**Preliminary Communication**

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# Microwave-assisted synthesis of isoindolinones via Pd-mediated tandem coupling reactions

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**Abstract:** Palladium (Pd) coupling reactions have become an indispensable tool in modern synthetic organic chemistry. A simple procedure to obtain isoindolinones **7** bearing a quaternary C-atom, featuring a Pd-mediated tandem process, is presented. Readily available iodoamidoacrylate **3** and boronic acids **6** are used as the starting materials.

**Keywords:** heterocyclic compounds; isoindolinones; palladium tandem reactions.

The use of palladium (Pd) to catalyze the formation of C-C bonds has matured to become an indispensable tool in modern synthetic organic chemistry [1]. Using Pd chemistry, simple organic molecules and structurally complex targets, such as natural products, have been constructed. Undoubtedly, heterocyclic chemistry has benefited from the growing repertoire of transformations that can be accomplished using Pd chemistry [2]. Besides its reproducibility and the use of sub-stoichiometric amounts of catalyst, a pursued feature of Pd chemistry is the possibility of performing tandem reactions, allowing the generation of complexity from simple and readily available starting materials, ideally in a one-pot operation [3].

Isoindolinones are present in pharmaceuticals and natural products, such as compounds isolated from the endophytic fungus *Emericella* sp. showing antiviral activity against influenza A virus [4]. These heterocyclic motifs have also been used for the synthesis of several bioactive alkaloids, such as lennoxamine which is an isoindolobenzazepine isolated from the Chilean plant *Berberis darwinii* [5, 6]. Several approaches have evolved over the years to synthesize isoindolinones. In 1996, Campbell reported the preparation of isoindolinones using a directed *ortho*-metallation [7]. A closely related strategy has afforded 2,3-dihydroisoindolinones in excellent yields [8]. 3,3-Diallylisoindolinones have been synthesized via an indium-mediated Barbier-type allylation reaction of *ortho*-cyanobenzoates in good yields [9]. The diallylisoindolinones thus obtained have been transformed into spiroisoindolinones via a ring closing metathesis. Isoindolinones have also been prepared via a Pd-catalyzed intramolecular aminocarbonylation of 2-iodobenzylamine to give 1-isoindolinone, a basic skeleton of an atypical antipsychotic agent [10]. Starting from a furan, an intramolecular Diels-Alder approach has been used to construct the isoindolinone ring of a drug indicated for schizophrenia [11]. Isoindolinones bearing a quaternary carbon have been prepared by Rovis et al. [12] by coupling of *O*-pivaloyl-substituted benzohydroxamic acids with diazo compounds. In a closely related process, isoindolinones have been constructed by a Rh(III)-catalyzed oxidative [4+1] cycloaddition of benzohydroxamic acids and α-diazoesters [13] and by Rh(III)-catalyzed one-pot reaction of benzamides, ketones and hydrazines [14]. An asymmetric version of this process has been recently developed by Cramer [15]. A Pd-catalyzed C-H activation/annulation approach has been employed for the fast and convenient synthesis of hydroxyisoindolones [16]. Single isoindolinones have been used for the preparation of structurally elaborated spirocyclic isoindoles using a metathesis strategy [17]. Spiroisoindolinones have also been prepared by a regiospecific 1,3-dipolar cycloaddition of 3-methylene-*N*-substituted isoindolones [18]. Herein, we report a simple and efficient procedure to obtain isoindolones using a Pd-mediated tandem protocol [19]. Originally, we aimed to obtain isoquinolones using an intramolecular *6-endo-trig* Heck reaction on the substituted methyl acrylate **3** (Scheme 1).

*N*-Boc-protected methyl 2-(2-iodobenzamido)acrylate **3** was easily obtained starting with condensation of DL-serine methyl ester hydrochloride (**2**) with acid chloride **1**. The intermediate product was subjected to elimination in the presence of MsCl and $Et_3N$ and a subsequent *N*-Boc protection to afford **3** in 73% yield over three steps

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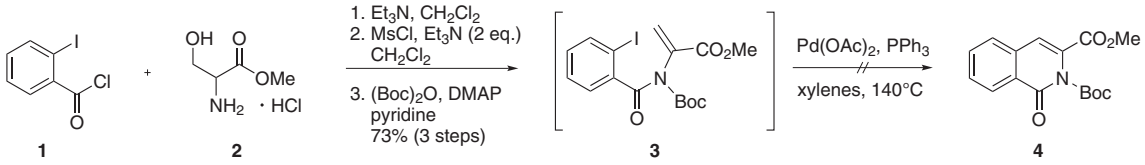


