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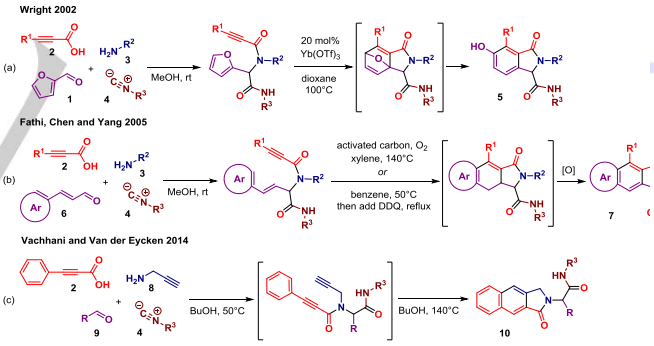
# Ugi Reaction Followed by the Intramolecular Diels-Alder and HCl-Elimination: a One-Pot Approach towards Arene-Fused Isoindolinones

Jianjun Huang,[#a] Xiaochen Du,[#a] Kristof Van Hecke,[b] Erik V. Van der Eycken,[c,d] Olga P. Pereshivko,*[a] Vsevolod A. Peshkov*[a]

**Abstract:** A one-pot procedure involving a four-component Ugi reaction followed by an intramolecular Diels-Alder/HCl-elimination cascade has been developed to provide rapid access to the isoindolinone framework in a diversity-oriented fashion. The scope of the process has been investigated with respect to all four components and a comparison between the one-pot and sequential approaches is given. The possibility of a late-stage one-pot functionalization through Suzuki coupling has been explored.

## Introduction

Multicomponent reactions (MCRs),[1] cascade processes[2] and one-pot approaches[3] are considered to be efficient tools for the rapid assembly of complex molecules. Furthermore, these intensification processes can help chemists to shorten reaction times and lower the costs of synthetic preparations, at the same time minimizing the amount of generated waste. The four-component Ugi reaction accompanied by a suitable post-transformation has become a landmark for the diversity-oriented synthesis of libraries of complex heterocyclic scaffolds. [4,5] Especially attractive are sequences where the Ugi reaction and the associated post-transformation could be accomplished in a one-pot or cascade manner. In this regard, the use of propiolic acids in combination with post-MCR triple bond functionalization has emerged as one of the most productive and convenient strategies for converting Ugi adducts into heterocycles. Others and we have demonstrated that propiolic acid-derived Ugi adducts could be readily converted into various types of pyrrolones[6] and β-lactams[7] taking advantage of the nucleophilicity of the peptidyl position through enolization-triggered 5-endo-dig and 4-exo-dig carbocyclizations, respectively. Using propiolic acid-derived Ugi adducts bearing an additional nucleophilic reactive center, a wide range of medium-ring-containing heterocycles[8] and structurally unique polycyclic frameworks[9] could be assembled through the activation of the triple bond towards nucleophilic attack, with the aid of coinage metal catalysts or strong Brønsted acids. The post-Ugi processes involving triple-bond carbopalladation have been extensively utilized to prepare indol-2-ones, [10] blue emissive isoquinolines[11] and 3-benzazepines. [12]




**Scheme 1.** Post-Ugi intramolecular Diels-Alder reaction for the synthesis of isoindolinones **5**, **7** and **10**.

In 2002, Wright and co-workers described a sequence towards isoindolinones **5** that involved Ugi reaction followed by $Yb(OTf)_3$-catalyzed intramolecular Diels–Alder reaction of furan (IMDAF) and subsequent oxo-bridge opening isomerization (Scheme 1a). [13] In that process, propiolic acid **2** and furfural **1** were used as dienophile and diene source, respectively. In 2005, Fathi, Chen, Yang and coworkers developed a one-pot approach encompassing Ugi reaction, intramolecular Diels-Alder reaction and oxidative aromatization to access arene-fused isoindolinones **7** (Scheme 1b). [14] In this case, the diene moiety was introduced with (E)-3-arylacrylaldehydes **6**, and the best results in the sequence were obtained for the substrates bearing an electron-rich 3-aryl group. In the above transformations, the

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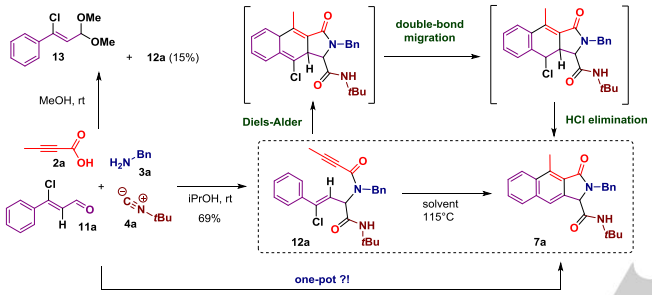
propiolic acid-originated fragments were exploited as dienophiles, while in the process elaborated by Vachhani, Van der Eycken and co-workers, phenyl propiolic acid was used as a source of enyne whereas the dienophile was brought by the propargylamine **8** (Scheme 1c). [15] This strategy provided access to benzo[f]isoindolones **10**.

## Results and Discussion

Inspired by these results, we designed an additional route for the assembly of isoindoles of type **7** via a post-Ugi Diels-Alder/HCl elimination cascade that employs (*Z*)-3-chloro-3-arylacrylaldehydes **11** (diene source) and propiolic acids **2** (dienophile source, Scheme 2).




**Scheme 2.** Post-Ugi Diels-Alder/HCl elimination cascade for the synthesis of isoindolinones **7**.

We have selected (*Z*)-3-chloro-3-phenylacrylaldehyde (**11a**), 2-butynoic acid (**2a**), benzyl amine (**3a**), and tert-butyl isocyanide (**4a**) to conduct the model synthesis. Attempting Ugi reaction under the classical settings with the methanol as solvent led to the formation of the unwanted acetal **13**, while the desired Ugi adduct **12a** was obtained in only low yield of 15%. However, when switching to isopropanol the Ugi adduct **12a** could be isolated in 69% yield (Scheme 1). Next, we have moved onto optimizing the intramolecular Diels-Alder/HCl-elimination cascade (Table 1). Heating **12a** at 115 °C in toluene for 60 min resulted in 70% conversion and only 30% yield of **7a** as was determined by the NMR analysis (Table 1, entry 1). Therefore, we decided to attempt the reaction in DMF hoping that a more basic solvent may facilitate the HCl-elimination step. As expected, the conversion of **12a** and yield of **7a** significantly improved reaching 93% and 60%, respectively (Table 1, entry 2). It is well known that the use of water as a (co-)solvent may increase the rate and improve the outcome of the Diels-Alder reactions.[16,17,18] Therefore, attempted several reactions in DMF/$H_2O$ mixtures (Table 1, entries 3-5). The best result was obtained for DMF/$H_2O$ (4:1) that in 1 h allowed achieving full conversion of **12a** yielding **7a** in 92% (Table 1, entry 3). Finally, we have investigated the reactions in isopropanol and an isopropanol/$H_2O$ (4:1) mixture (Table 1, entries 6-9). The reaction in isopropanol/$H_2O$ (4:1) could be accomplished in three hours furnishing **7a** in 88% yield, opening the way for conducting the whole Ugi/Diels-Alder/HCl-elimination sequence under one-pot settings (Table 1, entry 8).

