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Note

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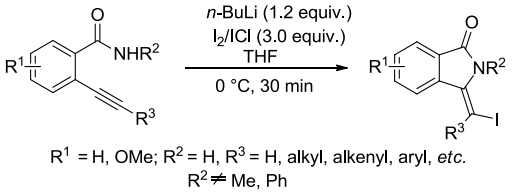
Regio- and Stereoselective Synthesis of Isoindolin-1-ones through BuLi-mediated Iodoaminocyclization of 2-(1-Alkynyl)benzamides

Dhirendra Brahmchari,[†] Akhilesh K. Verma[‡] and Saurabh Mehta[†,*]

[†]Department of Applied Chemistry, Delhi Technological University, Delhi, 110042 India.
[‡]Synthetic Organic Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110007 India

Abstract



R^1 = H, OMe; R^2 = H, R^3 = H, alkyl, alkenyl, aryl, *etc.*
$R^2 \neq$ Me, Ph

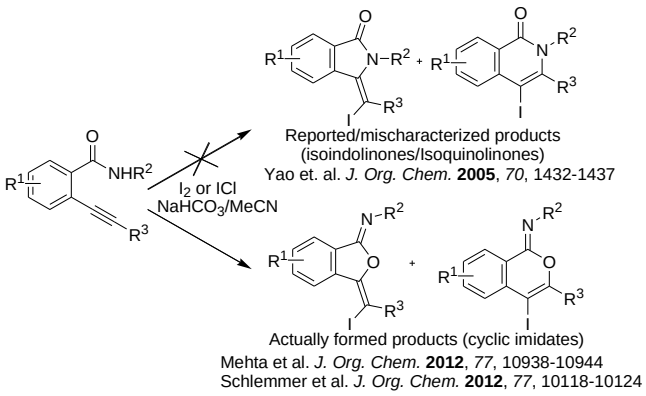
A simple and straightforward synthesis of isoindolin-1-ones is reported. Exclusive *N*-cyclization of the amide functional group, an ambident nucleophile, has been accomplished for the cyclization of 2-(1-alkynyl)benzamides using *n*-BuLi-I_2/ICl. The methodology works with the primary amide and affords the desired isoindolinones in yields of 38-94%. Interestingly, the isolated products exhibit a *Z*-stereochemistry across the C=C double bond. The reaction mechanism involving the formation of either a vinylic anion or an intimate ion pair intermediate is proposed.

Isoindolinones or phthalimidines represent an important class of nitrogen-containing heterocycles. This benzo-fused lactam scaffold is present in several naturally occurring, pharmacologically active substances such as alkaloids, *e.g.* Fumaridine, Chilenine, Nuevamine, Lennoxamine, and Stachybotrin C, *etc*.[1–3] Moreover, numerous molecules containing isoindolin-1-one scaffold display a wide array of important biological activities

such as vasodilatory,[4] anti-HIV,[5] antilcancer,[6] antimicrobial,[7] anticonvulsant,[8] sedative & hypnotic,[9] *etc.* A few specific examples of such drugs and other medicinally important compounds containing isoindolin-1-one scaffold include Chlortalidone,[10] JM-1232,[11] (*S*)-PD 172938,[12] Pagoclone (Cl-1043),[13] Pazinaclone (DN 2327), *etc*.[14] Owing to their widespread medicinal importance, there has been a continuous interest in developing new syntheses of isoindolin-1-ones that improve accessibility to a broad array of structurally related analogues. Several research groups have developed various interesting approaches (>200 research articles in the recent literature) for the synthesis of the isoindolin-1-ones.[15,16] More particularly, alkyne annulation reactions have been used for the synthesis of isoindolinones, *e.g.* through metal catalyzed, including Pd-catalyzed,[17–21] Cu-catalyzed/mediated,[22–26] Ru-catalyzed;[27] base-mediated annulations,[28–35] *etc*.[36,37]

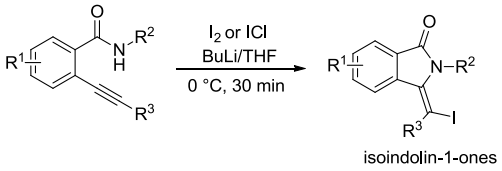
The electrophilic cyclization, particularly the iodocyclization of functionalized alkynes has emerged as a powerful method for the synthesis of a wide variety of heterocyclic and carbocyclic compounds.[38–40] These reactions have several practical advantages including the ease of performing the reactions, fast reactions, simple workup, compatibility with most functional groups, and importantly the fact that the products contain Iodine atom, which provides easy handle for various metal-catalyzed coupling reactions.[41] We have also studied this methodology and have used it to make a variety of heterocyclic compounds in the past.[42,43] Moreover, efforts have been made previously by Yao *et al.* for the iodocyclization of *o*-(1-alkynyl)benzamides for the synthesis of isoindolin-1-ones,[44] however, later it was found that the methodology resulted in the cyclization *via* the *O*-atom of the amide group leading to the formation of the cyclic imidates rather than isoindolin-1-ones, which was later on confirmed and corrected by us and others (Scheme 1).[45,46]

SCHEME 1. Previous work



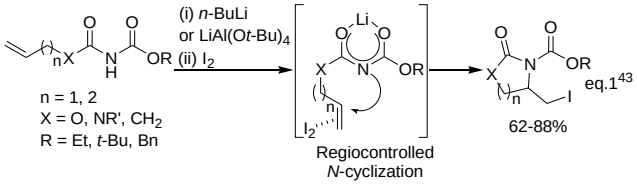
Furthermore, to the best of our knowledge, the synthesis of isoindolin-1-ones has not been accomplished *via* iodocyclization, probably due to the challenge posed by the ambident nucleophilic nature of the amide functionality (*N*- Vs. *O*-cyclization). Nonetheless, such methodology would be synthetically useful and would lead to diverse isoindolin-1-ones with interesting substitution patterns. Due to our continuous interest in developing new methodologies for heterocyclic synthesis, we became interested in tuning the reactivity of these 2-(1-alkynyl)benzamides to achieve regioselective synthesis of isoindolinones (Scheme 2), and report our findings here.