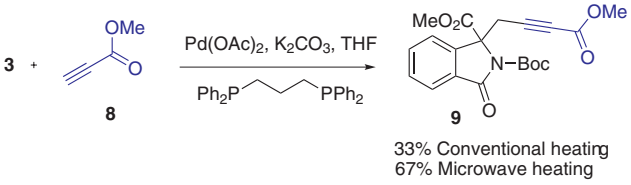

**Scheme 1**

(Scheme 1). With compound **3** in hand, an intramolecular Heck reaction was attempted. Unfortunately, all the attempted experiments to obtain isoquinolone **4** from **3** had failed (Scheme 1). A thin-layer chromatography (TLC) analysis showed the formation of a complex mixture that could not be resolved.

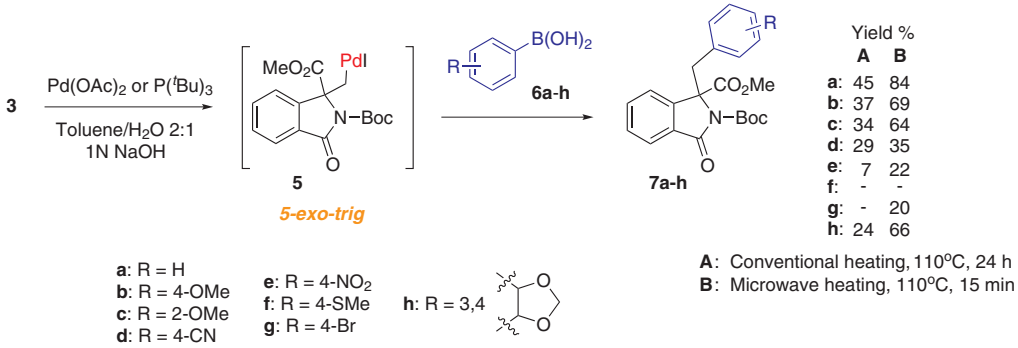
It was envisioned that the intermediate product **5** is generated during the Heck reaction as discussed above (Scheme 2). According to Baldwin's rules, the formation of isoindolinone **5** is allowed via a *5-exo-trig* process [20, 21]. To substantiate this hypothesis, an experiment to trap intermediate **5** by heating a mixture of *N*-Boc-protected substrate **3**, phenylboronic acid (**6a**), $Pd(OAc)_2$, and $Ph_3P$ in a mixture of tetrahydrofuran (THF)/1N NaOH was designed. We were delighted to observe the formation of isoindolinone **7a** via a Suzuki coupling, albeit in low yield of 15%. Suzuki couplings are performed using a two-phase solvent system of aqueous NaOH and an organic solvent [22]. When toluene was used instead of THF, the yield of **7a** increased to 45%. Attempts to further increase the yield, included the use of triton B (benzyltrimethylammonium hydroxide) instead of aqueous NaOH in a 2:1 mixture of toluene and water at 100°C and the use of $P(t\text{-Bu})_3$ as the ligand [23]. Under these conditions, compound **7a** was obtained in 40% yield.

Preparation of additional isoindolinones **7** in the system of toluene and aqueous NaOH is shown in Scheme 2. These products were obtained by the reaction of **3** with various boronic acids substituted with an electron-donating or electron-withdrawing group using two sources of heating (A: oil bath, B: microwave oven). As can be seen, for the successful reactions, the yields of products **7** are invariably greater under microwave-induced heating and the reaction times are greatly reduced. The optimized conditions are 110°C, 100 W, 15 min. However, product **7f** could not be obtained under either condition, and the conventional heating failed to produce **7g**.

