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Palladium-Catalyzed Synthesis of Isocoumarins and Phthalides via *tert*-Butyl Isocyanide Insertion

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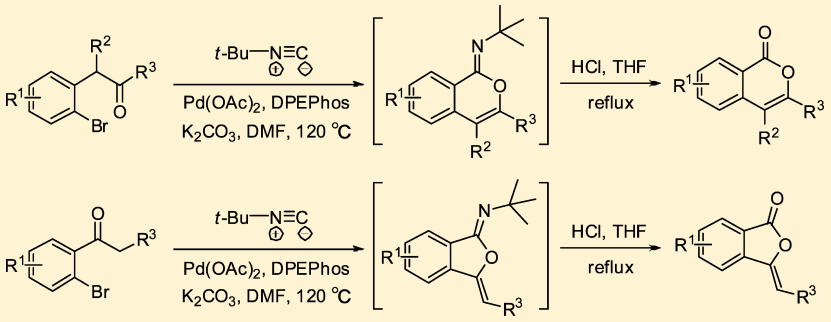
Supporting Information



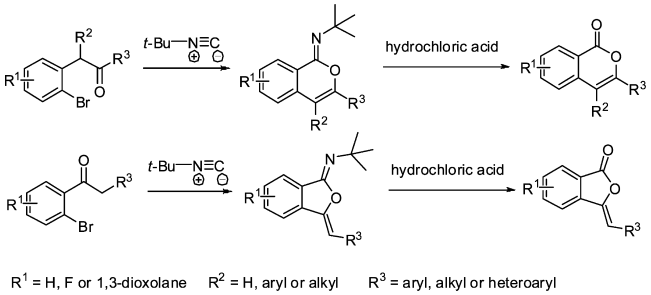
ABSTRACT: A novel and highly efficient strategy for the synthesis of isocoumarins and phthalides through a palladium(0)-catalyzed reaction incorporating *tert*-butyl isocyanide has been developed. This process, providing one of the simplest methods for the synthesis of this class of valuable lactones, involves two steps including cyclization reaction and simple acid hydrolysis. The methodology is tolerant of a wide range of substrates and applicable to library synthesis.

INTRODUCTION

Isocoumarins and phthalides represent an important class of naturally occurring lactones,[1] which are structural subunits in numerous natural products exhibiting a wide range of biological and pharmacological activities.[2] For example, 3-phenylisocoumarin (**3a**) could completely prevent visible growth of fungi, including *Alternaria maritime, Cochliobolus miyabeanus, Fusarium splendens*, etc.[2a] (*Z*)-3-(2-Chlorobenzylidene)phthalide (**6e**) strongly inhibits HIV replication via acting through inhibition interference with Tat function.[2f] In addition, isocoumarins and phthalides are useful synthetic intermediates, particularly for further elaboration to other biologically heterocyclic[3] and carbocyclic compounds.[4] So far, various methods for constructing lactones have been explored and reported.[5] Previously, we've reported copper-catalyzed synthesis of 3-substituted isocoumarins via a cascade intramolecular process.[6] In a continuation to our interest, we are making an effort to investigate some more novel and efficient methods for the synthesis of this class of lactones.

Recently, small molecular insertions for the synthesis of biologically important moieties have been reported. *tert*-Butyl isocyanide,[7−13] a kind of unsaturated molecule similar to carbon monoxide, has emerged as an irreplaceable building block in the construction of important molecules. A wide range of organic compounds including azaindole,[7] indoloquinoline,[8] quinazoline,[9] phthalazinone,[10] isoquinolinone,[11] azomethine[12] and (imino)isoindolinone[13] has been synthesized through this approach. Enlightened by the above literature, we surmised that the insertion of *tert*-butyl isocyanide into the substrate to synthesize isocoumarins and phthalides might be possible (Scheme 1). However, we considered whether isocyanide can be easily coupled with oxygen atom of enolic form by carbonyl tautomerism. To our delight, this method, which uses $Pd(OAc)_2$/DPEPhos as the catalyst system, has advantages such as simple handling, wide substrate scope and mild conditions over carbon monoxide.[14] To the best of our

Scheme 1. Strategy to Isocoumarins and Phthalides via *tert*-Butyl Isocyanide Insertion



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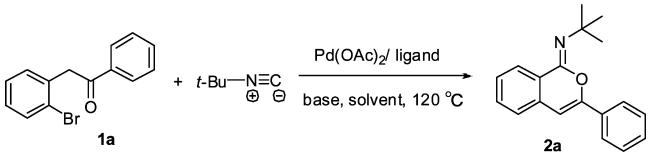
knowledge, no example of utilizing isocyanides as a carbonyl source to synthesize lactones have been reported. Herein, we report this novel and practical synthesis of lactones via palladium-catalyzed C−C and C−O coupling of substrates with *tert*-butyl isocyanide, followed by acid hydrolysis in almost theoretical yield.