SCHEME 2. Present work



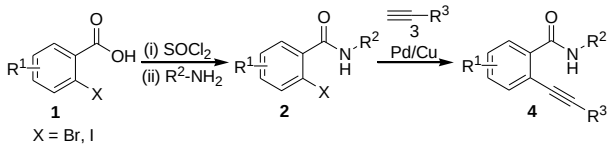
Amide group (–$CONH_2$) is an ambident nucleophile and is known to undergo *N* vs *O* cyclization in alkyne annulation reactions,[47,48] therefore, the choice of the suitable reagents is important for tuning the reactivity of the nucleophilic site.[29] Our efforts were directed towards the development of a suitable methodology employing I_2/ICl as efficient electrophile for the *N*-cyclization of 2-(1-alkynyl)benzamides to furnish isoindolin-1-ones. During a thorough literature survey, we came across an interesting methodology developed by Fujita *et al.* that involves a regiocontrolled iodoaminocyclization of the protected amide group at the

activated double bond (eq 1).[49] The authors also presented a rationale of *N*- Vs *O*-cyclization of unsaturated amides based on HSAB theory. Furthermore, the authors achieved regiocontrol (*N*-cyclization) in the iodocyclization of allyl or homoallyl carbamates, *etc*. through the use of suitable base/additives, *n*-BuLi/LiAl(O*t*-Bu)$_4$ (eq 1). The authors postulated that the reaction proceeds through the formation of a metal imino alkolate intermediate and explained the achieved regiocontrol through the increased reactivity of amide nitrogen atom.

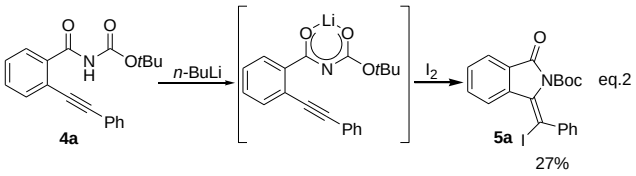


Inspired by the methodology developed by Fujita *et.al*, we envisioned a similar intramolecular iodoaminocyclization of 2-(1-alkynyl)benzamide derivatives. The required alkyne substrates would be conveniently prepared from the commercially available starting materials using the following approach (Scheme 3).

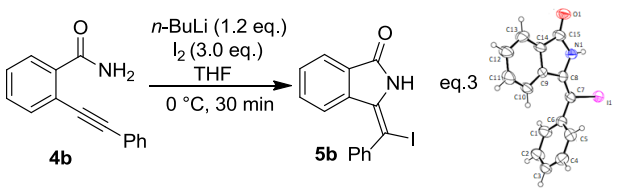
SCHEME 3. Strategy for preparing 2-(1-alkynyl)benzamides



Initially, we started our reactions (eq 2) with the cyclization of *tert*-butyl(2-(phenylethynyl)benzoyl)carbamate (**4a**), which involves the (-CO-NH-CO-) group for the formation of a metal imino alkolate intermediate with metallic base that makes the nitrogen atom more nucleophilic, leading to the formation of *N*-cyclized product. Although the desired product **5a** was isolated, however, it was not stable enough and isolated yield (27%) was poor.



We attributed the formation of unstable product and low reaction yield to the presence of the labile protecting group (*N*-Boc) and/or the sterically hindered substrate, and we decided to use the unprotected amide group instead. We then took 2-(1-phenylethynyl)benzamide (**4b**) as a model substrate for determining the optimum reagents/conditions for the cyclization reaction, using I_2/ICl as the iodine source (Table S1). To our pleasant surprise, the use of *n*-BuLi as base worked and the cyclized product **5b** was isolated with a yield of 67% (eq 3). The procedure involved the addition of *n*-BuLi to the alkyne substrate in THF at 0 °C, followed by the addition of I_2/ICl and stirring the reaction mixture at 0 °C. The cyclized product was thoroughly characterized using spectroscopy (IR, ^{1}H-NMR, ^{13}C-NMR), mass spectrometry (HRMS) as well as single crystal X-ray crystallography (see ORTEP diagram in eq 3). It is noteworthy that the cyclized product **5b** was found to possess *Z*-geometrical configuration. Also, the reaction at lower temperature (-78 ^{o}C) resulted in a mixture of stereoisomers (*E:Z* 1:9). The reaction also worked with ICl, however the yield was slightly lower (63%). It was attempted to improve the reaction yield through the use of other bases and other reaction parameters (reaction time, temperature, solvent, *etc.*) and the details are summarized in the optimization Table S1 (See Supplementary Information).

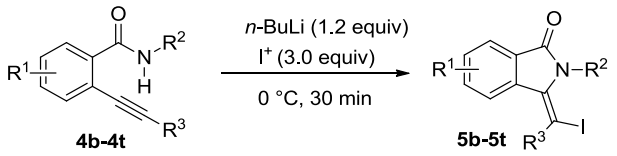


Overall, the yield could not be improved for this substrate. Therefore, we decided to proceed further and to study the scope and limitations of the cyclization reaction using the

same reaction conditions (eq 3). The required alkyne substrates **4b-4t** were prepared (Scheme 3) in yields ranging from 48-95% by using the palladium/copper-catalyzed Sonogashira cross coupling[50] and the results are summarized in Table S2 (See supporting information).

