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Efficient Assembly of 1-(1*H*-Imidazol-1-yl)-3-methylene-1*H*-indenes via Tandem Reaction of (2-(Alkynyl)benzylidene)malonates with Imidazoles

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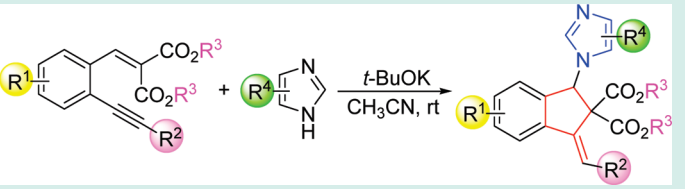
Supporting Information

ABSTRACT: The tandem nucleophilic addition and 5-exo-cyclization of (2-(alkynyl)benzylidene)malonates with imidazole derivatives in the presence of *t*-BuOK is reported. This reaction proceeds smoothly under mild conditions with high selectivity to afford the corresponding 1-(1*H*-imidazol-1-yl)-3-methylene-1*H*-indene-2,2(3*H*)-dicarboxylates in good to excellent yields.



KEYWORDS: 5-exo-cyclization, (2-(alkynyl)benzylidene)malonates, imidazole, nucleophilic addition

INTRODUCTION

The increasing significance of combinatorial chemistry in pharmaceutical and material sciences is well recognized, which demands the development of new strategies to generate a collection of analogues of interesting compounds.[1] It is well documented that imidazole or benzoimidazole derivatives are of particular interest for drug discovery since they are known to elicit a broad spectrum of biological activities,[2] and their applications in diverse therapeutic areas (including antivirals, antitumor, antifungals, etc) have been discovered.[3] Thus, the efficient generation of diversified imidazole-related library is of considerable interest for both medicinal and organic chemists. Meanwhile, the indene core may be found in many natural products and drug candidates as well, which show remarkable biological activities.[4] For instance, indene derivatives could be utilized to selectively modulate estrogen receptor (ER)-mediated transcription. Moreover, the 2,3-diarylindenes were found to bind with high affinity to the ER subtypes and a range of different biological activities was demonstrated both in transcriptional reporter gene assays and inhibition of estradiol-stimulated proliferation of MCF-7 cells.[4a] In addition, the function of indene-related compounds has been found applications in the filed of material science.[5] Thus, new methods continue to appear for the formation of indene-related compounds.[6−9] For example, Sanz reported a gold-catalyzed cycloisomerization or alkoxycyclization of *o*-(alkynyl)styrenes that provided functionalized 1*H*-indene derivatives in good yields.[6a] Tian and co-workers described an useful protocol for the synthesis of indene derivatives via $FeCl_3$-catalyzed reaction of *N*-benzylic sulfonamides and disubstituted alkynes.[6c] Roy reported indene formation via heterobimetallic Ir−Sn catalyzed reaction of propargylic alcohols.[6d] Because of the importance of indene compounds, development of novel approaches for efficient construction of diverse indenes is still of high interest. In our ongoing program aimed at developing new approaches[10] to generate small molecules for our specific biological assays, we conceived that the indene with an imidazole or benzoimidazole substituent might be a good candidate because of the importance of the imidazole skeleton. Recently, we described an efficient route for the formation of 1-methylene-2,3-dihydro-1*H*-indene with an indole substituent via base-promoted tandem reactions with high efficiency and selectivity.[5e,f] As mentioned above, our interest in these target imidazole-corporate indenes is stimulated by the core structures of molecules with known biological activity, and the presence of readily variable diversity points, which opens extensive possibilities for the synthesis of diverse library. Thus, we started to explore the solution-phase parallel method for the synthesis of this kind of designed compounds.

Recently, (2-(alkynyl)benzylidene)malonate has been identified as a versatile building block for carbo- and heterocycles formation.[9e,11] Prompted by this result, we envisioned that the presence of imidazole as a partner in the reaction of (2-(alkynyl)-benzylidene)malonate would occur to generate the desired indene derivatives. In the reaction process, the tandem nucleophilic addition and 5-exo-cyclization might be involved. With these considerations in mind, the reaction of (2-(alkynyl)benzylidene)malonate **1**{*1*} with imidazole **2**{*1*} was carried out in the presence of various bases in acetonitrile at room temperature (Scheme 1).