To investigate the scope of the tandem process, it was decided to study the use of methyl propiolate **8** (Scheme 3). In the initial experiment, a mixture of *N*-Boc-protected compound **3** and alkyne **8** was heated in THF at reflux temperature either under conventional heating (Method A: reflux, 36 h) or microwave irradiation (Method B: 100 W, 110°C, 15 min, sealed vial), in the presence of $Pd(OAc)_2$, $P(Ph)_3$ and $K_2CO_3$. After monitoring the course of the reaction for an extended period, in both cases only the unreacted starting material was recovered. However, when tris(*o*-tolyl)phosphine was used instead of $P(Ph)_3$ under microwave irradiation, desired product **9** was obtained in 43% yield. A switch to a bidentate ligand, [1,2-bis(diphenylphosphino)ethane




**Scheme 3**




**Scheme 2**

or 1,3-bis(diphenylphosphino)propane], had a positive effect on the outcome and resulted in the increase of the yield to 67%. The effect of the base was also explored. The use of $Cs_2CO_3$ instead of $K_2CO_3$ did not have any effect on the yield. The use of either 4-methylmorpholine or triethylamine resulted in a decrease in the yield to 33% compared with the use of $K_2CO_3$. The use of other solvents commonly employed in this type of coupling including toluene, dioxane and acetonitrile resulted in diminished yields to 0%, 31% and 25%, respectively. Thus, under the optimized conditions, this reaction is conducted in THF in the presence of $Pd(OAc)_2$, 1,3-bis(diphenylphosphino) propane and $K_2CO_3$ at 110°C in a sealed vial under microwave heating (Scheme 3).

In summary, a new Pd-mediated one-pot tandem synthetic procedure for isoindolinones bearing a quaternary C-atom was developed. This synthetic protocol is amenable to the synthesis of more complex organic structures. Further applications of our proposed protocol for the synthesis of natural products are currently underway, and the results will be published in due course.

# Experimental

All reactions were monitored using TLC on 25-mm silica gel 60 F254 plates, using ultraviolet (UV) light (254 and 366 nm) for detection. Proton nuclear magnetic resonance $^1$H NMR (300 MHz) and carbon-13 nuclear magnetic resonance $^{13}$C NMR (75 MHz) spectra were determined in $CDCl_3$ on a Varian Unity Inova 300 instrument. Infrared (IR) spectra were recorded on a Perkin Elmer Fourier-transform infrared FT-IR spectrophotometer equipped with attenuated total reflectance (ATR). Mass spectra (70 eV) were recorded on a JEOL SMX-102a or a Hewlett Packard 5989A mass spectrometer. Microwave heating was carried out using a CEM Discover 300 microwave oven.

### Methyl ester of *N*-(2-iodobenzoyl)serine

Oxalyl chloride (400 µL, 4.40 mmol) was added dropwise to a mixture of 2-iodobenzoic acid (1 g, 4.03 mmol) and a drops of DMF in dichloromethane (20 mL) under nitrogen atmosphere. The mixture was stirred at ambient temperature for 30 min and then concentrated *in vacuo*. The resultant crude acid chloride **1** was dissolved in dichloromethane (10 mL) and the solution was slowly added to a mixture of hydrochloride of methyl ester of serine (**2**, 0.63 g, 4.01 mmol) and triethylamine (1.2 mL, 8.95 mmol) in dichloromethane (10 mL) at 0°C under nitrogen atmosphere. Then, the mixture was stirred at 0°C for 30 min and 40 min at ambient temperature and diluted with hexanes/ethyl acetate (1:1, 60 mL). The diluted solution was washed successively with water (20 mL) and brine (20 mL), dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* to provide 1.34 g (95%) of the desired product; mp 63°C; IR: $\nu_{max}$ 2978, 2946, 2882, 1914, 1750, 1534, 1479, 1444, 1330, 1172, 1036, 851, 764 cm$^{-1}$; $^1$H NMR: δ 3,80 (s, 3H, $OCH_3$), 4.05–4.06 (m, 2H, $HOCH_2$), 4.79–4.81 (m, 1H, NCH), 7.04 (s, 1H, N-H) 7.07–7.12 (ddd, $J$=1 Hz, 2 Hz and 9 Hz, 1H, Ar-H), 7.34–7.39 (ddd, $J$=0.3 Hz, 1 Hz and 9 Hz, 1H, ArH), 7.44–7.46 (dd, $J$=2 Hz and 9 Hz, 1H, ArH), 7.84–7.86 (dd, $J$=1 Hz and 6 Hz, 1H, Ar); $^{13}$C NMR: δ 45.7, 52.7, 55.0, 92.5, 128.1, 128.4, 131.3, 139.8, 141.0, 169.3, 170.5; ESI-QTOF: $m/z$ 330, $[M\text{-}18]^+$.