Thus a variety of 2-(1-Alkynyl)benzamides were subjected to the cyclization conditions and the results are summarized in Table 1.

TABLE 1: BuLi-mediated Cyclization of 2-(1-Alkynyl)benzamides[a]



entry	substrate	R^1	R^2	R^3	I^+	product	yield (%)
1.	**4b**	H	H	Ph	I_2	**5b**	67
2.	**4b**				ICl	**5b**	63
3.	**4c**	H	H	4-MePh	I_2	**5c**	71
4.	**4c**				ICl	**5c**	61
5.	**4d**	H	H	3-MePh	I_2	**5d**	89
6.	**4d**				ICl	**5d**	71
7.	**4e**	H	H	4-OMePh	I_2	**5e**	52
8.	**4e**				ICl	**5e**	44
9.	**4f**	H	H	4-NMe_2Ph	I_2	**5f**	67
10.	**4g**	H	H	4-FPh	I_2	**5g**	69
11.	**4g**				ICl	**5g**	67
12.	**4h**	H	H	4-BrPh	I_2	**5h**	41[b,c]
13.	**4i**	H	H	2-BrPh	I_2	**5i**	-[b,d]
14.	**4j**	H	H	3-ClPh	I_2	**5j**	74
15.	**4j**				ICl	**5j**	73
16.	**4k**	H	H	*n*-hexyl	I_2	**5k**	75
17.	**4k**				ICl	**5k**	69
18.	**4l**	H	H	cyclohexyl	I_2	**5l**	94
19.	**4m**	H	H	cyclohexenyl	I_2	**5m**	57
20.	**4n**	H	H	TMS	I_2	**5n**	-[e]
21.	**4o**	H	H	H	I_2	**5o**	82
22.	**4p**	H	H	3-thienyl	I_2	**5p**	75
23.	**4q**	3,4-(OMe)$_2$	H	Ph	I_2	**5q**	78
24.	**4r**	H	Me	Ph	I_2	**5r**	-[f]
25.	**4s**	H	Ph	Ph	I_2	**5s**	-[g]
26.	**4t**	H	Ph	*n*-hexyl	I_2	**5t**	-[g]

[a]All reactions were run using 0.25 mmol of 2-(1-alkynyl)benzamide in 2 mL THF and 1.2 equiv of *n*-BuLi (1.6 M in Hexane), stirred for 10 minutes, followed by the dropwise addition (approx.1 min) of 3.0 equiv I_2/ICl in 1 mL THF and the reaction mixture was stirred at 0 °C for 20 minutes under Argon atmosphere (total reaction time 30 min). [b]1.0 equiv of *n*-BuLi (1.6 M in Hexane) was used. [c]corresponding debrominated product was also formed (yield: 9%). [d]only the corresponding debrominated product was isolated (yield: 38%). [e]corresponding desilylated product was isolated (yield: 75%). [f]*O*-cyclized product was formed (yield: 47%). [g]complex reaction mixture was obtained.

The reaction worked well with the substrates **4b-4g** containing electron donating and withdrawing groups, *e.g.* Me, OMe, NMe_2, F, *etc*. (Table 1, entries 3-11). The cyclization of bromine containing substrates **4h** and **4i** resulted in the isolation of partially (entry 12) or completely debrominated (entry 13) products. The cyclization of the substrate **4j** containing chloro group (entries 14 and 15) resulted in the formation of desired product. The substrate **4k** with *n*-hexyl group at the distal end of the alkyne was also cyclized to give good yield (entries 16 and 17). Even a cyclohexyl group containing substrate **4l** was successfully cyclized with an excellent yield (entry 18). Cyclization of alkyne substrate **4m** with unsaturation (cyclohexenyl group) resulted in moderate yield (entry 19). The cyclization of the substrate **4n** with TMS group resulted in the formation of desilylated product in 75% yield (entry 20). The reaction worked well for the terminal alkyne **4o** and the expected product was isolated in 82% yield (entry 21). The methodology also worked for the substrate **4p** with a heterocyclic moiety and resulted in the thienyl containing isoindolinone **5p** in 75% yield (entry 22). The substrate **4q** with electron donating methoxy groups at the benzamide ring in substrate was successfully converted to the desired product in 78% yield (entry 23). We then attempted the cyclization of secondary amide substrates (**4r-4t**). The *N*-Me substituted amide **4r** underwent cyclization (entry 24), however, the product was found to be the corresponding imidate (*O*-cyclized product) instead of the expected isoindollin-1-one. Furthermore, the cyclization of *N*-phenyl substituted amides **4s** and **4t** (entries 25 and 26 respectively) resulted in the formation of complex mixtures that could not be resolved. These results (entries 24-26) indicate that the steric hindrance due to the Methyl or Phenyl substituent on the nitrogen atom of the amide group presumably disfavors the desired *N*-cyclization under these reaction conditions.

All the cyclized products were characterized using the spectroscopy (IR, ^{1}H-NMR, ^{13}C-NMR) and Mass Spectrometry (HRMS). The stereochemistry of the cyclized products

was assigned by correlating the spectroscopic data with that of **5b**. It is noteworthy that the *N*-cyclized products were differentiated from the *O*-cyclized products by the presence of the diagnostic signals in the ^{13}C-NMR spectra of these compounds (Figure 1).