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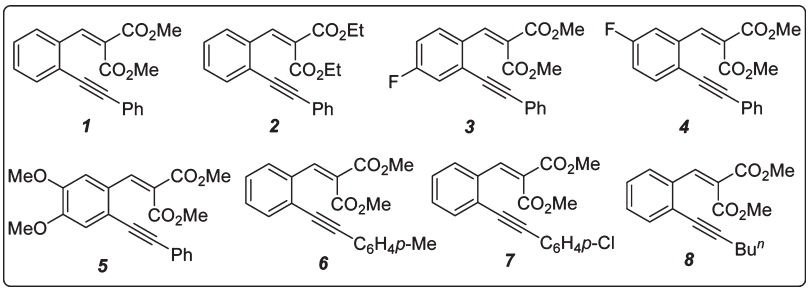


Figure 1. Diverse reagents **1**{*1*−*8*}.

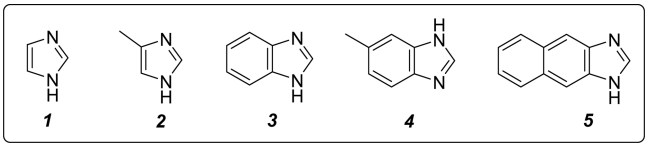
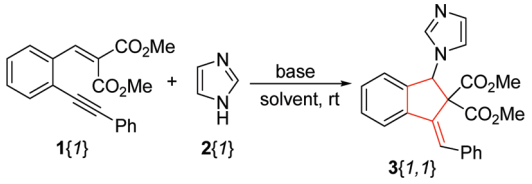


Figure 2. Diverse reagents **2**{*1*−*5*}.

Scheme 1. Initial Studies for Tandem Reaction of (2-(Alkynyl)-benzylidene)malonate 1{*1*} with Imidazole 2{*1*}

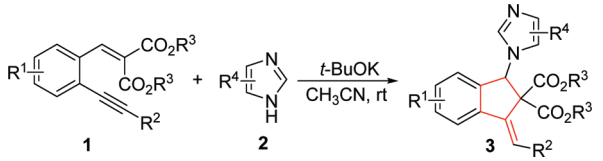


RESULT AND DISCUSSION

In the course of our investigations, we found that treatment of the reaction in the presence of Cs_2CO_3 allowed us to obtain the desired product **3**{*1,1*} in 62% yield. This reaction proceeded under mild conditions with excellent selectivity (*Z*/*E* >99/1). No reaction occurred in the absence of base. Further investigation showed that lower yield (54%) of compound **3**{*1,1*} was obtained when K_3PO_4 was used as a replacement. Inferior result was observed with addition of organic base, such as DABCO in the reaction (29% yield). The yield was dramatically increased when *t*-BuOK was utilized as a base (93% yield). This *t*-BuOK-promoted result was disclosed in our previous report as well.[9e] Subsequently, other solvents were screened (DCE, toluene, EtOH, and THF). However, no better results were obtained. In addition, no improvement was observed when an additive ($PdCl_2$, CuI, AgOTf, etc.) was presented in the reaction.

Encouraged by the optimized conditions (*t*-BuOK, CH_3CN, rt), we extended our studies to other substrates (Figures 1 and 2) and the result were shown in Table 1. As expected, for most cases, these base-promoted reactions of (2-(alkynyl)benzylidene)malonates with imidazole derivatives furnished the corresponding 1-(1*H*-imidazol-1-yl)-3-methylene-1*H*-indene-2,2(3*H*)-dicarboxylates in good to excellent yields. For instance, dimethyl 2-(2-(2-phenylethynyl)-benzylidene)malonate **1**{*1*} reacted with 4-methyl-1*H*-imidazole **2**{*2*} gave rise to the desired product **3**{*1,2*} in 80% yield (entry 2). In this case, the substitution was happened at 1N position of imidazole **2**{*2*} because of the steric effect. Moreover, no relation was found for each proton from the $^1H-^1H$ COSY spectrum of compound **3**{*1,2*}. When benzoimidazole **2**{*3*} or **2**{*4*} was employed as

Table 1. Synthesis of 1-(1*H*-Imidazol-1-yl)-3-methylene-1*H*-indene-2,2(3*H*)-dicarboxylates via Tandem Reaction of (2-(Alkynyl)benzylidene)malonates with Imidazole Derivatives