RESULTS AND DISCUSSION

In an initial study, reaction of **1a** with *tert*-butyl isocyanide was examined in DMF at 120 °C in the presence of $Pd(OAc)_2$ (5 mol %) and Xantphos (10 mol %), which was found to be effective for the *tert*-butyl isocyanide insertion (Table 1, entry 1). The reaction of **1a** took place efficiently to give product **2a** in 78% yield after 2 h. Then, several phosphorus ligands or no ligand were tested in this reaction, and a 94% yield of the expected product was obtained when DPEPhos was employed as the ligand (Table 1, entries 2−9). Bases were also tested, and in comparison use of K_2CO_3, Cs_2CO_3 resulted in diminished yield (Table 1, entry 10). When the solvent was switched to DMSO, toluene, or dioxane, the yield of **2a** decreased (Table 1, entries 11−13). On the basis of these considerations, the optimal reaction condition was set as $Pd(OAc)_2$ (5 mol %) and DPEPhos (10 mol %) in DMF using K_2CO_3 (2 equiv) as a base. Then, acid hydrolysis of **2a** could make the generation of 3-phenylisocoumarin **3a** in high yield.

Table 1. Condition Optimizations of 1a with *tert*-Butyl Isocyanide[a]



entry	ligand	base	solvent	yield[b] (%)
1	Xantphos	K_2CO_3	DMF	78
2	DPPF	K_2CO_3	DMF	79
3	(*R*)-BINAP	K_2CO_3	DMF	75
4	PPh_3	K_2CO_3	DMF	70
5	PCy_3	K_2CO_3	DMF	71
6	TFP	K_2CO_3	DMF	65
7	P(*o*-tol)$_3$	K_2CO_3	DMF	68
8	DPEPhos	K_2CO_3	DMF	94
9	–	K_2CO_3	DMF	62
10	DPEPhos	Cs_2CO_3	DMF	23
11	DPEPhos	K_2CO_3	DMSO	82
12[c]	DPEPhos	K_2CO_3	toluene	15
13[d]	DPEPhos	K_2CO_3	dioxane	68

[a]Reaction conditions: All reactions were performed with **1a** (0.5 mmol), *tert*-butyl isocyanide (0.75 mmol), $Pd(OAc)_2$ (2.5 mol %), ligand (5 mol %) and base (1.0 mmol) in 3.0 mL of solvent at 120 °C for 2 h. Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, DPPF = 1,1′-Bis(diphenylphosphino)ferrocene, (*R*)-BINAP = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, PCy_3 = tricyclohexylphosphine, TFP = tri(2-furyl)phosphine, DPEPhos = bis[(2-diphenylphosphino)phenyl]ether. [b]Isolated yield. [c]Reaction at 110 °C. [d]Reaction at 100 °C

With the optimized reaction conditions in hand, we then tested the scope and generality of the method. Various substitutes in R^3, including aryl (Table 2, entries 1−10), heteroaryl (Table 2, entries 11 and 12), and alkyl (Table 2, entries 13 and 14), were well tolerated. Substrates with electron rich and electron deficient aromatics both gave high yields (Table 2, entries 1−9). Note that good yields were also obtained when R^3 was a naphthalene, heteroaryl or aliphatic group (Table 2, entries 10−14). In addition, substrates including disubstituents R^2 and R^3, such as **1o** and **1p**, also generated **3o** and **3p** in moderate yields, respectively (Table 2, entries 15 and 16). Substrate **1q** gave product **3q** only in 39% yield because of hydrolyzation of the acetal (Table 2, entry 17).

To further evaluate this practical approach, a variety of substrates **4a**−**4i** were investigated, and the results are summarized in Table 3. This method was successfully applied to synthesize various phthalides. At the outset, we considered probably obtaining a mixture of *cis*−*trans* isomerism, which made the purification difficult. However, only one main spot was observed on TLC after completion of the reaction. Through comparing the NMR data of **6a** with the reference,[15] we confirmed **6a** as Z-configuration. Electron-rich substitutes afforded higher yields than electron-poor counterparts (Table 3, entries 2−7). Product **6e** was formed in only 37% yield due to side reaction during the cyclization step (Table 3, entry 5). Note, substrates with aliphatic groups such as decyl and cyclohexyl generated products **6h** and **6i** in moderate yields (Table 3, entries 8 and 9).

On the basis of the above experimental results and related reports,[9−11] a plausible mechanism for this reaction is outlined in Scheme 2. Oxidative addition of **1a** to the Pd(0) catalyst leads to a palladium complex **7**, followed by *tert*-butyl isocyanide insertion to form **8**. Palladium(II) in complex **8**, which coordinates to the oxygen atom of hydroxyl group, promotes the formation of **9**. Reductive elimination of **9** leads to the intermediate **2a**, which yields product **3a** by acid hydrolysis.

In summary, we have developed a simple and efficient method for the synthesis of isocoumarins and phthalides from easily accessible substrates and *tert*-butyl isocyanide. This process, which provides one of the easiest pathways for accessing this class of valuable compounds, uses $Pd(OAc)_2$/DPEPhos as the catalyst system and THF/hydrochloric acid as the hydrolysis condition. We obtained Z-configuration of 3-substituted phthalides. Characterized by mild reaction conditions and good to excellent yields, this protocol may be very attractive in synthetic organic and medicinal chemistry.