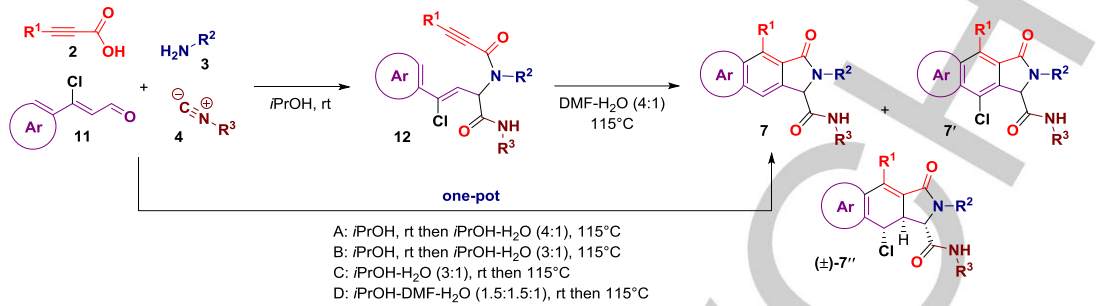
**Table 1.** Optimization of the intramolecular Diels-Alder/HCl-elimination cascade.[a]

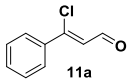
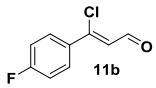
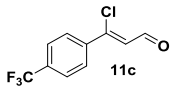
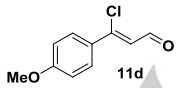
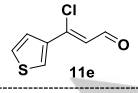
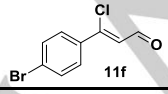
| Entry | Time, min | Solvent | Conversion of 12a, %[b] | Yield of 7a, %[b] |
|---|---|---|---|---|
| 1 | 60 | Toluene | 70 | 30 |
| 2 | 60 | DMF | 93 | 60 |
| 3 | 60 | DMF/$H_2O$ (4:1) | 100 | 92 |
| 4 | 40 | DMF/$H_2O$ (4:1) | 92 | 85 |
| 5 | 60 | DMF/$H_2O$ (1:1) | 100 | 88 |
| 6 | 60 | i-PrOH | 79 | 67 |
| 7 | 180 | i-PrOH | 97 | 73 |
| 8 | 180 | i-PrOH/$H_2O$ (4:1) | 100 | 88 |
| 9 | 120 | i-PrOH/$H_2O$ (4:1) | 95 | 86 |

[a] The reaction were run at 115 °C on 0.25 mmol scale in 2 mL of solvent. [b] The conversion of 12a and the yield of 7a were determined by NMR using 3,4,5-trimethoxybenzaldehyde as internal standard.

Keeping these results in mind, we proceeded with exploring the scope of our methodology (Table 2). We selected (*Z*)-3-chloro-3-phenylacrylaldehyde (**11a**) to study the reaction with various propiolic acids **2**, amines **3**, and isocyanides **4** (Table 2, entries 1-12). Propiolic and pentinoic acids **2a,b** worked equally well (Table 1, entries 1,5,9 and entries 2,6,10) while phenyl propiolic acid **2c** initially displayed some selectivity issues that were successfully resolved after minor adjustments to the reaction conditions (Table 1, entry 3). Supposedly the electron-rich nature of **2c** allows spontaneous oxidation to compete with the HCl-elimination producing minor amounts of isoindolinone **7c'**. For the amine component, a range of aliphatic amines **3b-d** and aniline **3e** was tested (Table 2, entries 4-8). The use of the bulky tert-butyl amine (**3c**) led to only moderate efficiency despite that the Ugi adducts **12e,f** started to convert into final isoindolinones **7e,f** already at room temperature (Table 2, entries 5 and 6). Application of n-butyl isocyanide (**4b**) furnished isoindolinones **7i,j** in up to 91% yield for the one-pot procedure (Table 2, entries 9 and 10). Aromatic isocyanides **4c,d** yielded isoindolinones **7k,l** in up to 52% yield with the Ugi step being a limiting factor for the overall efficiency (Table 2, entries 11 and 12). Next, we evaluated the aldehyde substrate scope (Table 2, entries 13-22). (*Z*)-3-Chloro-3-(4-fluorophenyl)acrylaldehyde (**11b**) and (*Z*)-3-chloro-3-(4-(trifluoromethyl)phenyl)acrylaldehyde (**11c**) worked well delivering a series of products **7m-q** with the yields ranging from 48% to 69% (Table 2, entries 13-17, one-pot settings) highlighting the suitability of our method for the synthesis of electron-deficient isoindolinones. Additionally, in one case we could detect and isolate minor amounts of non-aromatized isoindolinone **7p"** (Table 2, entry 16, stepwise settings). The electron-rich (*Z*)-3-chloro-3-(4-methoxyphenyl)acrylaldehyde (**11d**) initially gave poor results under the one-pot settings but then showed some improvements when the reaction was conducted in isopropanol/DMF/$H_2O$ (1.5:1.5:1) mixture (Table 2, entries 18 and 19). The application of another electron-rich

**Table 2.** The scope of the process.




| Entry | **11** | **2**, $R^1$ | **3**, $R^2$ | **4**, $R^3$ | Product code | Yields[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | **12** | **7+7''** | **7+7'** |
| | | | | | | | stepwise from **12** | one-pot[b] |
| 1 |  | **2a**, Me | **3a**, Bn | **4a**, *t*-Bu | **a** | 69 | 89 | 71 |
| 2 | **11a** | **2b**, Et | **3a**, Bn | **4a**, *t*-Bu | **b** | 83 | 84 | 73 |
| 3 | **11a** | **2c**, Ph | **3a**, Bn | **4a**, *t*-Bu | **c** | -[c] | - | (32)[d]+(7)[d] (43)[d]+(3)[d] (C) 52 (D) |
| 4 | **11a** | **2a**, Me | **3b**, PMB | **4a**, *t*-Bu | **d** | 63 | 81 | 59 |
| 5 | **11a** | **2a**, Me | **3c**, *t*-Bu | **4a**, *t*-Bu | **e** | -[c] | - | 40 |
| 6 | **11a** | **2b**, Et | **3c**, *t*-Bu | **4a**, *t*-Bu | **f** | -[c] | - | 44 |
| 7 | **11a** | **2a**, Me | **3d**, *n*-Bu | **4a**, *t*-Bu | **g** | 77 | 75 | 59 |
| 8 | **11a** | **2a**, Me | **3e**, Ph | **4a**, *t*-Bu | **h** | 62 | 95 | 61 (B) |
| 9 | **11a** | **2a**, Me | **3a**, Bn | **4b**, *n*-Bu | **i** | 82 | 94 | 91 |
| 10 | **11a** | **2b**, Et | **3a**, Bn | **4b**, *n*-Bu | **j** | -[e] | - | 78 (B) |
| 11 | **11a** | **2a**, Me | **3a**, Bn | **4c**, *p*-Tol | **k** | 52 | 81 | 52 |
| 12 | **11a** | **2a**, Me | **3a**, Bn | **4d**, 2-naphtyl | **l** | 43 | 68 | 39 (B) |
| 13 |  | **2b**, Me | **3a**, Bn | **4a**, *t*-Bu | **m** | -[e] | - | 62 |
| 14 | **11b** | **2b**, Et | **3a**, Bn | **4a**, *t*-Bu | **n** | 64 | 80 | 68 |
| 15 | **11b** | **2b**, Et | **3a**, Bn | **4b**, *n*-Bu | **o** | -[e] | - | 69 |
| 16 |  | **2a**, Me | **3a**, Bn | **4a**, *t*-Bu | **p** | 68 | 58 (66)[d] +6 (10)[d] | 48 |
| 17 | **11c** | **2b**, Et | **3a**, Bn | **4a**, *t*-Bu | **q** | -[e] | - | 53 (B) |
| 18 |  | **2a**, Me | **3a**, Bn | **4a**, *t*-Bu | **r** | 66 | 58 | 14[f] (B) 44 (D) |
| 19 | **11d** | **2a**, Me | **3a**, Bn | **4b**, *n*-Bu | **s** | 71 | 54 | 19[f] (B) 51 (D) |
| 20 |  | **2a**, Me | **3a**, Bn | **4a**, *t*-Bu | **t** | -[c] | - | 17 (21)[d]+9 (11)[d] |
| 21 | **11e** | **2b**, Et | **3a**, Bn | **4a**, *t*-Bu | **u** | -[c] | - | 23 (26)[d]+(10)[d] (B) |
| 22 |  | **2a**, Me | **3a**, Bn | **4b**, *n*-Bu | **v** | -[e] | - | 92 |

[a] Isolated yields. [b] Conditions A were used unless otherwise stated. [c] The Ugi adduct could not be isolated as the spontaneous cyclization takes places. [d] NMR yields are given in parenthesis. [e] Not attempted. [f] The formation of unidentified byproducts was observed.