entry	compound **1**	imidazole **2**	time (h)	product	yield (%)[a]
1	**1**{*1*}	**2**{*1*}	10	**3**{*1,1*}	93
2	**1**{*1*}	**2**{*2*}	8	**3**{*1,2*}	80
3	**1**{*1*}	**2**{*3*}	10	**3**{*1,3*}	88
4	**1**{*1*}	**2**{*4*}	12	**3**{*1,4*}	85
5	**1**{*1*}	**2**{*5*}	10	**3**{*1,5*}	99
6	**1**{*2*}	**2**{*1*}	10	**3**{*2,1*}	66
7	**1**{*2*}	**2**{*3*}	10	**3**{*2,3*}	80
8	**1**{*2*}	**2**{*4*}	8	**3**{*2,4*}	82
9	**1**{*2*}	**2**{*5*}	10	**3**{*2,5*}	91
10	**1**{*3*}	**2**{*1*}	12	**3**{*3,1*}	72
11	**1**{*3*}	**2**{*3*}	10	**3**{*3,3*}	84
12	**1**{*3*}	**2**{*4*}	12	**3**{*3,4*}	88
13	**1**{*4*}	**2**{*1*}	12	**3**{*4,1*}	80
14	**1**{*4*}	**2**{*3*}	8	**3**{*4,3*}	91
15	**1**{*4*}	**2**{*4*}	10	**3**{*4,4*}	86
16	**1**{*4*}	**2**{*5*}	10	**3**{*4,5*}	83
17	**1**{*5*}	**2**{*1*}	10	**3**{*5,1*}	42
18	**1**{*5*}	**2**{*3*}	12	**3**{*5,3*}	51
19	**1**{*5*}	**2**{*4*}	12	**3**{*5,4*}	60
20	**1**{*6*}	**2**{*1*}	12	**3**{*6,1*}	73
21	**1**{*6*}	**2**{*3*}	12	**3**{*6,3*}	76
22	**1**{*6*}	**2**{*5*}	12	**3**{*6,5*}	72
23	**1**{*7*}	**2**{*3*}	12	**3**{*7,1*}	56
24	**1**{*8*}	**2** {*1*}	12	**3**{*8,1*}	

[a] Isolated yield based on (2-(alkynyl)benzylidene)malonate **1**.

substrate in the reaction of (2-(alkynyl)benzylidene)malonate **1**{*1*}, the expected product **3**{*1,3*} or **3**{*1,4*} was generated in 88% and 85% yield, respectively (entries 3 and 4). 1*H*-Naphtho-[2,3-d]imidazole **2**{*5*} was a suitable partner as well, which reacted with compound **1**{*1*} to afford the corresponding product **3**{*1,5*} in almost quantitative yield (entry 5). Substrate **1**{*2*} was examined meanwhile in the reaction of imidazole or benzoimidazole, and all reactions worked smoothly to produce the desired products in good yields (entries 6−9). Reactions of

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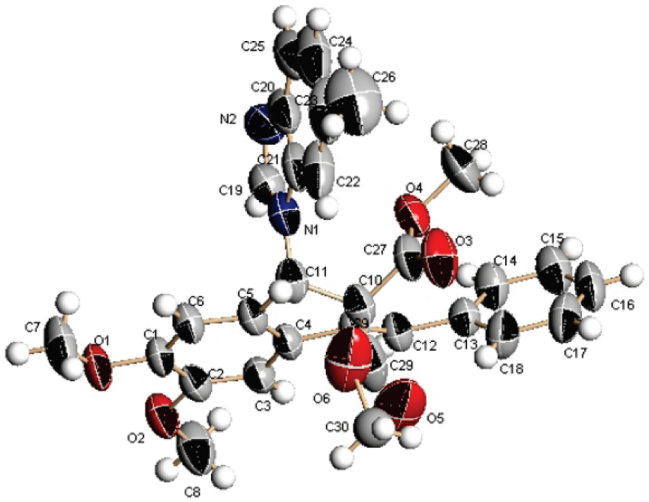

Figure 3. ORTEP illustration of compound **3**{*5,4*}.

fluoro-substituted (2-(alkynyl)benzylidene)malonate **1**{*3*} or **1**{*4*} were also examined, and the results demonstrated that the imidazole derivatives participated well in this tandem nucleophilic addition and 5-exo-cyclization reaction (entries 10−16). When methoxy-substituted (2-(alkynyl)benzylidene)malonate **1**{*5*} was utilized in the reactions with imidazoles, the desired products were obtained in moderate yields (entries 17−19). This result was reasonable since the electron-donating group attached on the aromatic ring of (2-(alkynyl)benzylidene)malonate might decrease the electrophilicity of olefin. The structure of **3**{*5,4*} was identified meanwhile by X-ray diffraction analysis (Figure 3), which confirmed the Z configuration. Additionally, the substitution was found to happen at 1N position of imidazole **2**{*4*}. We further recognized that in this kind of transformation, the R^2 group attached on the triple bond is crucial. When R^2 was replaced by 4-methylphenyl group (**1**{*6*}), similar yields were observed in the reactions of imidazoles (entries 20−22). However, no desired cyclized product was detected when dimethyl 2-(2-(hex-1-ynyl)benzylidene)-malonate **1**{*8*} was used as the substrate in the reaction of imidazole **2**{*1*} (entry 24).