### Methyl 2-(2-iodobenzamido)acrylate

Triethylamine (0.9 mL, 3.16 mmol) was added to a solution of methyl ester of *N*-(2-iodobenzoyl)serine (see above, 1 g, 2.86 mmol) in dichloromethane (28 mL) at 0°C, followed by a dropwise addition of MsCl (0.24 mL, 3.15 mmol). The mixture was stirred for 45 min at 0°C and then for 50 min at ambient temperature, diluted with hexanes/ethyl acetate (1:1, 30 mL), washed with saturated $NaHCO_3$ (3×20 mL), dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. The residue was fractionated using silica gel column chromatography eluting with hexanes/ethyl acetate, gradient from 9:1 to 8:2, to give the desired product as a yellow solid; yield 0.86 g (91%); mp 75°C; IR: $\nu_{max}$ 3331, 3057, 2953, 1963, 1832, 1711, 1665, 1630, 1517, 1441, 1338, 1210, 1179, 1014, 913, 753 cm$^{-1}$; $^1$H NMR: δ 3,87(s, 3H, $OCH_3$), 6.04 (d, $J$=1 Hz, 1H, C=CH), 6.81 (d, $J$=1 Hz, 1H, C=CH), 7.12–7.18 (m, 1H, Ar), 7.39–7.47 (m, 2H, Ar), 7.89–7.92 (ddd, $J$=0.6 Hz, 1 Hz and 8 Hz, 1H, Ar), 8.08 (s, 1H, NH); $^{13}$C NMR: δ 53.1, 92.2, 109.8, 128.2, 130.8, 131.6, 140.1, 141.4, 164.3, 167.6. EI-HRMS. Calcd for $C_{11}H_{11}INO_3$, $[M+H]^+$: $m/z$ 331.9783. Found: $m/z$ 331.9795.

### Methyl 2-[*N*-(*tert*-butoxycarbonyl)-2-iodobenzamido] acrylate (3)

$(Boc)_2O$ (0.79 g, 3.6 mmol) was added to a mixture of methyl 2-(2-iodobenzamido)acrylate (see above, 1 g, 3.0 mmol) and DMAP (0.037 g, 0.3 mmol) in pyridine (22 mL), and the resultant mixture was stirred at room temperature under nitrogen atmosphere for 22 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with hexanes/ethyl acetate, gradient from 9:1 to 8:2, to give the desired product **3** as a yellow solid; yield 1.11 g (85%); mp 46°C; IR: $\nu_{max}$ 3236, 3077, 2963, 1835, 1743, 1647, 1630, 1431, 1348, 1227, 1169, 935, 767 cm$^{-1}$; $^1$H NMR : δ 1.23 (s, 9H, $C(CH_3)_3$), 3.84 (s, 3H, $CO_2CH_3$), 6.04 (d, $J$=0.6 Hz, 1H, C=CH), 6.61 (d, $J$=0.6 Hz, 1H, C=CH), 7.11–7.12 (m, 1H, ArH), 7.40–7.42 (m, 2H, ArH), 7.82–7.86 (d, $J$=8 Hz, 1H, ArH); $^{13}$C NMR: δ 27.3, 52.6, 84.4, 91.7, 100.2, 126.9, 127.5, 127.8, 134.8, 139.2, 143.0, 151.4, 163.4, 170.9. EI-HRMS. Calcd for $C_{16}H_{19}INO_5$, $[M+H]^+$: $m/z$ 432.0307. Found: $m/z$ 432.0320.

### General procedure for compounds 7a-e and 7g, h

$Pd(OAc)_2$ (0.046 mmol) was added to a mixture of **3** (0.46 mmol), boronic acid **6a-h** (0.69 mmol), 1N NaOH (0.9 mL), P(*tert*-Bu)$_3$ (0.092 mmol), toluene (2 mL) and $H_2O$ (1 mL) under nitrogen atmosphere. The mixture was heated for 24 h in an oil bath at 110°C or for 15 min at 110°C in a microwave oven (100 W). After cooling, the mixture was filtered through celite and the filtrate was extracted with ethyl acetate (3×30 mL). The organic extracts were combined, washed with brine (30 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure.