EXPERIMENTAL SECTION

General Remarks. Chemicals and reagents were purchased from commercial suppliers and used without further purification. All anhydrous solvents used in the reactions were dried and freshly distilled. TLC was performed on silica HSGF254 plates. Melting points were determined with a digital melting-point apparatus. ^1H and ^{13}C NMR spectra were obtained from a solution in $CDCl_3$ or DMSO with TMS as internal standard using a 400/101 MHz ($^1H/^{13}C$) or 300/75 MHz ($^1H/^{13}C$) spectrometer. Chemical shifts (δ) are given in ppm and J in Hz. IR spectra were recorded in KBr tablets, and wavenumbers are given in cm^{-1}. HRMS analyses were carried out on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry.

General Procedure for the Synthesis of lactones. A sealed tube was charged with a magnetic stir bar, **1** or **4** (0.5 mmol),[16] *tert*-butyl isocyanide (0.75 mmol, 85 μL), $Pd(OAc)_2$ (2.5 mol %, 6 mg), DPEPhos (5 mmol %, 27 mg), K_2CO_3 (1.0 mmol, 138 mg) and anhydrous DMF (3 mL). The tube was purged with nitrogen gas and stirred at 120 °C for 2 h. After reaction completion, the mixture was filtered through a short plug of Celite, and DMF was removed by a vacuum. The combined filtrates were refluxed in THF (15 mL) and hydrochloric acid (1 M, 3 mL) for 2 h. Then, the mixture was

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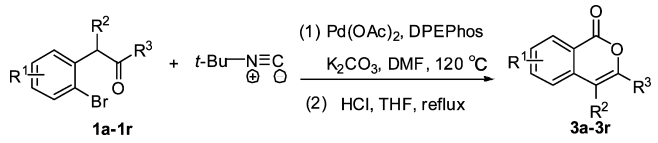
Table 2. Synthesis of Isocoumarins from Substrates (1a−1r) with *tert*-Butyl Isocyanide[a]



1a-1r 3a-3r

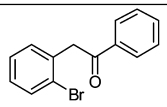
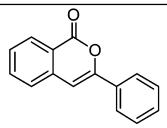
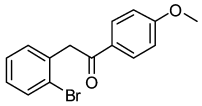
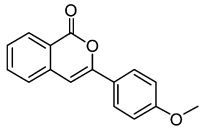
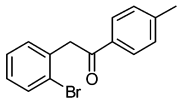
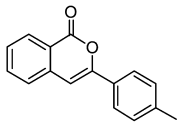
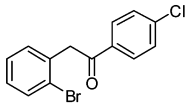
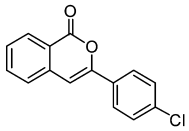
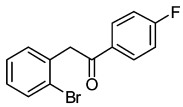
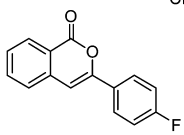
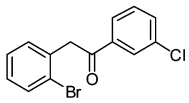
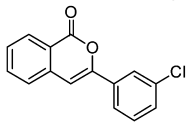
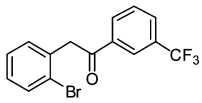
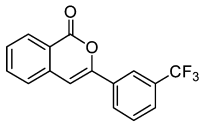
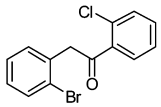
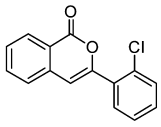
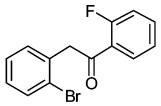
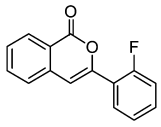
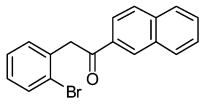
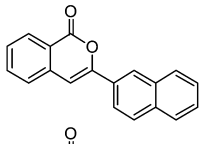
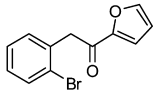
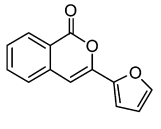
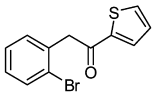
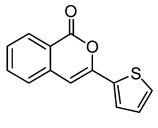
entry	substrate		product		yield[b] (%)
1		**1a**		**3a**	91
2		**1b**		**3b**	85
3		**1c**		**3c**	79
4		**1d**		**3d**	86
5		**1e**		**3e**	84
6		**1f**		**3f**	89
7		**1g**		**3g**	76
8		**1h**		**3h**	58
9		**1i**		**3i**	76
10		**1j**		**3j**	86
11		**1k**		**3k**	71
12		**1l**		**3l**	67

