (C), 166.82 (C); IR (neat) 2953, 1740, 1721, 1629, 1590, 1435, 1260, 1071 cm⁻¹; MS (EI) m/z 332 (M⁺, 3.5), 330 (M⁺, 9.9), 298 (75), 263 (76), 239 (100%); HRMS (EI) m/z 330.0656, 332.0631 (calcd for C₁₈H₁₅ClO₂ 330.0659, 332.0629).

17d: 6.5 mmol scale, 1.46 g, 63%; Rₛ = 0.1 (hexane-CH₂Cl₂ = 1:1); colorless crystals; mp 96–98 °C; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 3.24 (s, 3H), 3.85 (s, 3H), 3.885 (s, 3H), 3.890 (s, 3H), 4.69 (d, J = 3.5 Hz, 1H), 4.70 (d, J = 3.5 Hz, 1H), 6.42 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 2.1 Hz, 1H), 7.27 (dd, J = 7.6, 7.5, 1.1 Hz, 1H), 7.35 (dd, J = 7.6, 7.5 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 44.62 (CH₂), 51.81 (CH), 51.84 (CH₂), 52.63 (CH₂), 55.49 (CH₂), 55.68 (CH₂), 96.47 (CH), 97.80 (CH), 119.80 (CH), 123.12 (C), 125.55 (C), 127.19 (CH), 127.53 (CH), 141.51 (C), 144.45 (C), 156.91 (C), 161.66 (C), 167.88 (C), 169.93 (C); IR (KBr) 2925, 1732, 1595, 1428, 1053 cm⁻¹; MS (EI) m/z 356 (M⁺, 30), 296 (37), 225 (100%); HRMS (EI) m/z 356.1260 (calcd for C₁₇H₁₆O₅ 356.1260); anal. calcd for C₁₇H₁₆O₅: C, 67.41; H, 5.56. Found: C, 67.39; H, 5.56.

**Procedure for Preparation of 16a.** To a solution of 15a (182.2 g, 1.0 mmol) in CH₂Cl₂ (5 mL) were added dimethyl malonate 2a (132.1 mg, 1.1 mL, 1.0 mmol) and pyridine (316 mg, 0.32 mL, 4 mmol). After cooling to 0 °C, TiCl₄ (190 mg, 0.11 mL, 1.0 mmol) was slowly added to the reaction mixture.

Procedure for Preparation of 16a. To a solution of 15a (182.2 g, 1.0 mmol) in CH₂Cl₂ (5 mL) were added dimethyl malonate 2a (132.1 mg, 1.1 mL, 1.0 mmol) and pyridine (316 mg, 0.32 mL, 4 mmol). After cooling to 0 °C, TiCl₄ (190 mg, 0.11 mL, 1.0 mmol) was slowly added to the reaction mixture.
mixture was extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated in vacuo to give 17a (658 mg, 94%).

17a: colorless crystals; mp 129–131 °C; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 3.66 (s, 6H), 3.88 (d, J = 6.4 Hz, 1H), 4.70 (d, J = 6.4 Hz, 1H), 7.28 (dd, J = 7.6, 7.4, 1.2 Hz, 2H), 7.38 (dd, J = 7.6, 1.2 Hz, 2H), 7.46 (dd, J = 7.6, 0.8 Hz, 2H), 7.74 (d, J = 7.6 Hz, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 46.24 (CH₂), 52.56 (CH₃), 55.34 (CH), 120.02 (CH), 124.76 (CH), 127.22 (CH), 129.73 (CH), 141.26 (C), 143.65 (C), 168.56 (C); IR (KBr) 2948, 1740, 1715, 1437, 1267, 1247, 1109 cm⁻¹; MS (EI) m/z 296.1050 (calcd for C₁₉H₁₈O₄ 296.1049); anal. calcd for C₁₉H₁₈O₄ C 75.66; H 6.50; O 17.84; found C 75.64; H 6.48; O 17.80.

Preparation of 18a. To a solution of 17a (241 mg, 0.8 mmol) in CH₂Cl₂ (6.6 mL) was added DDQ (183 mg, 0.8 mmol). The reaction mixture was stirred at 40 °C for 17 h. After cooling to room temperature, the mixture was purified by chromatography over silica gel eluting with hexane-CH₂Cl₂ to give 18a (168 mg, 69%).

18a: R₂ = 0.1 (hexane-CH₂Cl₂ = 1:1); yellow crystals; mp 79.2–80.0 °C (hexane-CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ (ppm) 3.94 (s, 6H), 7.18 (dd, J = 8.0, 7.6, 1.2 Hz, 1H), 7.34 (dd, J = 7.6, 0.9 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 53.07 (CH₃), 119.75 (CH), 122.02 (C), 125.96 (CH), 127.67 (CH), 131.14 (C), 135.47 (C), 141.73 (C), 144.74 (C), 165.83 (C); IR (KBr) 2950, 1720, 1595, 1449, 1247, 1127, 1077 cm⁻¹; MS (EI) m/z 294 (M⁺, 100), 263 (27), 195 (56%); HRMS (EI) m/z 294.0894 (calcd for C₁₆H₁₄O₄ 294.0892).

18b: 80 °C in 1,2-dichloroethane, 0.54 mmol scale, 144 mg, 86%; R₂ = 0.4 (hexane-CH₂Cl₂ = 1:1); pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 2.39 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 7.00 (dd, J = 8.0, 0.9 Hz, 1H), 7.18 (dd, J = 7.8, 7.5, 1.2 Hz, 1H), 7.35 (dd, J = 7.6, 7.5, 0.9 Hz, 1H), 7.38 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 21.78 (CH₃), 53.05 (CH₃), 119.63 (CH), 120.53 (CH), 121.18 (C), 126.02 (CH), 126.08 (CH), 127.3 (CH), 128.66 (CH), 131.07 (CH), 132.99 (C), 136.04 (C), 141.82 (C), 141.85 (C), 142.08 (C), 145.13 (C), 166.01 (C), 166.04 (C); IR (neat) 2950, 1732, 1716, 1456, 1456, 1076 cm⁻¹; MS (EI) m/z 308 (M⁺, 100), 209 (67), 189 (64%); HRMS (EI) m/z 308.1044 (calcd for C₁₈H₁₆O₄ 308.1049).
22. 0.5 mmol scale, 116.7 mg, 74%; Rf = 0.1 (hexane-AcOEt = 10:1), pale yellow oil; 1H NMR (400 MHz, CDCl3) δ (ppm) 3.75 (s, 6H), 7.16 (ddd, J = 8.0, 7.2, 1.2 Hz, 2H), 7.31 (dd, J = 8.0, 1.0 Hz, 2H), 7.43 (ddd, J = 8.0, 7.2, 1.6 Hz, 2H), 7.65 (dd, J = 8.0, 1.6 Hz, 2H); 13C NMR (100.6 MHz, CDCl3) δ (ppm) 52.70 (CH2), 117.01 (CH3), 119.97 (C), 120.89 (C), 123.25 (CH), 127.06 (CH), 131.01 (CH), 137.94 (C), 152.59 (C), 166.28 (C); IR (KBr) 2955, 1740, 1712, 1600, 1449, 1250, 1071 cm⁻¹; MS (EI) m/z 310 (M⁺, 100), 279 (66%); HRMS (EI) m/z 310.0844 (calcd for C18H14O5 310.0841).

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**Notes**

The authors declare no competing financial interest.

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