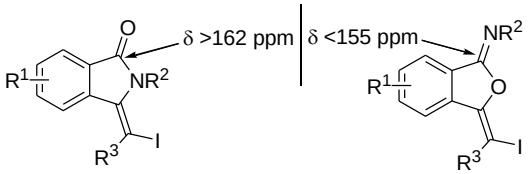


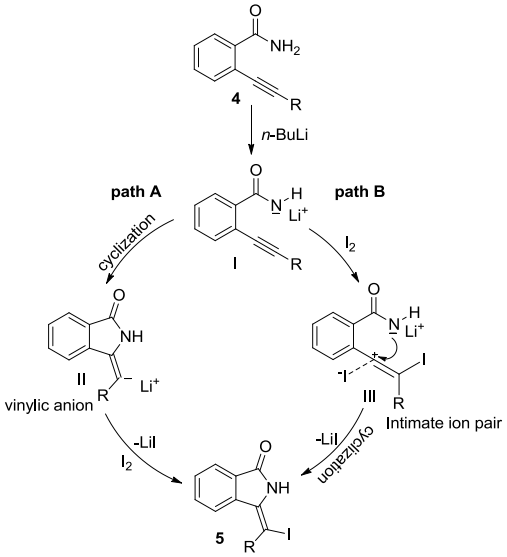
FIGURE 1. ^{13}C NMR data for the identification of *N* vs *O*-cyclized products

We think that the results of the presented methodology are quite interesting with respect to the exclusive *N*-cyclization, selective *5-exo-dig* cyclization, and especially the observed stereochemistry of the cyclized products. As mentioned above, our methodology yields the cyclized products with *Z*-stereochemistry and the products with *E*-configuration were not isolated except for one case involving the model substrate at -78 ^{o}C. As we attempted to rationalise our observations from a mechanistic perspective, we considered the possibility of the formation of a vinylic cation or an alkyne iodonium intermediate for our cyclization reaction. Both of these species have been reported in the literature as possible intermediates in iodocyclization reactions.[51] We also considered the possibility of an anionic cyclization (See Supporting Information).[21,32,33] Moreover, we came across a study in which while using metallaaromatic compounds, Wang *et al.* captured and characterized the key intermediates in the base-mediated alkyne iodocyclization reactions.[52] With the help of X-ray structural evidence of an isolated intermediate, the authors claimed the involvement of an intimate ion pair intermediate instead of the generally accepted iodonium ion.

In view of the evidence presented in the literature[53–55] as well as our own observations (see Supporting Information), we propose a possible mechanism (Scheme 4) where the alkynyl amide **4** is first deprotonated by BuLi yielding the corresponding amide anion (I). We believe that the amide anion (I) either undergoes *5-exo-dig* cyclization *via* path A leading to the formation of vinylic anion intermediate (II) which on reaction with iodine generates the

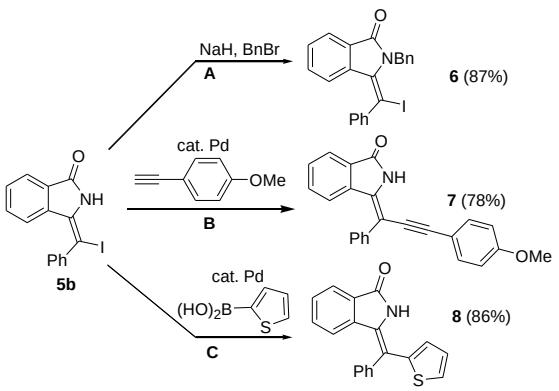
iodine containing isoindolin-1-one **5**. Alternatively, the amide anion (I) may react with iodine leading to the formation of an intimate ion pair (III) *via* path B, followed by the aminocyclization to yield the corresponding iodinated isoindolinone **5**.

SCHEME 4. Plausible mechanism



The resulting products contain iodine as well as a free -NH group, which are potential sites for further structural modifications. This has been explored by us and is demonstrated in Scheme 5. Thus, the resulting iodine containing isoindolin-1-ones are diversified *via N*-benzylation (Scheme 5A), and by using conventional palladium-catalyzed transformations, including Sonogashira alkynylation (Scheme 5B) and Suzuki-Miyaura (Scheme 5C) reactions. All these reactions resulted in the multi-substituted isoindolin-1-ones in good yields.

SCHEME 5: Diversification of iodine-containing isoindolin-1-ones



Method A (*N*-Benzylation): NaH (1.2 equiv), BnBr (1.1 equiv.), DMF, 0 °C, 2 h. **Method B** (Sonogashira coupling): 3 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, DIPA (4 equiv.), 1-ethynyl-4-methoxybenzene (1.2 equiv.), DMF, 70 °C, 2 h. **Method C** (Suzuki-Miyaura coupling): 5 mol % $PdCl_2$, Cs_2CO_3 (1.4 equiv.), thiophen-2-ylboronic acid (1.2 equiv.), 4:1 DMF/H_2O, 80 °C, 2 h.

Thus the methodology reported here represents the first successful iodoaminocyclization of easily accessible 2-(1-alkynyl)benzamides, yielding the corresponding isoindolin-1-ones regio- and stereoselectively. Further efforts for achieving broader reaction scope as well as for better understanding of the reaction mechanism, are currently underway in our laboratory.

EXPERIMENTAL SECTION

General

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 400 MHz and 100 MHz, respectively, with Me_4Si as an internal standard. The chemical shifts (δ) and coupling constants (*J*) are given ppm and in Hz, respectively. Thin layer chromatography was performed using commercially prepared 60-100-mesh silica gel plates and visualization was effected with short wavelength UV light (254 nm). Compounds were purified by column chromatography. All melting points are uncorrected.