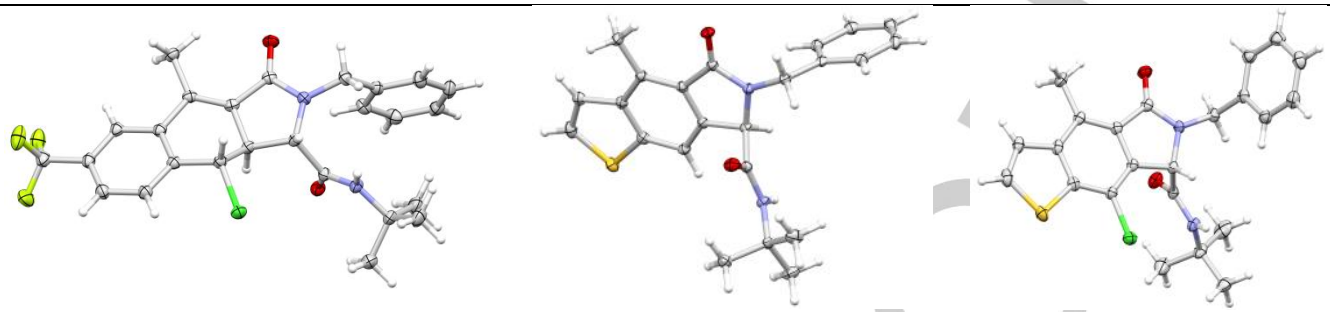
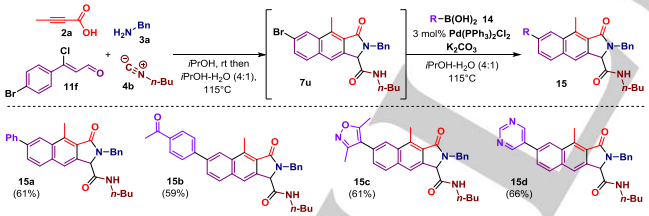


**Figure 1.** X-ray crystallographic molecular structures of compounds **7p"**, **7t** and **7t'**, showing thermal displacement ellipsoids at the 50% probability level.

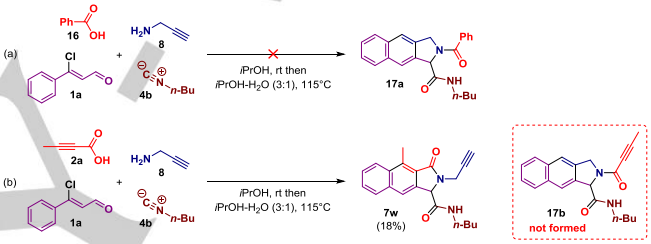
substrate (*Z*)-3-chloro-3-(thiophen-3-yl)acrylaldehyde (**11e**) always led to the formation of two kinds of isoindolinone products **7** and **7'** that resulted from following the standard Diels-Alder/HCl-elimination and competing Diels-Alder/oxidation pathways, respectively (Table 2, entries 20 and 21). In one case, we were able to obtain both **7t** and **7t'** in pure form and to perform their complete characterization (Table 2, entry 20). Engaging (*Z*)-3-(4-bromophenyl)-3-chloroacrylaldehyde (**11f**) in our process delivered isoindolinone **7v** in high 92% yield (Table 2, entry 22) providing a handle for the late-stage one-pot derivatizations of the isoindolinone core via Suzuki couplings (Scheme 3).

Adding Pd catalyst, base and an appropriate boronic acid **14** to the reaction mixture containing isoindolinone **7v** allowed to attain a series of additionally decorated isoindolinones **15** with rather good overall yields for this three-step one-pot process (Scheme 3).



**Scheme 3.** Late-stage functionalization of isoindolinone core using Suzuki coupling.

We have also evaluated propargylamine **8** as a dienophile source. Unfortunately, the corresponding reaction failed as no isoindolinone **17a** was obtained (Scheme 4a). When both propiolic acid- and propargylamine-derived triple bonds were present, not unexpectedly only the propiolic acid-derived triple bond reacted to give product **7w** albeit in a low yield of 18% (Scheme 4b).



**Scheme 4.** An attempt to employ propargylamine **8** as a dienophile source.

The prepared isoindolinones **7a-w**, **7t'** and **15a-d** were characterized by $^{1}$H- and $^{13}$C-NMR spectroscopy, infra-red (IR) spectroscopy and HRMS. In addition, the structures of **7p"**, **7t** and **7t'** were assured by single-crystal X-ray diffraction analysis (Figure 1).[19]

## Conclusions

In summary, we have elaborated an efficient Ugi/Diels-Alder/HCl-elimination process for the rapid one-pot synthesis of complex arene-fused isoindolinones from readily available (*Z*)-3-chloro-3-arylacrylaldehydes, propiolic acids, amines and isocyanides. Importantly, the developed protocol was found to be suitable for the assembly of electron-deficient isoindolinones rather than electron-rich making it complementary to the known Ugi/Diels-Alder/oxidation process. In addition, it was found to be compatible with a late-stage one-pot functionalization of title compounds through Suzuki coupling

## Experimental Section

**General Procedure for Ugi Reaction**

(*Z*)-3-Chloro-3-arylacrylaldehyde **11** (1.2 mmol) was dissolved in isopropanol (6.0 mL) followed by the addition of amine **3** (1.2 mmol), propiolic acid **2** (1.2 mmol) and isocyanide **4** (1.2 mmol). The reaction mixture was sealed and stirred at room temperature for 36 h. The resulting mixture was diluted with EtOAc and concentrated with silica. Column chromatography with petroleum ether/EtOAc (the ratio was adjusted according to TLC) as eluent delivered Ugi adduct **12**. Reacting substrates **11a**, **2a**, **3a** and **4a** in methanol instead of isopropanol led to the formation of acetal **13** as a major product, while the desired Ugi adduct **12a** was obtained in only low yield of 15%.

**General procedure for the post-Ugi Diels-Alder/HCl elimination cascade**

The Ugi adduct **12** (0.5 mmol) was dissolved in DMF (3.2 mL) followed by addition of $H_2O$ (0.8 mL). The reaction mixture was flashed with argon, sealed and stirred at 115°C for 1 h. The resulting mixture was diluted by EtOAc and washed with $H_2O$. The organic layer was dried with sodium sulfate and concentrated with silica. Column chromatography with petroleum ether/EtOAc (the ratio was adjusted according to TLC) as eluent delivered desired isoindolinone **7**. The product **7l** was purified by column chromatography with petroleum ether/DCM as eluent followed by washing with $Et_2O$. The product **7p** was isolated using petroleum ether/DCM/EtOAc (7:2:1) mixture as eluent. The mixed fractions containing **7p** and **7p''** were subjected to big board preparative TLC with petroleum ether/DCM/EtOAc (7:2:1) mixture as eluent to give pure **7p''**.

**General procedures for the one-pot synthesis of isoindolinones 7**

**Procedure A:** (*Z*)-3-Chloro-3-arylacrylaldehyde **11** (0.8 mmol) was dissolved in isopropanol (4.0 mL) followed by the addition of amine **3** (0.8 mmol), propiolic acid **2** (0.8 mmol) and isocyanide **4** (0.8 mmol). The reaction mixture was sealed and stirred at room temperature for 36 h. Upon completion of this time $H_2O$ (1 mL) was added. The reaction mixture was flashed with argon, sealed and stirred at 115°C for 3 h. The resulting mixture was diluted with EtOAc and concentrated with silica. Column chromatography with petroleum ether/EtOAc (the ratio was adjusted according to TLC) as eluent delivered isoindolinone **7**. Using substrates **11a**, **2c**, **3a** and **4a** led to the formation of isoindolinones **7c** and **7c′** that were obtained as a mixture after the column chromatography. Using substrates **11e**, **2a**, **3a** and **4a**, led to the formation of isoindolinones **7t** and **7t′** that were successfully separated by the column chromatography.

**Procedure B:** (*Z*)-3-Chloro-3-arylacrylaldehyde **11** (0.6 mmol) was dissolved in isopropanol (2.25 mL) followed by the addition of amine **3** (0.6 mmol), propiolic acid **2** (0.6 mmol) and isocyanide **4** (0.6 mmol). The reaction mixture was sealed and stirred at room temperature for 36 h. Upon completion of this time $H_2O$ (0.75 mL) was added. The reaction mixture was flashed with argon, sealed and stirred at 115°C for 3 h. The resulting mixture was diluted with EtOAc and concentrated with silica. Column chromatography with petroleum ether/EtOAc (the ratio was adjusted according to TLC) as eluent delivered isoindolinone **7**. The product **7l** was purified by column chromatography with petroleum ether/DCM as eluent followed by washing with $Et_2O$. Using substrates **11e**, **2b**, **3a** and **4a**, led to the formation of isoindolinones **7u** and **7u′**. The major product **7u** was isolated by the column chromatography.