**Methyl 1-benzyl-2-Boc-3-oxoisoindoline-1-carboxylate (7a)** This compound was obtained from boronic acid **6a**; white solid; yield 45% or 84% by conventional or microwave heating, respectively; mp 109°C; IR: $\nu_{max}$ 3483, 3407, 3062, 2981, 2953, 1784, 1742, 1709, 1604, 1455, 1369, 1306, 1243, 1144, 1092, 937, 748 cm$^{-1}$; $^1$H NMR: δ 1.64 (s, 9H, $C(CH_3)_3$), 3.71 (s, 3H, $CO_2CH_3$), 3.72 (d, $J$ = 14 Hz, 1H, $ArCH_2$), 3.99 (d, $J$ = 14 Hz, 1H, $ArCH_2$), 6.60 (d, $J$ = 9 Hz, 2H, Ar), 6.98–7.01 (m, 3H, Ar), 7.43–7.48 (m, 1H, Ar), 7.62–7.71 (m, 3H, Ar); $^{13}$C NMR: δ 27.9, 39.9, 52.9, 71.0, 83.6, 121.8, 124.9, 126.9, 127.8, 129.5, 130.3, 133.3, 133.7, 142.6, 149.5, 165.7, 170.1. EI-HRMS. Calcd for $C_{22}H_{23}NO_5$, $[M+H]^+$: $m/z$ 382.1655. Found: $m/z$ 382.1654.

**Methyl 2-Boc-1-(4-methoxybenzyl)-3-oxoisoindoline-1-carboxylate (7b)** This compound was obtained from boronic acid **6b**; white solid; yield 37% or 69% by conventional or microwave heating, respectively; mp 129°C; IR: $\nu_{max}$ 3476, 2979, 2954, 2838, 2254, 1782, 1741, 1712, 1611, 1513, 1369, 1328, 1306, 1298, 1244, 1143, 936, 733 cm$^{-1}$; $^1$H NMR: δ 1.64 (s, 9H, $C(CH_3)_3$), 3.65 (d, $J$ = 14 Hz, 1H, Ar-$CH_2$), 3.66 (s, 3H, $CO_2CH_3$), 3.71 (s, 3H, $OCH_3$), 3.92 (d, $J$ = 14 Hz, 1H, $ArCH_2$), 6.48–6.51 (m, 4H, Ar), 7.44–7.49 (m, 1H, Ar), 7.60–7.71 (m, 3H, Ar); $^{13}$C NMR: δ 28.1, 39.3, 52.9, 54.9, 71.3, 83.7, 113.4, 121.8, 125.0, 125.4, 129.6, 130.5, 130.6, 133.7, 142.9, 149.6, 158.5, 165.9, 170.3. EI-HRMS. Calcd for $C_{22}H_{25}NO_6$, $[M+H]^+$: $m/z$ 412.1761. Found: $m/z$ 412.1741.

**Methyl 2-Boc-(1-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxylate (7c)** This compound was obtained from boronic acid **6c**; white solid, yield 34% or 64% by conventional or microwave heating, respectively; mp 123°C; IR: $\nu_{max}$ 3473, 2989, 2944, 2829, 2248, 1779, 1743, 1711, 1609, 1514, 1364, 1325, 1304, 1292, 1240, 934, 737 cm$^{-1}$. $^1$H NMR: δ 1.62 (s, 9H, $C(CH_3)_3$), 3.50 (s, 3H, $OCH_3$), 3.69 (s, 3H, $CO_2CH_3$), 3.87 (d, $J$ = 14 Hz, 1H, $ArCH_2$), 3.97 (d, $J$ = 14 Hz, 1H, $ArCH_2$), 6.54–6.59 (m, 2H, Ar), 6.66 (dd, $J$ = 2 Hz and 8 Hz, 1H, Ar), 6.96–7.02 (m, 1H, Ar), 7.33–7.39 (m, 1H, Ar); $^{13}$C NMR: δ 28.3, 33.8, 53.0, 54.9, 71.7, 83.6, 110.2, 120.0, 122.1, 122.7, 124.7, 128.5, 129.3, 130.3, 132.3, 132.9, 143.0, 149.4, 157.7, 166.5, 170.7. EI-HRMS. Calcd for $C_{22}H_{25}NO_6$, $[M+H]^+$: $m/z$ 412.1761. Found: $m/z$ 412.1762.