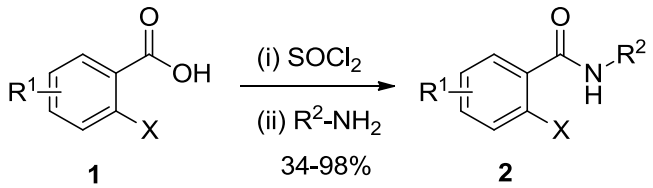
Reagents. All reagents were used directly as obtained commercially unless otherwise noted.

Solvents. All solvents were used directly as obtained commercially.

2-halobenzoic acids: 1a and **1b** are commercially available and were used as received.

Terminal alkyne building blocks. Commercially available terminal alkynes **(3)** were used as received.

Procedure for the preparation of 2-Halobenzamides:



1 **2**

R^1 = H, X = I (**1a**)
R^1 = 3,4-$(OMe)_2$, X = Br (**1b**)

R^1 = H, X =Br R^2 = Boc (**2a**)
R^1 = H, X = I R^2 = H (**2b**)
R^1 = 3,4-$(OMe)_2$, X =Br R^2 = H (**2c**)
R^1 = H, X = I R^2 = Ph (**2d**)
R^1 = H, X = I R^2 = Me (**2e**)

2-Halobenzoic acid (1gm) was refluxed in 5 mL $SOCl_2$ for 7 hrs. The solvent was evaporated under reduced pressure and the resulting yellow oil was treated with the corresponding primary amines at 0 °C. The resulting white solid was filtered and dried overnight in hot air oven at 50 °C. 2-bromobenzamide was commercially available and used as such.

tert-butyl (2-iodobenzoyl)carbamate **(2a):** Yield: (477 mg, 34%); light yellow Solid; TLC R_f = 0.22 (20% EtOAc:Hexanes, UV); mp 113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.37-7.33 (m, 1H), 7.28-7.26 (m, 1H), 7.10-7.05 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.9, 149.3, 141.0, 139.1, 131.0, 127.7, 127.5, 91.9, 82.7, 27.8.

2-iodobenzamide (2b):[56] Yield: (966 mg, 97%); White Solid: TLC R_f = 0.15 (30% EtOAc:Hexanes, UV); mp 183-185 °C; 1H NMR (400 MHz, CDCl3) δ = 7.90 (d, J = 10.4 Hz, 1H), 7.48-7.46 (m, 1H), 7.41-7.37 (m, 1H), 7.14-7.10 (m, 1H), 5.88 (s, 2H).

2-bromo-4,5-dimethoxybenzamide **(2c):**[57] Yield: (976 mg, 98%); White Solid; TLC R_f = 0.26 (40% EtOAc:Hexanes, UV); mp 177-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (s, 1H), 7.98 (s, 1H), 6.54 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 168.6, 151.0, 148.2, 127.6, 115.8, 113.2, 110.1, 56.2, 56.0.

2-iodo-N-phenylbenzamide **(2d):**[56] Yield: (1.211 g, 93%); White Solid; TLC R_f = 0.33 (10% EtOAc:Hexanes, UV); mp 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 7.2 Hz, 1H), 7.63-7.61 (m, 3H), 7.50-7.48 (m, 1H), 7.42-7.35 (m, 3H), 7.19-7.10 (m, 2H).

2-iodo-N-methylbenzamide **(2e):**[56] Yield: (998 mg, 95%); White Solid; TLC R_f = 0.23 (10% EtOAc:Hexanes, UV); mp 146-148 °C (lit. mp 145-147 °C)[58]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.0 Hz, 1H), 7.38-7.31 (m, 2H), 7.10-7.03 (m, 1H), 5.99 (s, 1H), 2.97 (d, *J* = 4.8 Hz, 3H).

Representative Sonogashira procedure: To a solution of the appropriate iodo/bromo starting material (0.25 mmol) in DMF (2 mL) were added $PdCl_2(PPh_3)_2$ (4 mol %) and CuI (2 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. TEA (4.0 equiv) was added by a syringe. The reaction mixture was then heated to 70 °C. A solution of the corresponding terminal alkyne (1.2 equiv) in DMF (1 mL) was added dropwise over 5 min, and the mixture was allowed to stir at 70 °C for 2 h (the reaction progress was monitored by TLC). After completion, the reaction mixture was cooled, diluted with EtOAc, and washed with satd. aq. NH_4Cl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using Hexanes-EtOAc as the eluent.

Sonogashira Coupling Procedure for the Preparation of 4h and 4i: Both 4h and 4i were synthesised using the slightly modified procedure as the reaction was performed at 50 °C and the corresponding terminal alkyne (1.2 equiv) in THF (1 mL) was added dropwise over 30 min.

Procedure for the synthesis of terminal alkyne 4o: A modified literature procedure was used.[59] To a solution of compound **4n** (0.25 mmol) in methanol (5 mL), $KF{\cdot}2H_2O$ (6 equiv) was added and the reaction mixture was stirred for 30 min at 25 °C. After the reaction was over, methanol was removed under vacuum and the residue was extracted with EtOAc (3 x 25 mL), washed with 0.1M HCl and brine, dried (anhydrous Na_2SO_4), filtered, and the solvent removed under vacuum. Purification by flash chromatography afforded the product.[60]

Sonogashira Coupling Procedure for the Preparation of 4q: This compound was synthesised using the slightly modified procedure using $PdCl_2(PPh_3)_2$ (15 mol %) and the reaction was carried at 80 °C.