**Procedure C:** (*Z*)-3-Chloro-3-phenylacrylaldehyde **11a** (100 mg, 0.6 mmol) was dissolved in isopropanol (2.25 mL) followed by the addition of $H_2O$ (0.75 mL), benzylamine **3a** (64 mg, 0.6 mmol), 3-phenylpropiolic acid **2c** (88 mg, 0.6 mmol) and tert-butyl isocyanide **4a** (50 mg, 0.6 mmol). The reaction mixture was flashed with argon, sealed and stirred at room temperature for 36 h. Upon completion of this time the reaction mixture was heated at 115°C for 6 h. The resulting mixture was diluted with EtOAc and concentrated with silica. Column chromatography with petroleum ether/EtOAc (9:1) as eluent delivered the mixture of isoindolinones **7c** and **7c′**.

**Procedure D:** (*Z*)-3-Chloro-3-arylacrylaldehyde **11** (0.6 mmol) was dissolved in isopropanol/DMF 1: 1 mixture (2.2 mL) followed by the addition of $H_2O$ (0.75 mL), amine **3** (0.6 mmol), propiolic acid **2** (0.6 mmol) and isocyanide **4** (0.6 mmol). The reaction mixture was flashed with argon, sealed and stirred at room temperature for 36 h. Upon completion of this time the reaction mixture was heated at 115°C for 3 h (6 h for the synthesis of **7c**). The resulting mixture was diluted by EtOAc and washed with $H_2O$. The organic layer was dried with sodium sulfate and concentrated with silica. Column chromatography with petroleum ether/EtOAc (the ratio was adjusted according to TLC) as eluent delivered isoindolinone **7**.

**2-Benzyl-*N*-(*tert*-butyl)-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7a).** Yield: 89% (stepwise from **12a**), 71% (one-pot, procedure A); pale yellow solid; mp 194-195°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22-8.15 (m, 1H), 7.92-7.84 (m, 2H), 7.62-7.55 (m, Hz, 2H), 7.41-7.26 (m, 5H), 5.54 (bs, 1H), 5.13 (d, *J* = 14.7 Hz, 1H), 4.82 (d, *J* = 0.8 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 3.15 (s, 3H), 1.17 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.0, 167.5, 136.9, 136.8, 136.4, 135.1, 133.4, 129.2, 129.1, 128.8, 128.2, 127.8, 126.6, 125.3, 124.3, 119.8, 64.4, 51.6, 46.7, 28.5, 12.2; IR (ATR): 3266, 3066, 3033, 2965, 2922, 1688, 1653, 1551, 1393, 1254, 1221, 1196, 767, 707, 692 cm$^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{25}H_{27}N_2O_2^+$ calcd 387.2067; found 387.2068.

**2-Benzyl-*N*-(*tert*-butyl)-4-ethyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7b).** Yield: 84% (stepwise from **12b**) 73% (one-pot, procedure A); pale yellow solid; mp 181-182°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.30-8.21 (m, 1H), 7.93-7.84 (m, 2H), 7.63-7.54 (m, 2H), 7.42-7.26 (m, 5H), 5.47 (bs, 1H), 5.11 (d, *J* = 14.7 Hz, 1H), 4.81 (d, *J* = 0.8 Hz, 1H), 4.50 (d, *J* = 14.7 Hz, 1H), 3.86 (dq, *J* = 12.9, 7.5 Hz, 1H), 3.71 (dq, *J* = 12.9, 7.5 Hz, 1H), 1.41 (t, *J* = 7.5 Hz, 3H), 1.16 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.6, 167.5, 143.2, 136.8, 136.5, 135.6, 132.3, 129.3, 129.2, 128.9, 128.2, 127.8, 126.6, 125.2, 123.6, 112.0, 64.5, 51.6, 46.8, 28.5, 19.4, 16.0; IR (ATR): 3275, 3071, 2965, 2932, 2905, 1676, 1658, 1551, 1397, 1251, 1220, 761, 701 cm$^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{26}H_{29}N_2O_2^+$ calcd 401.2224, found 401.2216.

**2-Benzyl-*N*-(*tert*-butyl)-3-oxo-4-phenyl-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7c).** Yield: 52% (one-pot, procedure D); pale yellow solid; mp 193-196°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.99-7.91 (m, 1H), 7.81-7.73 (m, 1H), 7.62-7.52 (m, 4H), 7.49-7.41 (m, 3H), 7.37-7.26 (m, 5H), 5.49 (bs, 1H), 5.06 (d, *J* = 14.7 Hz, 1H), 4.86 (d, *J* = 0.8 Hz, 1H), 4.41 (d, *J* = 14.7 Hz, 1H), 1.19 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 169.2, 167.3, 139.9, 136.5, 136.4, 135.4, 135.3, 133.1, 130.5, 130.1, 129.1, 128.9, 128.5, 128.14, 128.07, 127.99, 127.93, 127.91, 127.8, 126.7, 124.1, 121.4, 64.2, 51.6, 46.7, 28.5; IR (ATR): 3334, 2974, 2915, 1686, 1671, 1509, 1454, 1394, 1361, 1248, 1212, 766, 752, 699 cm$^{-1}$; HRMS (ESI, $[M+H]^+$) for: $C_{30}H_{29}N_2O_2^+$ calcd 449.2224, found 449.2222.

***N*-(*tert*-Butyl)-2-(4-methoxybenzyl)-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7d).** Yield: 81% (stepwise from **12d**), 59% (one-pot, procedure A); pale yellow solid; mp 183- 186°C; $^1$H NMR

(400 MHz, $CDCl_3$): δ 8.24-8.15 (m, 1H), 7.93-7.84 (m, 2H), 7.63-7.55 (m, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.52 (bs, 1H), 5.10 (d, *J* = 14.6 Hz, 1H), 4.80 (d, *J* = 0.8 Hz, 1H), 4.39 (d, *J* = 14.6 Hz, 1H), 3.78 (s, 3H), 3.16 (s, 3H), 1.19 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.9, 167.6, 159.6, 136.8, 136.4, 135.1, 133.4, 130.3, 129.1, 128.8, 127.8, 126.6, 125.3, 124.4, 119.8, 114.5, 64.2, 55.5, 51.6, 46.0, 28.5, 12.2; IR (ATR): 3273, 3070, 2969, 2926, 1682, 1655, 1550, 1514, 1453, 1396, 1362, 1293, 1241, 1218, 1178, 1047, 1026, 764 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{26}H_{29}N_2O_3^+$ calcd 417.2173, found 417.2161.

***N*,2-di-*tert*-Butyl-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7e).** Yield: 40% (one-pot, procedure A); pale yellow solid; mp 242-245°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.25-8.17 (m, 1H), 7.94-7.86 (m, 2H), 7.63-7.54 (m, 2H), 5.62 (bs, 1H), 5.10 (d, *J* = 0.7 Hz, 1H), 3.15 (s, 3H), 1.63 (s, 9H), 1.25 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.8, 136.5, 136.1, 135.0, 133.4, 129.0, 127.6, 126.4, 125.6, 125.2, 119.1, 64.4, 56.4, 51.5, 28.5, 28.3, 11.9; IR (ATR): 3311, 2976, 2923, 2854, 1692, 1650, 1538, 1454, 1373, 1362, 1248, 1211, 1201, 883, 761, 739, 712, 672 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{22}H_{29}N_2O_2^+$ calcd 353.2224, found 353.2237.