CONCLUSION

In conclusion, our present methodology allows efficient preparation of 1-methylene-2,3-dihydro-1*H*-indenes with an imidazole substituent via a tandem reaction of (2-(alkynyl)benzylidene)malonate with imidazole. This transformation, which involves nucleophilic addition and 5-exo-cyclization, proceeds smoothly under mild conditions with excellent selectivity and broad scope. Focused library construction and biological evaluation of these compounds are ongoing, and the results will be reported in due course.

EXPERIMENTAL PROCEDURES

General Procedure for Tandem Reaction of (2-(Alkynyl)-benzylidene)malonates with Imidazole Derivatives. Imidazole **2** (0.2 mmol) was added to a solution of 2-(2-(alkyny)benylidene)malonate **1** (0.24 mmol) and *t*-BuOK (0.2 mmol) in CH_3CN (2.0 mL), and the mixture was stirred at room temperature. After completion of reaction as indicated by TLC, the mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, and dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the product **3**.

(Z)-Dimethyl 1-Benzylidene-3-(1H-imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{1,1}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (s, 3H), 3.65 (s, 3H), 6.57 (s, 1H), 6.63 (s, 1H), 6.92 (s, 1H), 7.22−7.26 (m, 2H), 7.29−7.33 (m, 3H), 7.35−7.7.37 (m, 1H), 7.41 (s, 1H), 7.44−7.50 (m, 3H), 7.72 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 53.6, 67.0, 69.7, 121.0, 125.9, 127.9, 128.2, 128.3, 128.6, 128.8, 129.8, 130.5, 135.4, 135.8, 137.1, 142.2, 167.1, 168.7; HRMS calcd for $C_{23}H_{21}N_2O_4$ (M^++H) 389.1501; found 389.1512.

(Z)-Dimethyl 1-Benzylidene-3-(4-methyl-1H-imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{1,2}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.91 (s, 3H), 3.69(s, 3H), 6.32 (s, 1H), 6.48(s, 1H), 7.11 (s, 1H), 7.22−7.26 (m, 1H), 7.29−7.49(m, 8H), 7.70 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 52.3, 53.5, 66.8, 69.5, 115.5, 120.8, 125.7, 127.7, 128.0, 128.2, 128.5, 128.7, 129.5, 130.3, 135.5, 135.7, 136.5, 137.2, 142.1, 167.0, 168.7; HRMS calcd for $C_{24}H_{23}N_2O_4$ (M^+ + H) 403.1658; found 403.1651.

(Z)-Dimethyl 1-(1H-Benzo[d]imidazol-1-yl)-3-benzylidene-1H-indene-2,2(3H)-dicarboxylate 3{1,3}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.80 (s, 3H), 6.97 (s, 1H), 7.19 (s, 1H), 7.22−7.42 (m, 9H), 7.44 (s, 1H), 7.51−7.55 (m, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.8, 53.6, 64.5, 68.9, 109.9, 120.0, 121.0, 122.5, 123.0, 125.9, 127.7, 127.9, 128.4, 128.7, 129.9, 130.6, 133.9, 135.5, 135.7, 136.6, 142.2, 142.5, 143.2, 166.6, 169.0; HRMS calcd for $C_{27}H_{23}N_2O_4$ (M^+ + H): 439.1658; found 439.1659.

(Z)-Dimethyl 1-Benzylidene-3-(5-methyl-1H-benzo[d]imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{1,4}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.47 (s, 3H), 3.79 (s, 3H), 6.91 (d, J = 3.6 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 7.7 Hz, 2H), 7.21 (d, J = 7.7 Hz, 2H), 7.25−7.27 (m, 1H), 7.32−7.34 (m, 1H), 7.38−7.43(m, 3H), 7.49−7.58 (m, 3H), 7.76 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 51.9, 53.6, 64.4, 68.9, 109.5, 119.5, 121.0, 124.1, 124.6, 125.9, 127.8, 128.0, 128.5, 128.6, 129.9, 130.6, 133.2, 135.5, 135.7, 136.8, 141.7, 142.4, 142.5, 166.7, 169.0; HRMS calcd for $C_{28}H_{25}N_2O_4$ (M^+ + H) 453.1814; found 453.1807.

(Z)-Dimethyl 1-Benzylidene-3-(1H-naphtho[2,3-d]imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{1,5}: white solid; mp 179−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.82 (s, 3H), 7.08 (s, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.25−7.27 (m, 2H), 7.37−7.43 (m, 7H), 7.46 (s, 1H), 7.53−7.56 (m, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.95−8.01 (m, 2H), 8.02 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 53.7, 64.6, 68.8, 105.8, 117.2, 121.1, 123.6, 124.5, 125.8, 127.7, 127.8, 127.9, 128.3, 128.4, 128.7, 129.9, 130.2, 130.5, 130.7, 134.3, 135.4, 135.7, 136.7, 142.4, 143.2, 145.9, 166.6, 169.1; HRMS calcd for $C_{31}H_{25}N_2O_4$ (M^+ + H) 489.1814; found 489.1809.