**Methyl 2-Boc-1-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxylate (7d)** This compound was obtained from boronic acid **6d**; white solid; yield 29% or 35% by conventional or microwave heating, respectively; mp 139°C; IR: $\nu_{max}$ 3484, 2956, 2923, 2853, 2229, 1783, 1744, 1712, 1608, 1510, 1466, 1370, 1306, 1253, 1144, 1092, 938, 759 cm$^{-1}$; $^1$H NMR: δ 1.64 (s, 9H, $C(CH_3)_3$), 3.73 (s, 3H, $OCH_3$), 3.77 (d, $J$ = 12 Hz, 1H, $ArCH_2$), 4.06 (d, $J$ = 9 Hz, 1H, $ArCH_2$), 6.72 (d, $J$ = 6 Hz, 2H, Ar), 7.29 (dd, $J$ = 0.3 Hz and 8 Hz, 1H, Ar), 7.31 (d, $J$ = 6 Hz, 1H, Ar), 7.49–7.56 (m, 1H, Ar), 7.64 (dd $J$ = 0.6 Hz and 6 Hz, 2H, Ar), 7.69–7.74 (m, 2H, Ar); $^{13}$C NMR: δ 28.0, 40.1, 53.3, 70.6, 84.2, 111.2, 118.4, 121.7, 125.4, 130.2, 130.3, 130.4, 134.1, 139.4, 142.1, 149.8, 165.4, 169.8. EI-HRMS. Calcd for $C_{23}H_{22}N_2O_7$, $[M+H]^+$: $m/z$ 407.1608. Found: $m/z$ 407.1610.

**Methyl 2-Boc-1-(4-nitrobenzyl)-3-oxoisoindoline-1-carboxylate (7e)** This compound was obtained from boronic acid **6e**; yellow oil; yield 7% or 22% by conventional or microwave heating, respectively; IR: $\nu_{max}$ 3484, 2956, 2923, 2853, 1783, 1744, 1712, 1608, 1523, 1510, 1466, 1370, 1347, 1253, 1144, 1092, 938, 759 cm$^{-1}$; $^1$H NMR: δ 1.65 (s, 9H, $C(CH_3)_3$), 3.74 (s, 3H, $CO_2CH_3$), 3.82 (d, $J$ = 12 Hz, 1H, $ArCH_2$), 4.12 (d, $J$ = 15 Hz, 1H, $ArCH_2$), 6.78 (d, $J$ = 9 Hz, 2H, Ar), 7.50–7.55 (m, 1H, Ar), 7.65–7.77 (m, 3H, Ar), 7.87 (d, $J$ = 9 Hz, 2H, Ar); $^{13}$C NMR: δ 28.0, 39.8, 53.3, 70.6, 84.3, 121.8, 123.1, 125.4, 130.2, 130.3, 130.5, 134.2, 141.4, 142.1, 147.0, 165.3, 169.7. EI-HRMS. Calcd for $C_{22}H_{22}N_2O_7$, $[M+H]^+$: $m/z$ 427.4506. Found: $m/z$ 427.1502.

**Methyl 2-Boc-1-(4-bromobenzyl)-3-oxoisoindoline-1-carboxylate (7g)** This compound was obtained from boronic acid **6g**; yellow oil; yield 0% or 20% by conventional or microwave heating, respectively; IR: $\nu_{max}$ 2985, 2945, 2872, 1786, 1756, 1721, 1611, 1532, 1517, 1470, 1377, 1351, 1253, 1149, 1099, 943, 760 cm$^{-1}$; $^1$H NMR: δ 1.67 (s, 9H, $C(CH_3)_3$), 3.72 (d, $J$ = 14 Hz, 1H, $ArCH_2$), 3.75 (s, 3H, $CO_2CH_3$), 3.99 (d, $J$ = 12 Hz, 1H, Ar-$CH_2$), 6.51 (d, $J$ = 9 Hz, 2H, Ar-H), 7.15 (d, $J$ = 9 Hz, 2H, ArH), 7.49–7.55 (m, 1H, Ar), 7.64–7.76 (m, 3H, Ar); $^{13}$C NMR: δ 27.3, 52.6, 84.3, 91.7, 126.9, 127.5, 127.8, 130.7, 134.9, 139.2, 143.1, 163.3, 170.7. EI-HRMS. Calcd for $C_{22}H_{22}BrNO_5$, $[M+H]^+$: $m/z$ 460.0760. Found: $m/z$ 460.0758.