Sonogashira Coupling Procedure for the Preparation of 4s-4t: General Sonogashira was followed with the difference that DCE was used as solvent.

tert-butyl (2-(phenylethynyl)benzoyl)carbamate **(4a):** Yield: (14.4 mg, 18%); Yellow Solid; TLC R_f = 0.5 (20% EtOAc:Hexanes, UV); mp 108-110 °C; IR ($CHCl_3$, cm^{-1}) 3265, 2978, 1761, 1693, 1220; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.28 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.62-7.59 (m, 3H), 7.52-7.42 (m, 2H), 7.40-7.34 (m, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.9, 149.3, 139.3, 133.2, 131.6, 131.4, 130.4, 129.2, 128.9, 128.3, 121.7, 119.8, 86.5, 82.5, 67.4, 27.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_3$ 322.1438; Found 322.1449.

2-(phenylethynyl)benzamide **(4b):**[61] Yield: (51.3 mg, 95%); Yellow Solid; TLC R_f = 0.26 (30% EtOAc:Hexanes, UV); mp 146-148 °C; ^{1}H NMR (400 MHz, DMSO) δ = 7.82 (s, 1H), 7.62-7.60 (m, 2H), 7.58-7.55 (m, 1H), 7.54-7.52 (m, 2H), 7.49-7.47 (m, 2H), 7.46-7.45 (m, 1H), 7.44-7.43 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 169.5, 139.9, 132.9, 131.7, 130.0, 129.3, 129.1, 129.0, 128.1, 122.9, 120.2, 93.2, 88.5; MS (*m/z*) 222 $(M+H)^+$.

2-(p-tolylethynyl)benzamide **(4c):**[62] Yield: (38.2 mg, 65%); Yellow Solid; TLC R_f = 0.30 (30% EtOAc:Hexanes, UV); mp 142-144 °C; ^{1}H NMR (400 MHz, DMSO) δ = 7.82 (s, 1H), 7.59-7.54 (m, 3H), 7.47-7.40 (m, 4H), 7.26 (d, *J* = 7.88 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 169.5, 139.7, 139.1, 132.8, 131.6, 130.0, 129.8, 128.8, 128.1, 120.3, 119.9, 93.4, 87.9, 21.5; MS (*m/z*) 236 $(M+H)^+$.

2-(m-tolylethynyl)benzamide **(4d):** Yield: (40.6 mg, 69%); Yellow Solid; TLC R_f = 0.30 (30% EtOAc:Hexanes, UV); mp 128-129 °C; IR ($CHCl_3$, cm^{-1}) 3374, 3177, 2902, 2208, 1644; ^{1}H NMR (400 MHz, DMSO) δ = 7.83 (s, 1H), 7.61-7.56 (m, 3H), 7.50-7.43 (m, 2H), 7.35-7.32 (m, 3H), 7.26-7.24 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 169.5,

139.9, 138.4, 132.8, 132.1, 130.0, 130.0, 129.0, 128.9, 128.8, 128.1, 122.8, 120.2, 93.3, 88.2, 21.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}NO$ 236.1070; Found 236.1068.

2-((4-methoxyphenyl)ethynyl)benzamide **(4e)**:[61] Yield: (39.6 mg, 63%); Yellow Solid; TLC R_f = 0.23 (30% EtOAc:Hexanes, UV); mp 123-124 °C; ^{1}H NMR (400 MHz, DMSO) δ = 7.82 (s, 1H), 7.58-7.55 (m, 3H), 7.48-7.44 (m, 4H), 7.02-6.99 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 169.5, 160.1, 139.6, 138.5, 133.3, 132.7, 130.0, 128.5, 128.2, 120.6, 114.8, 93.5, 87.2, 55.7; MS (*m/z*) 252 $(M+H)^+$.

2-((4-(dimethylamino)phenyl)ethynyl)benzamide **(4f)**: Yield: (49.6 mg, 75%); Brown yellow Solid; TLC R_f = 0.22 (30% EtOAc:Hexanes, UV); mp 151-153 °C; IR ($CHCl_3$, cm^{-1}) 3025, 2940, 2204, 1662, 1218; ^{1}H NMR (400 MHz, DMSO) δ = 7.79 (s, 1H), 7.58-7.52 (m, 3H), 7.44-7.32 (m, 4H), 6.73-6.71 (m, 2H), 2.96 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ = 169.6, 150.7, 138.9, 132.8, 132.5, 130.0, 128.2, 128.0, 121.1, 112.2, 108.9, 95.3, 86.5, 40.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}N_2O$ 265.1335; Found 265.1345.

2-((4-fluorophenyl)ethynyl)benzamide **(4g)**:[62] Yield: (39.4 mg, 66%); Yellow Solid; TLC R_f = 0.21 (30% EtOAc:Hexanes, UV); mp 159-160 °C; ^{1}H NMR (400 MHz, DMSO) δ = 7.84 (s, 1H), 7.60-7.54 (m, 5H), 7.47-7.30 (m, 2H), 7.28-7.26 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 169.5, 163.7, 161.3, 139.9, 134.1, 134.0, 132.8, 130.0, 129.0, 128.2, 120.1, 119.4, 119.4, 116.5, 116.3, 92.1, 88.3; MS (*m/z*) 240 $(M+H)^+$.

2-((4-bromophenyl)ethynyl)benzamide **(4h):** Yield: (54.7 mg, 73%); Brown yellow Solid; TLC R_f = 0.25 (30% EtOAc:Hexanes, UV); mp 178-180 °C; IR ($CHCl_3$, cm^{-1}) 3455, 3177, 2890, 2217, 1652; ^{1}H NMR (400 MHz, DMSO) δ =7.89 (s, 1H), 7.71-7.69 (m, 2H), 7.67-7.65 (m, 1H), 7.62-7.60 (m, 2H), 7.54-7.50 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ = 169.4, 139.9, 133.6, 132.9, 132.2, 130.1, 129.2, 128.2, 122.7, 122.2, 119.9, 92.0, 89.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}BrNO$ 300.0019; Found 300.0002.