(Z)-Diethyl 1-Benzylidene-3-(1H-imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{2,1}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.50 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 3.23−3.32 (m, 2H), 4.09−4.31 (m, 2H), 6.58 (s, 1H), 6.62 (s, 1H), 6.89 (s, 1H), 7.24−7.40 (m, 6H), 7.41 (s, 1H), 7.42−7.50 (m, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 13.6, 62.2, 62.8, 66.6, 69.8, 119.3, 120.8, 125.7, 127.7, 127.9, 128.2, 128.5, 128.8, 129.6, 130.3, 135.2, 135.8, 137.2, 142.3, 166.6, 168.0; HRMS calcd for $C_{25}H_{25}N_2O_4$ (M^+ + H) 417.1814; found 417.1811.

(Z)-Diethyl 1-(1H-Benzo[d]imidazol-1-yl)-3-benzylidene-1H-indene-2,2(3H)-dicarboxylate 3{2,3}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.3 Hz, 3H),

2.60−2.69 (m, 2H), 4.18−4.40 (m, 2H), 6.99 (s, 1H), 7.19−7.35 (m, 6H), 7.40 (t, J = 7.3 Hz, 1H), 7.45 (s, 1H), 7.47−7.54 (m, 4H), 7.65−7.71 (m, 2H), 7.76 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 13.7, 62.0, 62.9, 64.3, 69.3, 110.1, 119.9, 121.0, 122.5, 123.0, 125.9, 127.7, 127.8, 127.9, 128.7, 129.8, 130.6, 134.0, 135.6, 135.7, 136.8, 142.3, 142.6, 143.2, 166.5, 168.5; HRMS calcd for $C_{29}H_{27}N_2O_4$ (M^+ + H) 467.1971; found 467.1963.

(Z)-Diethyl 1-Benzylidene-3-(5-methyl-1H-benzo[d]imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{2,4}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.47 (s, 3H), 2.63−2.72 (m, 2H), 4.18−4.39 (m, 2H), 6.94 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 7.12 (d, J = 6.2 Hz, 1H), 7.19−7.21 (m, 1H), 7.24−7.28 (m, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.37−7.40 (m, 1H), 7.44 (s, 1H), 7.46−7.58 (m, 4H), 7.65−7.71 (m, 2H), 7.76 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 13.7, 62.0, 62.9, 64.3, 69.3, 109.5, 119.4, 120.9, 124.0, 124.5, 125.8, 127.8, 127.9, 128.6, 128.7, 129.0, 129.8, 130.5, 132.1, 132.9, 135.7, 136.9, 141.8, 142.5, 166.4, 168.5; HRMS calcd for $C_{30}H_{29}N_2O_4$ (M^+ + H) 481.2127; found 481.2125.

(Z)-Diethyl 1-Benzylidene-3-(1H-naphtho[2,3-d]imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{2,5}: white solid; mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (t, J = 7.3 Hz, 3H), 1.37 (t, J = 7.3 Hz, 2H), 2.61−2.70 (m, 2H), 4.30−4.50 (m, 2H), 7.17 (s, 1H), 7.23−7.27 (m, 1H), 7.30−7.35(m, 3H), 7.41−7.50 (m, 5H), 7.54 (s, 1H), 7.56−7.62 (m, 3H), 7.86 ((d, J = 7.7 Hz, 1H), 8.01−8.07 (m, 2H), 8.13 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 13.8, 62.1, 63.0, 64.5, 69.2, 105.9, 117.1, 121.1, 123.6, 124.5, 125.9, 127.6, 127.8, 127.9, 128.4, 128.7, 128.8, 129.9, 130.5, 130.6, 134.5, 135.6, 135.8, 136.9, 142.6, 146.1, 166.5, 168.6; HRMS calcd for $C_{33}H_{29}N_2O_4$ (M^+ + H) 517.2127; found 517.2125.

(Z)-Dimethyl 3-Benzylidene-5-fluoro-1-(1H-imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{3,1}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (s, 3H), 3.72 (s, 3H), 6.52 (s, 1H), 6.61 (s, 1H), 6.91 (s, 1H), 7.00−7.10 (m, 1H), 7.23−7.38 (m, 7H), 7.43 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 53.6, 66.2, 70.1, 107.6 (d, $^2J_{CF}$ = 23.7 Hz), 117.3 (d, $^2J_{CF}$ = 23.6 Hz), 119.1, 127.3 (d, $^3J_{CF}$ = 9.16 Hz), 128.2, 128.8, 128.9, 132.7, 134.4 (d, $^4J_{CF}$ = 3.0 Hz), 135.3, 137.3, 144.5 (d, $^3J_{CF}$ = 9.16 Hz), 164.4 (d, $^1J_{CF}$ = 248 Hz), 166.6, 168.4; HRMS calcd for $C_{23}H_{20}FN_2O_4$ (M^+ + H) 407.1407; found 407.1396.