***N*,2-di-*tert*-Butyl-4-ethyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7f).** Yield: 44% (one-pot, procedure A); white solid; mp 243-244°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.28-8.20(m, 1H), 7.95-7.86 (m, 2H), 7.61-7.53 (m, 2H), 5.62 (bs, 1H), 5.09 (d, *J* = 0.8 Hz, 1H), 3.85 (dq, *J* = 12.9, 7.5 Hz, 1H), 3.64 (dq, *J* = 12.9, 7.5 Hz, 1H), 1.63 (s, 9H), 1.38 (t, *J* = 7.5 Hz, 3H), 1.25 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.5, 169.9, 142.6, 136.7, 135.5, 132.3, 129.3, 127.5, 126.4, 125.1, 124.9, 119.3, 64.4, 56.4, 51.5, 28.5, 28.3, 19.1, 15.9; IR (ATR): 3309, 2976, 2923, 2851, 1683, 1657, 1542, 1452, 1361, 1248, 1220, 766, 746, 671 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{23}H_{31}N_2O_2^+$ calcd 367.2380, found 367.2393.

***N*-(*tert*-Butyl)-2-butyl-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7g).** Yield: 75% (stepwise from **12g**), 59% (one-pot, procedure A); pale yellow solid; mp 207-208°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.24-8.16 (m, 1H), 7.98-7.87 (m, 2H), 7.63-7.56 (m, 2H), 5.54 (bs, 1H), 4.98 (d, *J* = 0.8 Hz, 1H), 4.10-3.97 (m, 1H), 3.25-3.15 (m, 1H), 3.13 (s, 3H), 1.74-1.61 (m, 2H), 1.44-1.32 (m, 2H), 1.26 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.7, 168.0, 136.5, 136.3, 135.0, 133.4, 129.1, 127.7, 126.6, 125.3, 124.7, 119.7, 64.3, 51.8, 42.1, 30.1, 28.7, 20.4, 13.9, 12.1; IR (ATR): 3273, 2962, 2925, 2873, 1680, 1653, 1552, 1457, 1393, 1365, 1255, 1221, 1200, 890, 767, 744, 711, 692 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{22}H_{29}N_2O_2^+$ calcd 353.2224, found 353.2235.

***N*-(*tert*-Butyl)-4-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7h).** Yield: 95% (stepwise from **12h**), 61% (one-pot, procedure B); pale yellow solid; mp 227-229°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.30-8.22 (m, 1H), 8.08 (s, 1H), 8.00-7.92 (m, 1H), 7.87-7.78 (m, 2H), 7.68-7.58 (m, 2H), 7.51-7.43 (m, 2H), 7.29-7.21 (m, 1H), 5.60 (d, *J* = 0.9 Hz, 1H), 5.46 (bs, 1H), 3.21 (s, 3H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 169.1, 167.5, 138.2, 137.6, 135.4, 135.1, 133.5, 129.5, 129.1, 128.0, 126.7, 125.5, 125.3, 124.6, 120.7, 119.8, 64.7, 51.7, 28.4, 12.2; IR (ATR): 3356, 2967, 2922, 2852, 1690, 1669, 1600, 1528, 1497, 1456, 1355, 1295, 1220, 1199, 762, 753, 739, 687 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{24}H_{25}N_2O_2^+$ calcd 373.1911, found 373.1914.

**2-Benzyl-*N*-butyl-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7i).** Yield: 94% (stepwise from **12i**), 91% (one-pot, procedure A); yellow solid; mp 217-219°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.17-8.07 (m, 1H), 7.93-7.82 (m, 2H), 7.63-7.53 (m, 2H), 7.37-7.25 (m, 5H), 6.02 (bt, *J* = 5.4 Hz, 1H), 5.33 (d, *J* = 14.7 Hz, 1H), 4.94 (d, *J* = 0.8 Hz, 1H), 4.33 (d, *J* = 14.7 Hz, 1H), 3.29-3.16 (m, 1H), 3.15-3.05 (m, 1H), 3.04 (s, 3H), 1.39-1.28 (m, 2H), 1.28-1.15 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.7, 168.4, 136.8, 136.3, 136.1, 135.0, 133.4, 129.1, 129.0, 128.7, 128.2, 127.9, 126.6, 125.2, 124.3, 120.1, 63.2, 46.1, 39.5, 31.4, 20.1, 13.8, 12.0; IR (ATR): 3291, 2956, 2924, 2871, 1689, 1654, 1547, 1449, 1391, 1238, 1198, 1015, 968, 886, 766, 750, 711, 696 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{25}H_{27}N_2O_2^+$ calcd 387.2067, found 387.2074.

**2-Benzyl-*N*-butyl-4-ethyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7j).** Yield: 78% (one-pot, procedure B); pale yellow solid; mp 206-208°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.24-8.16 (m, 1H), 7.92-7.83 (m, 2H), 7.62-7.53 (m, 2H), 7.37-7.25 (m, 5H), 5.94 (t, *J* = 5.5 Hz, 1H), 5.32 (d, *J* = 14.7 Hz, 1H), 4.93 (d, *J* = 0.9 Hz, 1H), 4.34 (d, *J* = 14.7 Hz, 1H), 3.75 (dq, *J* = 12.9, 7.5 Hz, 1H), 3.63 (dq, *J* = 12.9, 7.5 Hz, 1H), 3.29-3.16 (m, 1H), 3.13-3.01 (m, 1H), 1.40-1.28 (m, 5H), 1.27-1.15 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.2, 168.4, 143.1, 136.3, 136.2, 135.5, 132.2, 129.2, 129.1, 128.7, 128.1, 127.8, 126.6, 125.1, 123.6, 120.2, 63.1, 46.1, 39.5, 31.4, 20.1, 19.1, 15.9, 13.8; IR (ATR): 3275, 2956, 2927, 2871, 1686, 1657, 1543, 1453, 1396, 1241, 1201, 766, 711, 695 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{26}H_{29}N_2O_2^+$ calcd 401.2224, found 401.2225.

**2-Benzyl-4-methyl-3-oxo-*N*-(*p*-tolyl)-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide. (7k).** Yield: 81% (stepwise from **12k**) 52% (one-pot, procedure A); pale yellow solid; mp 211-213°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.16 (bs, 1H), 8.01-7.91 (m, 2H), 7.90-7.81 (m, 1H), 7.62-7.48 (m, 2H), 7.43-7.25 (m, 7H), 7.07 (d, *J* = 8.3 Hz, 2H), 5.40 (d, *J* = 14.8 Hz, 1H), 5.08 (s, 1H), 4.50 (d, *J* = 14.8 Hz, 1H), 2.78 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.8, 166.7, 137.1, 136.2, 135.6, 135.0, 134.9, 134.6, 133.4, 129.5, 129.3, 129.0, 128.8, 128.3, 128.0, 126.7, 125.2, 124.2, 120.3, 120.2, 64.0, 46.4, 21.0, 11.8; IR (ATR): 3060, 3034, 2922, 2855, 1688, 1655, 1607, 1541, 1514, 1410, 1249, 1203, 820 760, 746, 701 $cm^{-1}$; HRMS (ESI, $[M+Na]^+$) for $C_{28}H_{24}N_2O_2Na^+$ calcd 443.1730, found 443.1726.

**2-Benzyl-4-methyl-*N*-(naphthalen-2-yl)-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7l).** Yield: 68% (stepwise from **12l**), 39% (one-pot, procedure B); brown solid; mp 251-253°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.68 (bs, 1H), 8.25 (d, *J* = 1.2 Hz, 1H), 8.02 (s, 1H), 7.87 (t, *J* = 8.7 Hz, 2H), 7.79-7.70 (m, 3H), 7.61-7.55 (m, 1H), 7.55-7.26 (m, 9H), 5.47 (d, *J* = 14.8 Hz, 1H), 5.18 (s, 1H), 4.61 (d, *J* = 14.8 Hz, 1H), 2.64 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.2, 137.1, 136.1, 135.6, 135.2, 135.0, 133.8, 133.3, 130.9, 129.3, 129.0, 128.9, 128.7, 128.4, 128.1, 127.9, 127.6, 126.7, 126.6, 125.3, 125.2, 124.2, 120.3, 120.1, 117.3, 64.3, 46.5, 11.6; IR (ATR): 3248, 3087, 3058, 2923, 2853, 1693, 1662, 1587, 1561, 1397, 1236, 863, 828, 762, 703 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{31}H_{25}N_2O_2^+$ calcd 457.1911, found 457.1900.