2-((2-bromophenyl)ethynyl)benzamide **(4i):** Yield: (55.5 mg, 74%); White Solid; TLC R_f = 0.25 (30% EtOAc:Hexanes, UV); mp 177-179°C; IR ($CHCl_3$, cm^{-1}) 3446, 3161, 2926, 1669; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.16-8.13 (m, 1H), 7.69-7.67 (m, 1H), 7.64-7.57 (m, 2H), 7.50-7.48 (m, 3H), 7.35-7.32 (m, 1H), 7.26-7.22 (m, 2H, including solvent protons), 6.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.8, 134.3, 133.8, 133.6, 132.5, 131.0, 130.4, 130.3, 129.2, 127.2, 125.1, 124.3, 119.7, 94.2, 91.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}BrNO$ 300.0019; Found 300.0002.

2-((3-chlorophenyl)ethynyl)benzamide **(4j):**[58] Yield: (30.7 mg, 48%); Brown yellowish Solid; TLC R_f = 0.24 (30% EtOAc:Hexanes, UV); mp 139-141 °C; ^1H NMR (400 MHz, DMSO) δ = 7.87 (s, 1H), 7.63-7.57 (m, 4H), 7.50-7.48(m, 5H); ^{13}C NMR (100 MHz, DMSO) δ = 169.4, 140.1, 133.7, 133.0, 131.1, 131.1, 130.3, 130.1, 129.4, 129.3, 128.2, 124.9, 119.7, 91.5, 89.9; MS (*m/z*) 256 $(M+H)^+$, 258.

2-(oct-1-yn-1-yl)benzamide **(4k):**[63] Yield: (41.8 mg, 73%); Yellow Solid; TLC R_f = 0.32 (30% EtOAc:Hexanes, UV); mp 88-89 °C; ^1H NMR (400 MHz, DMSO) δ = 7.68 (s, 1H), 7.53-7.51 (m, 2H), 7.42-7.37 (m, 3H), 2.44-2.40 (m, 2H), 1.55-1.52 (m, 2H), 1.44-1.41 (m, 2H), 1.30-1.29 (m, 4H), 0.90-0.87 (m, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 169.4, 139.3, 133.1, 129.9, 128.1, 128.0, 121.0, 95.2, 79.5, 31.2, 28.4, 28.4, 22.4, 19.3, 14.3; MS (*m/z*) 230 $(M+H)^+$.

2-(cyclohexylethynyl)benzamide **(4l):**[62] Yield: (46.6 mg, 82%); White Solid; TLC R_f = 0.31 (30% EtOAc:Hexanes, UV); mp 119-121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.14-8.11 (m, 1H), 7.75 (s, 1H), 7.50-7.48 (m, 1H), 7.41-7.38 (m, 2H), 6.44 (s, 1H), 2.70-2.63 (m, 1H), 1.92-1.89 (m, 2H), 1.77-1.71 (m, 2H), 1.56-1.53 (m, 2H), 1.39-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 133.8, 133.6, 130.8, 130.2, 128.0, 120.9, 101.7, 79.6, 32.2, 29.8, 25.6, 24.8.

2-(cyclohex-1-en-1-ylethynyl)benzamide **(4m):**[61] Yield: (47.8 mg, 85%); White Solid; TLC R_f = 0.28 (30% EtOAc:Hexanes, UV); mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12-8.09 (m, 1H), 7.57 (s, 1H), 7.50-7.48 (m, 1H), 7.43-7.36 (m, 2H), 6.56 (s, 1H), 6.27-6.25 (m, 1H), 2.22-2.19 (m, 2H), 2.17-2.14 (m, 2H), 1.69-1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.3, 137.0, 133.9, 133.3, 130.8, 130.2, 128.2, 120.6, 119.9, 97.9, 85.2, 28.7, 25.7, 22.0, 21.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{16}NO$ 226.1226; Found 226.1214.

2-((trimethylsilyl)ethynyl)benzamide (4n):[61] Yield: (50 mg, 93%); White Solid; R_f = 0.55 (30% EtOAc:Hexanes); mp 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ =8.13-8.11 (m, 1H), 7.70 (s, 1H), 7.55-7.52 (m, 1H), 7.42-7.40 (m, 2H), 6.46 (s,1H), 0.26 (s, 9H).

2-ethynylbenzamide **(4o):**[61] Yield: (34.8 mg, 95%); Yellow Solid; TLC R_f = 0.16 (30% EtOAc:Hexanes, UV); mp 146-148 °C (lit. mp 145- 147 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08-8.06 (m, 1H), 7.60-7.58 (m, 1H), 7.49-7.43 (m, 2H), 7.34 (s, 1H), 6.30 (s, 1H), 3.52 (s, 1H).

2-(thiophen-3-ylethynyl)benzamide **(4p):**[61] Yield: (52.8 mg, 93%); White Solid; TLC R_f = 0.24 (30% EtOAc:Hexanes, UV); mp 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99-7.84 (m, 2H), 7.51-7.44 (m, 2H), 7.37-7.18 (m, 3H), 7.14-7.04 (m, 1H), 6.70 (d, *J* = 21.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.5, 139.9, 134.5, 133.3, 131.8, 130.8, 129.9, 129.6, 129.4, 128.6, 125.8, 90.8, 87.0.