(Z)-Dimethyl 1-(1H-Benzo[d]imidazol-1-yl)-3-benzylidene-5-fluoro-1H-indene-2,2(3H)-dicarboxylate 3{3,3}: yellow solid; mp 74−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.81 (s, 3H), 6.92 (s, 1H), 7.10−7.13 (m, 1H), 7.19−7.33 (m, 7H), 7.37−7.43 (m, 4H), 7.61 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 53.7, 63.7, 69.5, 107.8 (d, $^2J_{CF}$ = 23.6 Hz), 109.9, 117.4 (d, $^2J_{CF}$ = 23.7 Hz), 120.0, 122.5, 123.1, 127.5, 127.5, 128.0, 128.1, 128.5, 128.7, 130.0, 132.2, 133.7, 134.8 (d, $^4J_{CF}$ = 3.0 Hz), 135.0, 141.9, 143.1, 144.8 (d, $^3J_{CF}$ = 8.4 Hz), 164.5 (d, $^1J_{CF}$ = 249 Hz), 166.3, 168.7; HRMS calcd for $C_{27}H_{22}FN_2O_4$ (M^+ + H) 457.1564; found 457.1564.

(Z)-Dimethyl 3-Benzylidene-5-fluoro-1-(5-methyl-1H-benzo[d]imidazol-1-yl)-1H indene-2,2(3H)-dicarboxylate 3{3,4}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.47 (s, 3H), 3.80 (s, 3H), 6.87 (d, J = 3.3 Hz, 1H), 7.05−7.14 (m, 3H), 7.22 (d, J = 7.7 Hz, 1H), 7.26−7.31 (m, 2H), 7.36−7.42 (m, 5H), 7.48 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 52.0, 53.7, 63.7, 69.4, 107.8 (d, $^2J_{CF}$ = 22.9 Hz), 109.7, 117.5 (d, $^2J_{CF}$ = 23.6 Hz), 119.5, 123.9, 124.2, 124.7, 127.5(d, $^3J_{CF}$ = 9.16 Hz), 128.0, 128.1, 128.6, 129.9, 132.3 (d, $^3J_{CF}$ = 7.0 Hz), 132.5, 133.2, 134.9 (d, $^4J_{CF}$ = 2.29 Hz), 135.1, 141.5, 144.8 (d, $^3J_{CF}$ = 8.40 Hz), 164.5 (d, $^1J_{CF}$ = 249 Hz), 166.4, 168.8; HRMS calcd for $C_{28}H_{24}FN_2O_4$ (M^+ + H) 471.1720; found 417.1718.

(Z)-Dimethyl 1-Benzylidene-5-fluoro-3-(1H-imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{4,1}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (s, 3H), 3.70 (s, 3H), 6.54 (s, 1H), 6.62 (s, 1H), 6.93 (s, 1H), 7.00 (dd, J = 2.2, 8.0 Hz, 1H), 7.20−7.33 (m, 6H), 7.43 (d, J = 7.7 Hz, 2H), 7.67−7.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 53.5, 66.3, 69.7, 112.5 (d, $^2J_{CF}$ = 23.7 Hz), 118.3 (d, $^2J_{CF}$ = 23.7 Hz), 119.0, 122.4 (d, $^3J_{CF}$ = 9.16 Hz), 127.8, 127.9, 128.0, 128.6, 128.9, 134.1, 135.5, 137.3, 138.1, 138.8 (d, $^3J_{CF}$ = 8.40 Hz), 163.5 (d, $^1J_{CF}$ = 249 Hz), 166.6, 168.5; HRMS calcd for $C_{23}H_{20}FN_2O_4$ (M^+ + H) 407.1407; found 407.1401.