**2-Benzyl-*N*-(*tert*-butyl)-7-fluoro-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamid (7m).** Yield: 62% (one-pot, procedure A); yellow solid; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.92-7.83 (m, 2H), 7.74 (dd, *J* = 11.0, 2.4 Hz, 1H), 7.41-7.26 (m, 6H), 5.58 (bs, 1H), 5.12 (d, *J* = 14.7 Hz, 1H), 4.81 (s, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 3.05 (s, 3H), 1.17 (s 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.6, 167.4, 161.1 (d, *J* = 247.5 Hz), 136.6, 135.9 (d, *J* = 6.0 Hz), 135.8 (d, *J* = 2.7 Hz), 134.5 (d, *J* = 8.5 Hz), 132.0, 131.3 (d, *J* = 9.0 Hz), 129.2, 128.8, 128.2, 125.2, 119.7, 118.2 (d, *J* = 25.4 Hz), 108.9 (d, *J* = 21.6 Hz), 64.2, 51.7, 46.6, 28.5, 12.2; IR (ATR): 3363, 3331, 2969, 2923, 1684, 1666, 1618, 1527, 1387, 1363, 1292, 1224, 1200, 1171, 967, 857, 817, 750, 696, 679, 668 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{25}H_{26}FN_2O_2^+$ calcd 405.1973, found 405.1974.

**2-Benzyl-*N*-(*tert*-butyl)-4-ethyl-7-fluoro-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7n).** Yield: 80% (stepwise from **12n**), 68% (one-pot, procedure A); yellow solid; mp 142-144°C; $^1$H NMR (400

MHz, $CDCl_3$) δ 7.93-7.78 (m, 3H), 7.41-7.26 (m, 6H), 5.48 (bs, 1H), 5.10 (d, *J* = 14.7 Hz, 1H), 4.80 (s, 1H), 4.50 (d, *J* = 14.7 Hz, 1H), 3.79 (dq, *J* = 13.1, 7.5 Hz, 1H), 3.61 (dq, *J* = 13.1, 7.5 Hz, 1H), 1.39 (t, *J* = 7.5 Hz, 3H), 1.17 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.3, 167.4, 161.2 (d, *J* = 247.0 Hz), 142.4 (d, *J* = 6.0 Hz), 136.7, 136.0 (d, *J* = 2.6 Hz), 133.4 (d, *J* = 8.5 Hz), 132.5, 131.6 (d, *J* = 9.0 Hz), 129.2, 128.9, 128.2, 124.5, 119.9, 118.2 (d, *J* = 25.5 Hz), 108.8 (d, *J* = 21.7 Hz), 64.4, 51.7, 46.8, 28.5, 19.5, 15.7; IR (ATR): 3277, 2968, 2925, 1669, 1656, 1619, 1543, 1516, 1456, 1396, 1363, 1222, 1173, 1080, 886, 816, 750, 700 $cm^{-1}$; HRMS (ESI, $[M+Na]^+$) for $C_{26}H_{27}FN_2O_2Na^+$ calcd 441.1949, found 441.1962.

**2-Benzyl-*N*-butyl-4-ethyl-7-fluoro-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7o).** Yield: 69% (one-pot, procedure A); pale yellow solid; mp 200-203°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.86 (dd, *J* = 9.1, 5.9 Hz, 1H), 7.77 (dd, *J* = 11.2, 2.2 Hz, 1H), 7.40-7.26 (m, 6H), 5.96 (bt, *J* = 5.4 Hz, 1H), 5.31 (d, *J* = 14.7 Hz, 1H), 4.92 (s, 1H), 4.34 (d, *J* = 14.7 Hz, 1H), 3.68 (dq, *J* = 13.1, 7.5 Hz, 1H), 3.52 (dq, *J* = 13.1, 7.5 Hz, 1H), 3.30-3.17 (m, 1H), 3.14-3.01 (m, 1H), 1.38-1.16 (m, 7H), 0.84 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 169.9, 168.3, 161.2 (d, *J* = 247.1 Hz), 142.1 (d, *J* = 6.0 Hz), 136.2, 135.7 (d, *J* = 2.5 Hz), 133.2 (d, *J* = 8.6 Hz), 132.4, 131.5 (d, *J* = 9.0 Hz), 129.1, 128.6, 128.2, 124.5, 120.2, 118.2 (d, *J* = 25.5 Hz), 108.6 (d, *J* = 21.7 Hz), 63.0, 46.1, 39.6, 31.4, 20.1, 19.1, 15.5, 13.7; IR (ATR): 3285, 2954, 2925, 2871, 1687, 1652, 1618, 1553, 1514, 1457, 1387, 1225, 1172, 1080, 985, 884, 860, 812, 720, 698 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{26}H_{28}FN_2O_2^+$ calcd 419.2129, found 419.2135.

**2-Benzyl-*N*-(*tert*-butyl)-4-methyl-3-oxo-7-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7p).** Yield: 58% (stepwise from **12p**), 48% (one-pot, procedure A); pale yellow solid; mp 154-157°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.96 (s, 1H), 7.75 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.41-7.28 (m, 5H), 5.51 (bs, 1H), 5.11 (d, *J* = 14.7 Hz, 1H), 4.84 (s, 1H), 4.51 (d, *J* = 14.7 Hz, 1H), 3.21 (s, 3H), 1.16 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): 170.4, 167.0, 138.6, 137.9, 136.5, 136.3, 132.5, 130.2, 129.3, 128.9, 128.5 (q, *J* = 32.2 Hz), 128.3, 125.6, 124.4 (q, *J* = 272.3 Hz), 123.4 (q, *J* = 3.0 Hz), 123.0 (q, *J* = 4.6 Hz), 119.8, 64.4, 51.8, 46.8, 28.5, 12.2; IR (ATR): 3350, 3287, 2967, 2925, 2856, 1685, 1658, 1539, 1455, 1327, 1302, 1220, 1170, 1116, 1066, 893, 699 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{26}H_{26}F_3N_2O_2^+$ calcd 455.1941, found 455.1929.

**(±)-(1*S*,9*S*,9a*S*)-2-Benzyl-*N*-(*tert*-butyl)-9-chloro-4-methyl-3-oxo-6-(trifluoromethyl)-2,3,9,9a-tetrahydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7p'').** Yield: 6% (stepwise from **12p**); white solid; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.74 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.42-7.24 (m, 5H), 5.49 (s, 1H), 5.38 (d, *J* = 15.0 Hz, 1H), 4.96 (d, *J* = 14.7 Hz, 1H), 3.85 (d, *J* = 15.1 Hz, 1H), 3.52 (d, *J* = 6.0 Hz, 1H), 3.47-3.34 (m, 1H), 2.67 (d, *J* = 2.6 Hz, 3H), 1.37 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 167.6, 166.9, 138.2, 137.7, 136.7, 135.9, 131.3 (q, J = 32.7 Hz), 129.0, 128.8, 128.1, 127.3, 126.9, 126.1 (q, J = 3.7 Hz), 123.9 (q, J = 272.5 Hz), 122.3 (q, J = 3.6 Hz), 64.2, 62.2, 52.2, 45.3, 44.9, 28.6, 12.7; HRMS (ESI, $[M+H]^+$) for $C_{27}H_{26}ClF_3NO_2$ cacld 491.1706, found 491.1716.

**2-Benzyl-*N*-(*tert*-butyl)-4-ethyl-3-oxo-7-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7q).** Yield: 53% (one-pot, procedure B); white solid; mp 158-160°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.96 (s, 1H), 7.74 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.42-7.28 (m, 5H), 5.45 (bs, 1H), 5.10 (d, *J* = 14.7 Hz, 1H), 4.84 (s, 1H), 4.53 (d, *J* = 14.7 Hz, 1H), 3.90 (dq, *J* = 13.1, 7.5 Hz, 1H), 3.74 (dq, *J* = 13.1, 7.4 Hz, 1H), 1.42 (t, *J* = 7.5 Hz, 3H), 1.16 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): 169.9, 167.0, 144.2, 138.8, 136.8, 136.6, 131.3, 130.4, 129.3, 128.9, 128.5 (q, *J* = 32.3 Hz), 128.3, 124.9, 124.4 (q, *J* = 272.3 Hz), 123.3 (q, *J* = 2.9 Hz), 122.8 (q, *J* = 4.5 Hz), 119.9, 64.5, 51.7, 46.8, 28.5, 19.3, 16.1; IR (ATR): 3309, 3272, 3070, 2970, 2932, 2877, 1681, 1656, 1552, 1454, 1330, 1301, 1219, 1164, 1123, 1072, 886, 701 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{27}H_{28}F_3N_2O_2^+$ calcd 469.2097, found 469.2082.