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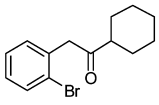
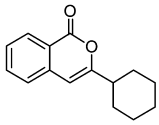
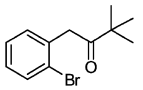
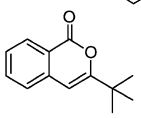
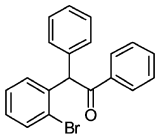
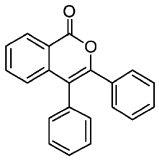
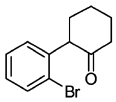
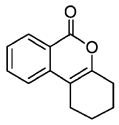
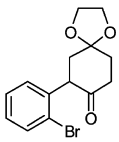
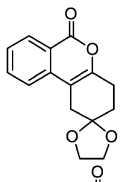
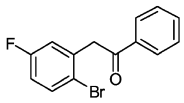
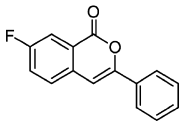
Table 2. continued

entry	substrate		product		yield[b] (%)
13		**1m**		**3m**	87
14		**1n**		**3n**	89
15		**1o**		**3o**	94
16		**1p**		**3p**	89
17		**1q**		**3q**	39
18		**1r**		**3r**	57

[a]All reactions were performed under N_2 on a 0.5 mmol scale, using *tert*-butyl isocyanide (0.75 mmol), $Pd(OAc)_2$ (2.5 mol %), DPEPhos (5 mol %), and K_2CO_3 (1.0 mmol) in DMF (3 mL) at 120 °C for 2 h, followed by refluxing in THF/hydrochloric acid for 2 h. [b]Isolated yield.

extracted with EtOAc, dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column using petroleum ether/EtOAc as the eluent to give the pure target product.

(Z)-(1H)-3-Phenyl-N-tert-butylisochromen-1-imine (**2a**).[17a] Yellow solid (130 mg, 94%); 69−71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.46−7.31 (m, 4H), 7.26 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.54 (s, 1H), 1.51 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 146.5, 133.2, 132.8, 131.2, 129.1, 128.7, 127.7, 127.3, 125.1, 124.9, 100.7, 53.3, 29.8; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO$ $[M + H]^+$, 278.1539, found 278.1540.

3-Phenyl-1H-isochromen-1-one (**3a**).[6] White solid (101 mg, 91%); 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.52−7.41 (m, 5H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 153.6, 137.5, 134.9, 131.9, 129.9, 129.6, 128.8, 128.1, 125.9, 125.2, 120.5, 101.8; IR (KBr) ν = 3071, 3054, 2963, 2927, 1719, 1636, 1482, 1072, 1028, 1011, 764, 746, 685 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{11}O_2$ $[M + H]^+$, 223.0754, found 223.0754.

3-(4-Methoxyphenyl)-1H-isochromen-1-one (**3b**).[6] White solid (107 mg, 85%); 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.46−7.38 (m, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.78 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 161.0, 153.6, 137.8, 134.8, 129.5, 127.6, 126.7, 125.6, 124.4, 120.0, 114.1, 100.2, 55.3; IR (KBr) ν = 2999, 2846, 1738, 1634, 1604, 1514, 1264, 1066, 1023, 837, 820, 752, 687 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{13}O_3$ $[M + H]^+$, 253.0859, found 253.0859.

3-p-Tolyl-1H-isochromen-1-one (**3c**).[6] White solid (93 mg, 79%); 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.70−7.64 (m, 1H), 7.48−7.41 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.86 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 153.7, 140.1, 137.6, 134.7, 129.4, 129.0, 127.8, 125.8, 125.0, 120.2, 100.9, 21.3; IR (KBr) ν = 3067, 3034, 2965, 2920, 1734, 1630, 1608, 1510, 1483, 1236, 1067, 818, 753, 688 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{13}O_2$ $[M + H]^+$, 237.0910, found 237.0904.

3-(4-Chlorophenyl)-1H-isochromen-1-one (**3d**).[17b] White solid (110 mg, 86%); 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.6 Hz, 2H), 7.72 (td, J = 7.7, 1.1 Hz, 1H), 7.53−7.46 (m, 2H), 7.41 (d, J = 8.6 Hz, 2H), 6.92 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 152.4, 137.2, 135.9, 134.9, 130.3, 129.6, 129.0, 128.3, 126.4, 126.0, 120.4, 102.0; IR (KBr) ν = 3101, 1726, 1707, 1639, 1492, 1090, 1070, 1037, 1009, 828, 752, 685 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClO_2$ $[M + H]^+$, 257.0364, found 257.0377.

3-(4-Fluorophenyl)-1H-isochromen-1-one (**3e**).[6] Yellow solid (101 mg, 84%); 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.8 Hz, 1H), 7.92−7.81 (m, 2H), 7.72 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.3 Hz, 2H), 7.14 (t, J = 8.2 Hz, 2H), 6.88 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 162.4, 162.1, 152.6, 137.3, 134.9, 129.6, 128.2, 127.2, 125.9, 120.3, 116.0, 115.8, 101.5; IR (KBr) ν = 3104, 1721, 1639, 1600, 1510, 1483, 1234, 1069, 829, 747, 684 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{10}FO_2$ $[M + H]^+$, 241.0659, found 241.0665.