(Z)-Diethyl 3-(1H-Benzo[d]imidazol-1-yl)-1-benzylidene-5-fluoro-1H-indene-2,2(3H)-dicarboxylate 3{4,3}: white solid; mp 150−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.80 (s, 3H), 6.93 (s, 1H), 7.05 (dd, J = 2.2, 7.7 Hz, 1H), 7.18−7.33 (m, 7H), 7.36 (s, 1H), 7.39 (d, J = 7.7 Hz, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.71−7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 53.7, 63.9, 69.2, 109.7, 112.6 (d, $^2J_{CF}$ = 22.9 Hz), 118.5 (d, $^2J_{CF}$ = 22.9 Hz), 120.1, 122.6, 122.7, 123.2, 127.8, 128.0, 128.3, 128.4, 128.7, 133.7, 134.5, 135.4, 138.4, 138.5, 141.9, 143.1, 163.6 (d, $^1J_{CF}$ = 249.6 Hz), 166.3, 168.8; HRMS calcd for $C_{27}H_{22}FN_2O_4$ (M^+ + H) 457.1564; found 457.1566.

(Z)-Dimethyl 1-Benzylidene-5-fluoro-3-(5-methyl-1H-benzo[d]imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{4,4}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.47 (s, 3H), 3.79 (s, 3H), 6.88 (d, J = 3.7 Hz, 1H), 7.01−7.08 (m, 1H), 7.12−7.18 (m, 1H), 7.20−7.29 (m, 4H), 7.39−7.41 (m, 4H), 7.49(s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.71−7.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 52.0, 53.7, 63.9, 69.2, 109.3, 112.6 (d, $^2J_{CF}$ = 23.6 Hz), 118.5 (d, $^2J_{CF}$ = 23.6 Hz), 119.6, 122.6 (d, $^3J_{CF}$ = 8.30 Hz), 124.2, 124.7, 127.8, 128.0, 128.3, 128.4, 128.8, 132.2, 133.3, 134.5, 135.4, 138.3 (d, $^4J_{CF}$ = 2.29 Hz), 138.7, 141.5, 141.8, 163.6 (d, $^1J_{CF}$ = 248.8 Hz), 166.4, 168.9; HRMS calcd for $C_{28}H_{24}FN_2O_4$ (M^+ + H) 471.1720; found 471.1711.

(Z)-Dimethyl 1-Benzylidene-5-fluoro-3-(1H-naphtho[2,3-d]imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{4,5}: white solid; mp 200−201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.82 (s, 3H), 7.04−7.09 (m, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.24−7.28 (m, 3H), 7.34−7.46 (m, 6H), 7.74−7.77 (m, 1H), 7.95−8.00 (m, 3H), 8.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 53.8, 64.2, 69.1, 105.8, 112.6 (d, $^2J_{CF}$ = 21.9 Hz), 117.4, 118.6 (d, $^2J_{CF}$ = 23.6 Hz), 122.7 (d, $^3J_{CF}$ = 8.39 Hz), 123.8, 124.7, 127.5, 127.9, 128.0, 128.4, 128.5, 130.3, 130.5, 134.5, 135.3, 138.3 (d, $^4J_{CF}$ = 2.29 Hz), 138.6, 145.6, 163.6 (d, $^1J_{CF}$ = 249.5 Hz), 166.4, 169.0; HRMS calcd for $C_{31}H_{24}FN_2O_4$ (M^+ + H) 507.1720; found 507.1718.

(Z)-Dimethyl 1-Benzylidene-3-(1H-imidazol-1-yl)-5,6-dimethoxy-1H-indene-2,2(3H)-dicarboxylate 3{5,1}: white solid; mp 166−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (s, 3H), 3.73 (s, 3H), 3.85 (s, 3H), 4.01 (s, 3H), 6.48 (s, 1H), 6.65 (s, 1H), 6.74 (s, 1H), 6.94 (s, 1H), 7.12(s, 1H), 7.20−7.24 (m, 2H), 7.28−7.32 (m, 3H), 7.43 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 53.5, 56.5, 56.5, 66.9, 70.0, 102.4, 106.9, 125.7, 127.5, 128.0, 128.5, 129.3, 135.1, 135.5, 135.8, 151.3, 151.6, 167.0, 168.8; HRMS calcd for $C_{25}H_{25}N_2O_6$ (M^+ + H) 449.1713; found 449.1707.

(Z)-Dimethyl 1-(1H-Benzo[d]imidazol-1-yl)-3-benzylidene-5,6-dimethoxy-1H-indene-2,2(3H)-dicarboxylate 3{5,3}: white solid; mp 240−241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 4.04 (s, 3H), 6.78 (s, 1H), 6.88 (s, 1H), 7.17−7.19 (m, 2H), 7.23−7.27 (m, 5H), 7.30 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 7.3 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.71

(d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.8, 53.6, 56.1, 56.1, 64.5, 69.4, 102.6, 107.0, 110.0, 120.0, 122.5, 123.0, 126.5, 127.5, 127.9, 128.4, 128.9, 133.8, 135.4, 135.7, 135.9, 142.3, 143.3, 151.4, 151.7, 166.7, 169.2; HRMS calcd for $C_{29}H_{27}N_2O_6$ (M^++H) 499.1869; found 499.1866.