**2-Benzyl-*N*-(*tert*-butyl)-7-methoxy-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7r).** Yield: 58% (stepwise from **12r**), 14% (one-pot, procedure B), 44% (one-pot, procedure D); pale yellow solid; mp 176-178°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.41-7.23 (m, 7H), 5.52 (bs, 1H), 5.12 (d, *J* = 14.7 Hz, 1H), 4.79 (d, *J* = 0.8 Hz, 1H), 4.48 (d, *J* = 14.7 Hz, 1H), 3.96 (s, 3H), 3.09 (s, 3H), 1.16 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.0, 167.7, 158.2, 136.8, 134.9, 134.6, 134.4, 130.5, 130.4, 129.2, 128.8, 128.1, 124.8, 120.5, 119.5, 103.4, 64.3, 55.4, 51.6, 46.5, 28.5, 12.2; IR (ATR): 3318, 2969, 2921, 1671, 1616, 1531, 1425, 1391, 1297, 1233, 1193, 1174, 1021, 698, 678 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{26}H_{29}N_2O_3^+$ calcd 417.2173, found 417.2161.

**2-Benzyl-*N*-butyl-7-methoxy-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7s).** Yield: 54% (stepwise from **12s**), 19% (one-pot, procedure B), 51% (one-pot, procedure D); pale yellow solid; mp 203-206°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.37-7.21 (m, 7H), 6.07 (t, *J* = 5.3 Hz, 1H), 5.33 (d, *J* = 14.7 Hz, 1H), 4.91 (s, 1H), 4.33 (d, *J* = 14.7 Hz, 1H), 3.92 (s, 3H), 3.30-3.18 (m, 1H), 3.16-3.02 (m, 1H), 2.92 (s, 3H), 1.39-1.17 (m, 4H), 0.84 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.7, 168.6, 158.2, 136.4, 134.9, 134.6, 134.2, 130.43, 130.42, 129.1, 128.7, 128.2, 124.7, 120.6, 119.8, 103.3, 63.1, 55.4, 46.1, 39.5, 31.5, 20.2, 13.8, 11.9; IR (ATR): 3288, 2962, 2926, 2872, 1688, 1652, 1617, 1542, 1427, 1396, 1230, 1175, 1015, 838, 710, 694 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{26}H_{29}N_2O_3^+$ calcd 417.2173, found 417.2182.

**6-Benzyl-*N*-(*tert*-butyl)-4-methyl-5-oxo-6,7-dihydro-5*H*-thieno[2,3-*f*]isoindole-7-carboxamide (7t).** Yield: 17% (one-pot, procedure A); yellow solid; mp 194-197°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.53 (d, *J* = 5.7 Hz, 1H), 7.52 (d, *J* = 5.7 Hz, 1H), 7.39-7.26 (m, 5H), 5.53 (bs, 1H), 5.08 (d, *J* = 14.8 Hz, 1H), 4.76 (d, *J* = 0.7 Hz, 1H), 4.47 (d, *J* = 14.8 Hz, 1H), 3.03 (s, 3H), 1.16 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.9, 167.3, 143.6, 140.6, 137.4, 136.8, 133.6, 129.2, 128.7, 128.1, 127.4, 123.5, 122.3, 114.2, 64.4, 51.6, 46.5, 28.5, 13.9; IR (ATR): 3299, 2960, 2917, 2852, 1682, 1657, 1605, 1529, 1439, 1402, 1247, 1211, 1169, 1024, 757, 724, 694, 672 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{23}H_{25}N_2O_2S^+$ calcd 393.1631, found 393.1644.

**6-Benzyl-*N*-(*tert*-butyl)-8-methyl-5-oxo-6,7-dihydro-5*H*-thieno[2,3-*f*]isoindole-7-carboxamide (7t').** Yield: 9% (one-pot, procedure A); yellow solid, mp 194-197°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 5.6 Hz, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 7.38-7.26 (m, 5H), 5.42 (d, *J* = 15.0 Hz, 1H), 5.38 (bs, 1H), 4.67 (s, 1H), 4.09 (d, *J* = 15.0 Hz, 1H), 3.05 (s, 3H), 1.32 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 168.7, 165.1, 142.46, 142.39, 136.6, 133.5, 132.6, 129.0, 128.8, 128.2, 128.0, 127.3, 123.6, 120.2, 63.2, 52.3, 45.0, 28.6, 13.8; IR (ATR): 3324, 3076, 2967, 2920, 1698, 1680, 1659, 1555, 1541, 1439, 1398, 1360, 1331, 1247, 1224, 1000, 755, 730, 694 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{23}H_{23}ClN_2O_2SNa^+$ calcd 449.1061, found 449.1050.

**6-Benzyl-*N*-(*tert*-butyl)-4-ethyl-5-oxo-6,7-dihydro-5*H*-thieno[2,3-*f*]isoindole-7-carboxamide (7u).** Yield: 23% (one-pot, procedure B); yellow solid; mp 162-165°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 7.53 (d, *J* = 5.6 Hz, 1H), 7.39-7.26 (m, 5H), 5.47 (bs, 1H), 5.07 (d, *J* = 14.8 Hz, 1H), 4.75 (s, 1H), 4.47 (d, *J* = 14.7 Hz, 1H), 3.66 (dq, *J* = 12.7, 7.5 Hz, 1H), 3.51 (dq, *J* = 12.7, 7.5 Hz, 1H), 1.39 (t, *J* = 7.5 Hz, 3H), 1.16 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.5, 167.3, 144.0, 140.2, 139.8, 137.5, 136.8, 129.1, 128.7, 128.1, 127.4, 122.7, 122.1, 114.3, 64.4, 51.6, 46.6, 28.5, 21.5, 15.8; IR (ATR): 3262, 3069,

2961, 2926, 2872, 1680, 1656, 1552, 1455, 1436, 1399, 1362, 1246, 1221, 1176, 752, 698 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{24}H_{27}N_2O_2S^+$ calcd 407.1788, found 407.1786.

**2-Benzyl-7-bromo-*N*-butyl-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7v).** Yield: 92% (one-pot, procedure A); yellow solid; mp 215-218°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.86 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.64 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.38-7.26 (m, 5H), 6.19 (t, *J* = 5.1 Hz, 1H), 5.32 (d, *J* = 14.7 Hz, 1H), 4.91 (s, 1H), 4.33 (d, *J* = 14.7 Hz, 1H), 3.29-3.18 (m, 1H), 3.17-3.04 (m, 1H), 2.93 (s, 3H), 1.40-1.16 (m, 4H), 0.84 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.3, 168.1, 136.6, 136.1, 135.9, 134.6, 133.4, 131.3, 130.5, 129.2, 128.7, 128.3, 127.6, 125.2, 121.1, 120.1, 63.1, 46.2, 39.6, 31.4, 20.1, 13.8, 12.0; IR (ATR): 3278, 2961, 2922, 2859, 1687, 1656, 1557, 1395, 1237, 884, 739, 696 $cm^{-1}$; HRMS (ESI, $[M+H]^+$) for $C_{25}H_{25}BrN_2O_2Na^+$ calcd 487.0992, found 487.0980.

***N*-Butyl-4-methyl-3-oxo-2-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (7w).** Yield: 18% (one-pot, procedure B); yellow solid; mp 178-180°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.17-8.09 (m, 1H), 7.98 (s, 1H), 7.94-7.85 (m, 1H), 7.66-7.54 (m, 2H), 6.20 (bt, *J* = 5.2 Hz, 1H), 5.26 (s, 1H), 4.74 (dd, *J* = 17.6, 2.0 Hz, 1H), 4.17 (dd, *J* = 17.6, 2.0 Hz, 1H), 3.40-3.24 (m, 1H), 3.21-3.07 (m, 1H), 3.00 (s, 3H), 2.33 (t, *J* = 2.1 Hz, 1H), 1.48-1.36 (m, 2H), 1.31-1.20 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.4, 168.3, 137.0, 136.0, 135.1, 133.3, 129.1, 128.0, 126.7, 125.3, 123.8, 120.2, 77.5, 73.6, 63.2, 39.6, 32.0, 31.4, 20.1, 13.8, 12.0; HRMS (ESI, $[M+Na]^+$) for $C_{21}H_{22}N_2O_2Na^+$ calcd 357.1573, found 357.1572.