3-(3-Chlorophenyl)-1H-isochromen-1-one (**3f**).[6] White solid (114 mg, 89%); 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 7.71 (t, J = 6.6 Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 7.35 (d, J = 4.1 Hz, 2H), 6.91 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 161.8, 151.8, 136.9, 134.9, 133.5, 130.0, 129.8, 129.6, 128.5, 126.1, 125.1, 123.1, 120.5, 102.6; IR (KBr) ν = 3111, 1720, 1639, 1606, 1483, 1419, 1238, 1070, 754, 681 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClO_2$ $[M + H]^+$, 257.0364, found 257.0373.

3-(3-(Trifluoromethyl)phenyl)-1H-isochromen-1-one (**3g**). White solid (110 mg, 76%); 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.1 Hz, 1H), 8.11 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.78−7.71 (m, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.56−7.50 (m, 2H), 7.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8,

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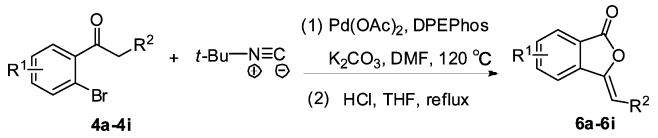
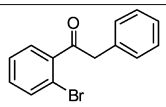
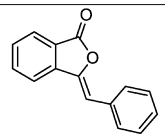
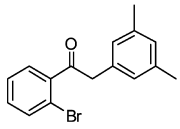
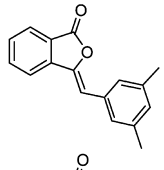
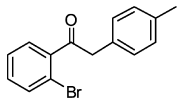
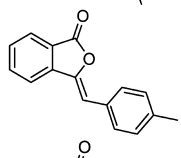
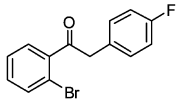
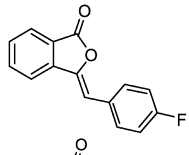
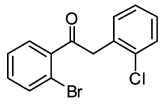
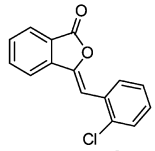
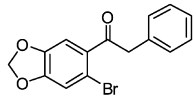
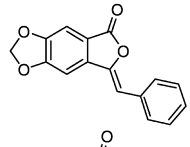
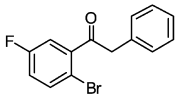
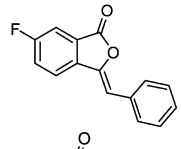
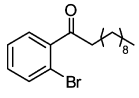
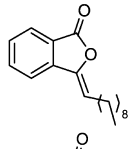
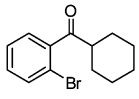
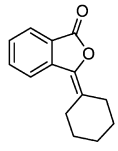
Table 3. Synthesis of Phthalides from Substrates (4a−4i) with *tert*-Butyl Isocyanide[a]



entry	substrate		product		yield[b] (%)
1		**4a**		**6a**	90
2		**4b**		**6b**	86
3		**4c**		**6c**	83
4		**4d**		**6d**	71
5		**4e**		**6e**	37
6		**4f**		**6f**	67
7		**4g**		**6g**	60
8		**4h**		**6h**	56
9		**4i**		**6i**	49

[a]All reactions were performed under N_2 on a 0.5 mmol scale, using *tert*-butyl isocyanide (0.75 mmol), $Pd(OAc)_2$ (2.5 mol %), DPEPhos (5 mol %), and K_2CO_3 (1.0 mmol) in DMF (3 mL) at 120 °C for 2 h, followed by refluxing in THF/hydrochloric acid for 2 h. [b]Isolated yield

151.9, 136.9, 135.0, 132.8, 129.7, 129.4, 128.7, 128.2, 126.4, 126.4, 126.2, 122.0, 120.7, 102.9; IR (KBr) ν = 3103, 1731, 1640, 1605, 1491, 1341, 1333, 1230, 1170, 1109, 1068, 802, 752, 690 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{10}F_3O_2$ $[M + H]^+$, 291.0627, found 291.0625.

*3-(2-Chlorophenyl)-1H-isochromen-1-one (**3h**).*[17b] White solid (74 mg, 58%); 114−116 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 7.9 Hz, 1H), 7.80−7.66 (m, 2H), 7.59−7.44 (m, 3H), 7.40−7.33 (m, 2H), 6.98 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 151.3, 136.9, 134.9, 132.3, 131.5, 130.6, 129.5, 128.6, 127.0, 126.2, 120.6, 107.6; IR (KBr) ν = 3066, 1735, 1644, 1605, 1484, 1343, 1229, 1049, 1031, 839, 760, 745, 685 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClO_2$ $[M + H]^+$, 257.0364, found 257.0369.