**Methyl 1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2-Boc-3-oxoisoindoline-1-carboxylate (7h)** Yellow oil; yield 24% or 66% by conventional or microwave heating, respectively; IR: $\nu_{max}$ 3456, 3055, 2991, 2952, 2903, 2789, 1750, 1732, 1706, 1603, 1499, 1491, 1442, 1370, 1304, 1248, 1156, 1095, 932, 749 cm$^{-1}$; $^1$H NMR: δ 1.63 (s, 9H, $C(CH_3)_3$) 3.63 (d, $J$ = 12 Hz, 1H, $ArCH_2$), 3.71 (s, 3H, $CO_2CH_3$), 3.90 (d, $J$ = 9 Hz, 1H, $ArCH_2$), 5.80 (d, $J$ = 2 Hz, 2H, $OCH_2O$), 6.02 (d, $J$ = 2 Hz, 1H, ArH), 6.06 (dd, $J$ = 2 Hz and 8 Hz, 1H, ArH), 6.44 (d, $J$ = 8 Hz, 1H, Ar-H), 7.50 (td, $J$ = 1 Hz and 7 Hz, 1H, ArH), 7.62 (d, $J$ = 8 Hz, 1H, ArH), 7.67–7.74 (m, 2H, ArH); $^{13}$C NMR: δ 28.1, 39.9, 53.0, 71.2, 83.8, 100.8, 107.8, 109.8, 121.8, 123.0, 125.1, 127.0, 129.8, 130.5, 133.9, 142.9, 146.6, 149.7, 165.9, 170.2. EI-HRMS. Calcd for $C_{23}H_{23}NO_7$, $[M+H]^+$: $m/z$ 426.1554. Found: $m/z$ 426.1556.

## Methyl 2-Boc-1-(4-methoxy-4-oxobut-2-yn-1-yl)-3-oxoisoindoline-1-carboxylate (9)

To a mixture of compound **3** (0.23 mmol), $K_2CO_3$ (0.35 mmol) and molecular sieves (4Å, 40 mg) in THF (2 mL) at room temperature, under nitrogen atmosphere, $Pd(OAc)_2$ (0.023 mmol) and 1,3-bis(diphenylphosphino)propane (0.046 mmol) were added. The mixture was stirred at room temperature for 15 min and then treated with methyl propiolate **8** (0.46 mmol). The stirring was continued for 10 min at room temperature and then under reflux for an additional 36 h using a conventional heating. Alternatively, the mixture in a sealed vial was microwave irradiated for 15 min at 110°C and 100 W. After cooling, the mixture was filtered through celite and subjected to flash column chromatography on silica gel eluting with hexanes/ethyl acetate (7:3) to provide a white solid; yield 33% or 67% by conventional or microwave heating, respectively; IR: $\nu_{max}$ 3442, 2981, 2931, 2443, 1805, 1769, 1749, 1731, 1645, 1475, 1369, 1334, 1312, 1256, 1154, 1101, 1060, 934, 767 cm$^{-1}$; $^1$H NMR: δ 1.59 (s, 9H, $C(CH_3)_3$), 3.57 (d, $J$ = 18 Hz, 1H, $C\equiv CCH_2$), 3.62 (s, 3H, $CO_2CH_3$), 3.69 (s, 3H, $CO_2CH_3$), 3.76 (d, $J$ = 18 Hz, 1H, $C\equiv CCH_2$), 7.48 (dd, $J$ = 3 Hz and 9 Hz, 1H, ArH), 7.59 (ddd, $J$ = 3 Hz, 6 Hz and 9 Hz, 1H, ArH), 7.7 (dd, $J$ = 3 Hz and 6 Hz, 1H, Ar), 7.96 (dd, $J$ = 6 Hz and 9 Hz, 1H, Ar). EI-HRMS. Calcd for $C_{20}H_{21}NO_7$, $[M+2H]^+$: $m/z$ 389.1318. Found: $m/z$ 389.1301.

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