**General Procedure for the three-step one-pot synthesis of isoindolinones 15**

(*Z*)-3-(4-Bromophenyl)-3-chloroacrylaldehyde **11f** (123 mg, 0.5 mmol) was dissolved in isopropanol (2.5 mL) followed by the addition of benzylamine **3a** (54 mg, 0.6 mmol), but-2-ynoic acid **2a** (42 mg, 0.6 mmol) and n-butyl isocyanide **4b** (42 mg, 0.6 mmol). The reaction mixture was sealed and stirred at room temperature for 36 h. Upon completion of this time $H_2O$ (0.6 mL) was added. The reaction mixture was flashed with argon, sealed and stirred at 115°C for 3 h. Upon completion of this time the reaction mixture was cooled down followed by addition of boronic acid **14** (0.75 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.015 mmol) and $K_2CO_3$ (207 mg, 1.5 mmol). The reaction mixture was flashed with argon, sealed and stirred at 115°C for another 1.5 h. The resulting mixture was diluted with DCM and washed with $H_2O$. The organic layer was dried with sodium sulfate and concentrated with silica. Column chromatography with DCM/EtOAc (the ratio was adjusted according to TLC) as eluent delivered isoindolinone **15**.

**2-Benzyl-*N*-butyl-4-methyl-3-oxo-7-phenyl-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (15a).** Yield: 61%; pale yellow solid; mp 257-259°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.99-7.89 (m, 2H), 7.88-7.80 (m, 1H), 7.74-7.65 (m, 2H), 7.54-7.45 (m, 2H), 7.44-7.26 (m, 6H), 5.98 (bt, *J* = 5.4 Hz, 1H), 5.33 (d, *J* = 14.7 Hz, 1H), 4.96 (s, 1H), 4.35 (d, *J* = 14.7 Hz, 1H), 3.29-3.03 (m, 5H), 1.39-1.15 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.6, 168.4, 140.8, 139.4, 136.9, 136.3, 136.2, 134.1, 133.6, 129.5, 129.1, 129.0, 128.7, 128.2, 127.8, 127.61, 127.57, 124.8, 123.0, 119.9, 63.2, 46.1, 39.6, 31.5, 20.1, 13.8, 12.1; IR (ATR): 3300, 2961, 2924, 2874, 1690, 1655, 1546, 1450, 1390, 1234, 1184, 887, 754, 697 $cm^{-1}$; HRMS (ESI, $[M+Na]^+$) for $C_{31}H_{30}N_2O_2Na^+$ calcd 485.2199, found 485.2188.

**7-(4-Acetylphenyl)-2-benzyl-*N*-butyl-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (15b).** Yield: 59%; pale yellow solid; mp 272-275°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.94 (s, 1H), 7.85 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.40-7.26 (m, 5H), 6.11 (bt, *J* = 5.6 Hz, 1H), 5.34 (d, *J* = 14.7 Hz, 1H), 4.96 (s, 1H), 4.36 (d, *J* = 14.7 Hz, 1H), 3.31-3.18 (m, 1H), 3.18-3.03 (m, 4H), 2.66 (s, 3H), 1.41-1.17 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.8, 170.5, 168.3, 145.3, 137.9, 137.1, 136.7, 136.23, 136.20, 134.6, 133.5, 129.9, 129.18, 129.15, 128.7, 128.3, 127.6, 127.2, 125.0, 123.6, 119.9, 63.2, 46.2, 39.6, 31.5, 26.8, 20.1, 13.8, 12.1; IR (ATR): 3306, 2962, 2923, 2867, 1690, 1676, 1653, 1603, 1545, 1390, 1357, 1270, 1224, 1183, 967, 885, 838, 807, 714, 697 $cm^{-1}$; HRMS (ESI, $[M+Na]^+$) for $C_{33}H_{32}N_2O_3Na^+$ calcd 527.2305, found 527.2298.

**2-Benzyl-*N*-butyl-7-(3,5-dimethylisoxazol-4-yl)-4-methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (15c).** Yield: 61%; yellow solid; mp 199-202°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.02-7.98 (m, 1H), 7.97-7.90 (m, 2H), 7.51-7.45 (m, 1H), 7.35 - 7.26 (m, 5H), 6.29 (bt, *J* = 5.7 Hz, 1H), 5.34 (d, *J* = 14.7 Hz, 1H), 4.95 (s, 1H), 4.33 (d, *J* = 14.8 Hz 1H), 3.31-3.19 (m, 1H), 3.18-3.02 (m, 4H), 2.44 (s, 3H), 2.29 (s, 3H), 1.41-1.31 (m, 2H), 1.29-1.18 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.4, 168.2, 165.7, 158.7, 136.6, 136.4, 136.2, 134.0, 133.4, 129.6, 129.1, 128.7 (two merged signals), 128.6, 128.2, 125.3, 125.1, 120.0, 116.7, 63.0, 46.1, 39.5, 31.4, 20.1, 13.7, 12.1, 11.7, 11.0; IR (ATR): 3277, 2960, 2926, 2872, 1689, 1655, 1544, 1421, 1396, 1238, 1030, 885, 699 $cm^{-1}$; HRMS (ESI, $[M+Na]^+$) for $C_{30}H_{31}N_3O_3Na^+$ calcd 504.2258, found 504.2241.

**2-Benzyl-*N*-butyl-4-methyl-3-oxo-7-(pyrimidin-5-yl)-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxamide (15d).** Yield: 66%; pale yellow solid; mp 278-279°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 9.06 (s, 2H), 8.32 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.97 (s, 1H), 7.80 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.40-7.27 (m, 5H), 5.92 (bt, *J* = 5.8 Hz, 1H), 5.32 (d, *J* = 14.7 Hz 1H), 4.97 (s, 1H), 4.37 (d, *J* = 14.7 Hz, 1H), 3.28-3.05 (m, 5H), 1.38-1.15 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.3, 168.1, 157.9, 155.2, 137.3, 137.1, 136.2, 134.8, 134.1, 133.6, 132.4, 130.6, 129.2, 128.8, 128.3, 126.3, 125.4, 123.6, 120.1, 63.2, 46.3, 39.6, 31.4, 20.1, 13.8, 12.1; IR (ATR): 3270, 3062, 3032, 2960, 2928, 2870, 1683, 1652, 1547, 1412, 1352, 1231, 807, 720, 700, 638 $cm^{-1}$; HRMS (ESI, $[M+Na]^+$) for $C_{29}H_{28}N_4O_2Na^+$ calcd 487.2104, found 487.2093.

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[19] CCDC 1550762 (**7p''**), CCDC 1550763 (**7t**), and CCDC 1550764 (**7t'**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via: www.ccdc.cam.ac.uk/data_request/cif

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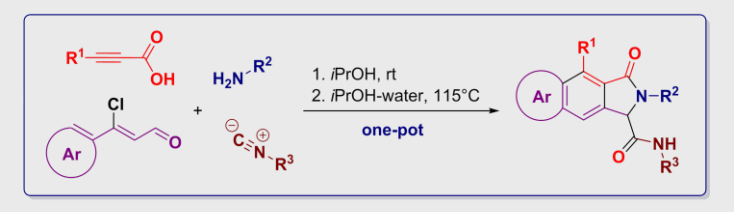


A one-pot procedure involving a four-component Ugi reaction followed by an intramolecular Diels-Alder/HCl-elimination cascade has been developed to provide rapid access to the isoindolinone framework in a diversity-oriented fashion.

**One-pot synthesis**

*Jianjun Huang, Xiaochen Du, Kristof Van Hecke, Erik V. Van der Eycken, Olga P. Pereshivko, * Vsevolod A. Peshkov**

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**Ugi Reaction Followed by the Intramolecular Diels-Alder and HCl-Elimination: a One-Pot Approach towards Arene-Fused Isoindolinones**