*3-(2-Fluorophenyl)-1H-isochromen-1-one (**3i**).*[17b] White solid (91 mg, 76%); 111−113 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 7.8 Hz, 1H), 7.99 (td, J = 7.9, 1.6 Hz, 1H), 7.72 (td, J = 7.7, 1.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.41−7.34 (m, 1H), 7.29−7.22 (m, 1H), 7.19 (s, 1H), 7.17−7.12 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 161.2, 158.7, 148.0, 137.3, 134.8, 131.1, 131.0, 129.4, 128.5, 128.4, 126.4, 124.5, 120.7, 120.1, 120.0, 116.5, 116.2, 107.2, 107.1; IR (KBr) ν = 3080, 1733, 1629, 1605, 1487, 1459, 1230, 1069, 752, 684 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{10}FO_2$ $[M + H]^+$, 241.0659, found 241.0671.

*3-(Naphthalen-2-yl)-1H-isochromen-1-one (**3j**).*[6] White solid (117 mg, 86%); 151−153 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H),

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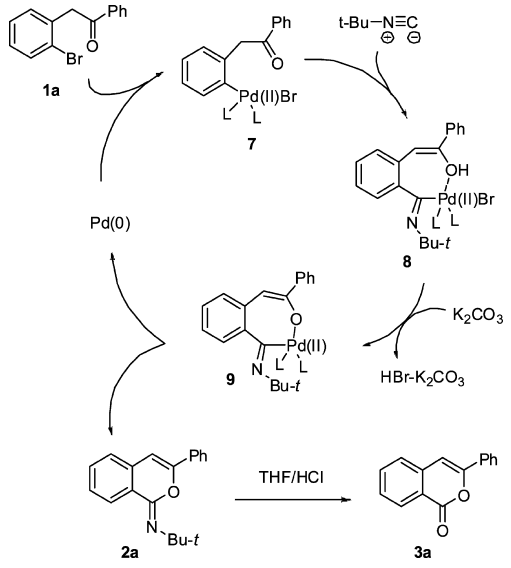
Scheme 2. Plausible Mechanism for the Synthesis of 3a



8.32 (d, J = 7.9 Hz, 1H), 7.96−7.89 (m, 1H), 7.89−7.80 (m, 3H), 7.76−7.68 (m, 1H), 7.56−7.46 (m, 4H), 7.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 153.4, 137.5, 134.9, 133.8, 133.1, 129.6, 128.8, 128.6, 128.2, 127.6, 127.2, 126.8, 126.0, 125.2, 121.9, 120.5, 102.2; IR (KBr) ν = 3106, 3053, 3030, 1717, 1636, 1607, 1560, 1508, 1485, 1373, 1192, 1074, 747, 681 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{12}O_2Na$ [M + Na]$^+$, 295.0730, found 295.0743.

3-(Furan-2-yl)-1H-isochromen-1-one (**3k**).[6] White solid (75 mg, 71%); 116−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8.1 Hz, 1H), 7.70−7.61 (m, 1H), 7.50−7.38 (m, 3H), 6.90 (d, J = 3.4 Hz, 1H), 6.81 (s, 1H), 6.52−6.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 146.8, 145.9, 143.9, 137.2, 134.9, 129.7, 127.9, 125.9, 120.3, 112.0, 110.0, 99.9; IR (KBr) ν = 3152, 3130, 3119, 1736, 1719, 1646, 1479, 1230, 1164, 1090, 1005, 759, 748, 687 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_9O_3$ [M + H]$^+$, 213.0546, found 213.0556.

3-(Thiophen-2-yl)-1H-isochromen-1-one (**3l**).[6] Yellow solid (76 mg, 67%); 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 7.9 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 3.6 Hz, 1H), 7.48−7.35 (m, 3H), 7.12−7.04 (m, 1H), 6.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 149.3, 137.4, 135.6, 134.9, 129.7, 128.1, 127.9, 127.3, 126.1, 125.7, 120.2, 100.8; IR (KBr) ν = 3103, 3082, 2927, 1733, 1719, 1629, 1559, 1231, 1070, 1059, 818, 752, 707, 686, 669 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_9O_2S$ [M + H]$^+$, 229.0318, found 229.0327.

3-Cyclohexyl-1H-isochromen-1-one (**3m**).[6] White solid (99 mg, 87%); 89−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 6.23 (s, 1H), 2.44 (t, J = 11.1 Hz, 1H), 2.03 (d, J = 11.6 Hz, 2H), 1.85 (d, J = 11.9 Hz, 2H), 1.74 (d, J = 13.4 Hz, 1H), 1.52−1.17 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.3, 137.7, 134.6, 129.4, 127.4, 125.2, 120.2, 100.8, 41.8, 30.5, 25.9, 25.8; IR (KBr) ν = 2930, 2902, 2851, 1722, 1649, 1604, 1482, 1330, 1163, 1060, 1043, 1024, 829, 764 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{17}O_2$ [M + H]$^+$, 229.1223, found 229.1233.

3-tert-Butyl-1H-isochromen-1-one (**3n**).[6] Colorless oil (90 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.9 Hz, 1H), 7.60 (td, J = 7.8, 1.1 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 6.25 (s, 1H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 162.7, 137.4, 134.4, 129.0, 127.4, 125.3, 119.8, 99.5, 35.4, 27.7; IR (KBr) ν = 2967, 2928, 2871, 1733, 1725, 1647, 1603, 1568, 1481, 1338, 1114, 1087, 1050, 1015, 953, 828, 765, 690 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{15}O_2$ [M + H]$^+$, 203.1067, found 203.1075.