(Z)-Dimethyl 1-Benzylidene-5,6-dimethoxy-3-(5-methyl-1H-benzo[d]imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{5,4}: white solid; mp 227−228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.47 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 4.06 (s, 3H), 6.75 (d, J = 3.7 Hz, 1H), 6.83 (d, J = 3.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.16−7.19 (m, 3H), 7.24−7.27 (m, 3H), 7.36−7.39 (m, 2H), 7.48−7.50 (m, 1H), 7.58 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 51.8, 53.6, 56.1, 56.1, 64.5, 69.4, 102.6, 106.9, 109.7, 119.5, 119.7, 124.1, 124.5, 126.1, 127.5, 127.9, 128.4, 129.2, 132.1, 133.1, 135.3, 135.7, 135.9, 141.8, 142.2, 151.4, 151.6, 166.7, 169.2; HRMS calcd for $C_{30}H_{29}N_2O_6$ (M^++ H) 513.2026; found 513.2011.

(Z)-Dimethyl 1-(4-methyl)benzylidene-3-(1H-imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{6,1}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.91 (s, 3H), 3.72 (s, 3H), 6.56 (s, 1H), 6.62 (s, 1H), 6.91 (s, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.23 (s, 1H), 7.29−7.37 (m, 5H), 7.46−7.49 (m, 1H), 7.70 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 52.4, 53.5, 66.9, 69.6, 119.3, 120.7, 125.7, 128.3, 128.6, 128.7, 128.8, 129.4, 130.4, 132.7, 134.4, 136.9, 137.4, 137.8, 142.4, 167.0, 168.5; HRMS calcd for $C_{24}H_{23}N_2O_4$ (M^+ + H) 403.1658; found 403.1645.

(Z)-Dimethyl 1-(1H-Benzo[d]imidazol-1-yl)-3-(4-methyl)benzylidene-1H-indene-2,2(3H)-dicarboxylate 3{6,3}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2. 28 (s, 3H), 2.36 (s, 3H), 3.80 (s, 3H), 6.96 (s, 1H), 7.07 (d, J = 8.0 Hz, 2H), 7.19 (s, 1H), 7.23−7.27 (m, 1H), 7.29−7.35 (m, 4H), 7.37−7.40 (m, 2H), 7.50−7.54 (m, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 51.9, 53.6, 64.6, 69.0, 110.1, 120.0, 120.9, 122.5, 123.1, 125.9, 128.6, 128.7, 128.8, 129.7, 130.6, 132.6, 133.9, 134.7, 136.5, 137.8, 142.3, 142.7, 166.7, 169.1; HRMS calcd for $C_{28}H_{25}N_2O_4$ (M^+ + H) 453.1814; found 453.1815.

(Z)-Diethyl 1-Benzylidene-3-(1H-naphtho[2,3-d]imidazol-1-yl)-1H-indene-2,2(3H)- dicarboxylate 3{6,5}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2. 27 (s, 3H), 2.31 (s, 3H), 3.83 (s, 3H), 7.06−7.07 (m, 3H), 7.32 (d, J = 8.4 Hz, 2H), 7.35−7.45 (m, 6H), 7.52−7.56 (m, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.95−8.03 (m, 3H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 52.1, 53.7, 64.8, 68.9, 106.0, 117.1, 121.0, 123.7, 124.6, 125.8, 127.8, 128.4, 128.6, 128.7, 128.9, 129.8, 130.3, 130.7, 132.6, 134.8, 136.6, 137.9, 142.6, 146.1, 166.7, 169.2; HRMS calcd for $C_{32}H_{27}N_2O_4$ (M^+ + H) 503.1971; found 503.1969.

(Z)-Dimethyl 1-(4-Chlorobenzylidene)-3-(1H-benzo[d]imidazol-1-yl)-1H-indene-2,2(3H)-dicarboxylate 3{7,1}: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.81 (s, 3H), 6.97 (s, 1H), 7.18 (s, 1H), 7.23−7.27 (m, 3H), 7.31 (d, J = 8.4 Hz, 1H), 7.34−7.37 (m, 4H), 7.40−7.44 (m, 1H), 7.51−7.55 (m, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.71−7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 53.9, 64.6, 69.1, 110.1, 120.2, 120.3, 121.3, 122.7, 123.3, 126.1, 127.5, 128.3, 130.0, 130.3, 130.4, 130.8, 133.8, 134.2, 136.5, 136.9, 142.3, 166.7, 168.9. HRMS calcd for $C_{27}H_{22}ClN_2O_4$ (M^+ + H) 473.1268; found 473.1276.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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