3,4-Diphenyl-1H-isochromen-1-one (**3o**).[17c] White solid (140 mg, 94%); 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 7.9 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 5.3 Hz, 3H), 7.35−7.31 (m, 2H), 7.27−7.23 (m, 2H), 7.22−7.15 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 150.8, 138.7, 134.5, 134.2, 132.8, 131.1, 129.4, 129.1, 129.0, 128.8, 128.0, 128.0, 127.8, 125.3, 120.3, 116.8; IR (KBr) ν = 3072, 3049, 3025, 1738, 1725, 1623, 1603, 1480, 1311, 1244, 1198, 1080, 1057, 783, 760, 712, 693 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{15}O_2$ [M + H]$^+$, 299.1067, found 299.1065.

3,4-Dihydro-1H-benzo[c]chromen-6(2H)-one (**3p**).[14e] White solid (89 mg, 89%); 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 1H), 7.74−7.67 (m, 1H), 7.44 (t, J = 8.3 Hz, 2H), 2.61−2.52 (m, 4H), 1.89−1.81 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 152.3, 137.9, 134.5, 129.6, 127.0, 121.3, 120.4, 109.2, 27.3, 22.6, 22.0; IR (KBr) ν = 2936, 2918, 2868, 2842, 1724, 1653, 1603, 1489, 1455, 1186, 1063, 756, 689 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{13}O_2$ [M + H]$^+$, 201.0910, found 201.0917.

3,4-Dihydrospiro[benzo[c]chromene-2,2′-[1,3]dioxolan]-6(1H)-one (**3q**).[14e] White solid (50 mg, 39%); 111−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (dd, J = 7.9, 0.6 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 4.07−4.00 (m, 4H), 2.82−2.74 (m, 4H), 1.98 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 151.0, 137.4, 134.6, 129.7, 127.4, 121.1, 120.2, 107.2, 107.1, 64.7, 33.2, 30.5, 26.2; IR (KBr) ν = 2970, 2941, 2893, 2862, 1731, 1721, 1661, 1605, 1492, 1365, 1306, 1062, 1032, 849, 768, 693 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{15}O_4$ [M + H]$^+$, 259.0971, found 259.0987.

7-Fluoro-3-phenyl-1H-isochromen-1-one (**3r**).[6] White solid (68 mg, 57%); 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 6.3 Hz, 2H), 7.55−7.42 (m, 5H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 161.4, 160.1, 153.1, 134.0, 131.6, 130.0, 128.8, 128.2, 128.1, 123.5, 123.2, 122.1, 122.0, 115.3, 115.0, 101.0; IR (KBr) ν = 3086, 1715, 1641, 1619, 1499, 1448, 1338, 1256, 1069, 864, 758, 681 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_9FO_2Na$ [M + Na]$^+$, 263.0479, found 263.0481.

(Z)-3-Benzylideneisobenzofuran-1(3H)-one (**6a**).[17d] White solid (100 mg, 93%); 81−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.7, 0.7 Hz, 1H), 7.85−7.79 (m, 2H), 7.76−7.66 (m, 2H), 7.54−7.48 (m, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.33−7.27 (m, 1H), 6.39 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 144.5, 140.5, 134.4, 133.0, 130.0, 129.7, 128.7, 128.3, 125.4, 123.3, 119.7, 107.0; IR (KBr) ν = 3067, 3026, 1785, 1774, 1655, 1607, 1472, 1354, 1270, 1084, 1071, 970, 763, 688 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{11}O_2$ [M + H]$^+$, 223.0754, found 223.0752.

(Z)-3-(3,5-Dimethylbenzylidene)isobenzofuran-1(3H)-one (**6b**). White solid (108 mg, 86%); 142−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.7, 0.9 Hz, 1H), 7.77−7.67 (m, 2H), 7.56−7.49 (m, 1H), 7.47 (s, 2H), 6.96 (s, 1H), 6.35 (s, 1H), 2.36 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 144.0, 140.4, 137.9, 134.1, 132.7, 130.1, 129.3, 127.7, 125.1, 123.0, 119.5, 107.2, 21.1; IR (KBr) ν = 3053, 2918, 1773, 1663, 1603, 1474, 1354, 1280, 1082, 977, 856, 762, 690, 627 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{15}O_2$ [M + H]$^+$, 251.1067, found 251.1058.

(Z)-3-(4-Methylbenzylidene)isobenzofuran-1(3H)-one (**6c**).[17d] White solid (98 mg, 83%); 147−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.7 Hz, 1H), 7.75−7.62 (m, 4H), 7.52−7.43 (m, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.34 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 143.8, 140.5, 138.5, 134.3, 130.2, 130.0, 129.4, 125.3, 123.1, 119.6, 107.1, 21.3; IR (KBr) ν = 3092, 3035, 3023, 1779, 1767, 1661, 1605, 1474, 1352, 1269, 1077, 971, 858, 760, 688 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{13}O_2$ [M + H]$^+$, 237.0910, found 237.0905.

(Z)-3-(4-Fluorobenzylidene)isobenzofuran-1(3H)-one (**6d**).[17d] White solid (85 mg, 71%); 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.7, 0.9 Hz, 1H), 7.82−7.74 (m, 2H), 7.73−7.64 (m, 2H), 7.54−7.47 (m, 1H), 7.05 (t, J = 8.7 Hz, 2H), 6.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 164.0, 160.7, 144.1, 140.4, 134.5, 131.9, 131.7, 129.7, 129.3, 129.2, 125.5, 123.1, 119.7, 115.9, 115.6, 105.7; IR (KBr) ν = 3085, 3036, 1794, 1664, 1599, 1508, 1272, 1231, 1078, 970, 859, 827, 756, 685 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_9FO_2Na$ [M + Na]$^+$, 263.0479, found 263.0484.

(Z)-3-(2-Chlorobenzylidene)isobenzofuran-1(3H)-one (**6e**).[2f] White solid (47 mg, 37%); 156−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.84 (d, J

= 7.9 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.24−7.18 (m, 1H), 6.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 145.8, 140.4, 134.6, 133.8, 131.7, 130.9, 130.2, 129.6, 129.2, 127.2, 125.6, 123.4, 120.2, 102.2; IR (KBr) ν = 3065, 2963, 1793, 1781, 1655, 1610, 1478, 1358, 1279, 1263, 1080, 966, 758, 746, 685 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClO_2$ $[M + H]^+$, 257.0364, found 257.0372.

*(Z)-7-Benzylideneisobenzofuro[5,6-d][1,3]dioxol-5(7H)-one (**6f**).*[17e] White solid (90 mg, 67%); 197−199 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.66 (d, J = 7.6 Hz, 2H), 7.52 (s, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 7.2 Hz, 1H), 7.23 (s, 1H), 6.66 (s, 1H), 6.17 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 165.7, 154.1, 150.1, 144.1, 137.1, 133.3, 129.5, 128.8, 128.1, 116.7, 105.9, 103.3, 103.1, 99.9; IR (KBr) ν = 3023, 2910, 1771, 1753, 1610, 1477, 1325, 1304, 1075, 967, 939, 849, 778, 692, 642 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{10}O_4Na$ $[M + Na]^+$, 289.0471, found 289.0478.

*(Z)-3-Benzylidene-6-fluoroisobenzofuran-1(3H)-one (**6g**).*[17e] White solid (72 mg, 60%); 152−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.5, 4.7 Hz, 1H), 7.85−7.78 (m, 2H), 7.44−7.35 (m, 3H), 7.35−7.28 (m, 1H), 7.22 (td, J = 8.6, 2.1 Hz, 1H), 6.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 165.8, 165.1, 143.5, 143.4, 143.2, 143.0, 132.6, 130.2, 128.8, 128.0, 127.9, 119.5, 118.3, 118.0, 108.2, 106.7, 106.4; IR (KBr) ν = 3067, 3025, 1771, 1619, 1599, 1480, 1445, 1288, 1195, 994, 934, 879, 774, 687 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_9FO_2Na$ $[M + Na]^+$, 263.0479, found 263.0489.

*(Z)-3-Decylideneisobenzofuran-1(3H)-one (**6h**).* Colorless oil (76 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.7 Hz, 1H), 7.67−7.58 (m, 2H), 7.50−7.43 (m, 1H), 5.61 (t, J = 7.8 Hz, 1H), 2.44 (dd, J = 15.1, 7.6 Hz, 2H), 1.54−1.43 (m, 2H), 1.39−1.14 (m, 12H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 145.5, 139.5, 134.1, 129.2, 125.1, 124.3, 119.5, 109.7, 31.8, 29.5, 29.3, 29.2, 25.8, 22.6, 14.0; IR (KBr) ν = 2955, 2926, 2854, 1853, 1783, 1686, 1468, 1272, 1258, 1065, 982, 761, 690 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{25}O_2$ $[M + H]^+$, 273.1854, found 273.1864.

*3-Cyclohexylideneisobenzofuran-1(3H)-one (**6i**).*[17f] White solid (53 mg, 49%); 73−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J = 11.5, 7.9 Hz, 2H), 7.69−7.61 (m, 1H), 7.45 (t, J = 7.5 Hz, 1H), 2.70 (t, J = 5.9 Hz, 2H), 2.61 (t, J = 5.9 Hz, 2H), 1.76−1.62 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 138.9, 138.6, 134.1, 128.3, 128.2, 125.9, 125.5, 122.8, 29.4, 28.6, 27.6, 27.2, 26.1; IR (KBr) ν = 2935, 2922, 2855, 1766, 1704, 1608, 1472, 1446, 1279, 1257, 1103, 1032, 766, 692 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{15}O_2$ $[M + H]^+$, 215.1072, found 215.1077.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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