4,5-dimethoxy-2-(phenylethynyl)benzamide **(4q):** Yield: (65.4 mg, 93%); Brown Solid; TLC R_f = 0.20 (50% EtOAc:Hexanes, UV); mp 148-150 °C; IR ($CHCl_3$, cm^{-1}) 3445, 3170, 2995, 1666,1216, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (s, 1H), 7.68-7.63 (m, 1H), 7.53-7.51 (m, 2H), 7.47-7.43 (m, 1H), 7.39-7.37 (m, 2H), 7.04 (s, 1H), 6.10 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 150.9, 149.5, 132.1, 132.0, 131.4, 129.1,

128.6, 128.4, 115.1, 112.9, 94.7, 88.0, 56.1, 56.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_3$ 282.1125; Found 282.1120.

N-methyl-2-(phenylethynyl)benzamide **(4r):**[45] Yield: (48 mg, 82%); White Solid; TLC R_f = 0.23 (10% EtOAc:Hexanes, UV); mp 105-106 °C (lit. mp 103-105 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ =8.02-8.00 (m, 1H), 7.59-7.56 (m, 1H), 7.52-7.50 (m, 2H), 7.43-7.30 (m, 5H), 3.06 (d, *J* = 4.8 Hz, 3H).

N-phenyl-2-(phenylethynyl)benzamide **(4s):**[45] Yield: (62.4 mg, 84%); White Solid; TLC R_f = 0.60 (20% EtOAc:Hexanes, UV); mp 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.22 (s, 1H), 8.13-8.11 (m, 1H), 7.68-7.63 (m, 3H), 7.50-7.44 (m, 4H), 7.41-7.32 (m, 5H), 7.16-7.12 (m, 1H).

2-(oct-1-yn-1-yl)-N-phenylbenzamide **(4t):**[45] Yield: (68 mg, 89%); Brownish semi-solid; TLC R_f = 0.64 (20% EtOAc:Hexanes, UV); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.43 (s, 1H), 8.09-8.07 (m, 1H), 7.69-7.67 (m, 2H), 7.50-7.48 (m, 1H), 7.40-7.34 (m, 4H), 7.16-7.12 (m, 1H), 2.51-2.47 (m, 2H), 1.62-1.55 (m, 2H), 1.44-1.36 (m, 2H), 1.28-1.21 (m, 4H), 0.89-0.85 (m, 3H).

Representative procedure for the cyclization reaction: All cyclization reactions have been performed using the appropriate alkyne starting material (0.25 mmol) in 2 mL of THF placed in an ice bath at 0 °C and flushed with Argon. 1.2 equiv *n*-BuLi (1.6 M in Hexane) was added dropwise (approx. 1 min). After 10 min, I_2 (3 equiv)/ [ICl (1.0 molar in THF)] (3 equiv), dissolved in 1 ml THF, was added dropwise (approx. 1 min) and the reaction was stirred in ice bath for 20 minutes (total reaction time 30 min). After the reaction was over, the reaction mixture was quenched with satd. aq. NH_4Cl solution, diluted with 10 mL of EtOAc, washed with 25 mL of satd. aq. $Na_2S_2O_3$ and dried (anhydrous Na_2SO_4). The solvent was evaporated

under reduced pressure and the product was isolated by chromatography on a silica gel column.

(*E*)-*tert*-butyl 1-(iodo(phenyl)methylene)-3-oxoisoindoline-2-carboxylate (5a): Yield: (30.2 mg, 27%); Yellow Solid; TLC R_f = 0.5 (10% EtOAc:Hexanes, UV); mp 171-173 °C. IR ($CHCl_3$, cm^{-1}) 2925, 2854, 1816, 1710, 1470, 1216. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.08 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.77-7.73 (m, 1H), 7.62-7.59 (m, 1H), 7.45-7.42 (m, 2H), 7.36-7.32 (m, 2H), 7.24-7.21 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 148.1, 144.3, 137.9, 133.8, 133.1, 130.2, 129.9, 129.2, 128.6, 128.3, 124.8, 124.0, 84.5, 84.0, 27.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}INO_3$ 448.0404; Found 448.0416.

(Z)-3-(iodo(phenyl)methylene)isoindolin-1-one (**5b**): Yield: (58.2 mg, 67%); Yellow Solid; TLC R_f = 0.62 (30% EtOAc:Hexanes, UV); mp 165-167 °C; IR ($CHCl_3$, cm^{-1}) 3184, 3068, 2965, 1703, 1469; ^1H NMR (400 MHz, DMSO) δ = 10.26 (s, 1H), 7.70 (d, *J* = 7.48 Hz, 1H), 7.52-7.40 (m, 6H), 7.33-7.29 (m, 1H), 6.29 (d, *J* = 7.96 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 167.9, 142.6, 139.0, 135.1, 132.5, 131.8, 129.7, 129.6, 129.6, 129.4, 123.5, 123.1, 78.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}INO$ 347.9880; Found 347.9869.

(E)-3-(iodo(phenyl)methylene)isoindolin-1-one **(5b'):** Yellow Solid; TLC R_f = 0.60 (30% EtOAc:Hexanes, UV); mp 172-173 °C; IR ($CHCl_3$, cm^{-1}) 3257, 3059, 2961, 1705, 1470; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.95 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.76-7.74 (m, 1H), 7.63-7.61 (m, 1H), 7.59 (s, 1H), 7.44-7.40 (m, 4H), 7.37-7.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0, 141.9, 136.1, 135.4, 132.0, 131.0, 130.1, 129.2, 129.1, 128.9, 123.8, 123.7, 72.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}INO$ 347.9880; Found 347.9869.

(Z)-3-(iodo(p-tolyl)methylene)isoindolin-1-one **(5c):** Yield: (64.1 mg, 71%); White Solid; TLC R_f = 0.66 (30% EtOAc:Hexanes, UV); mp 192-194 °C; IR ($CHCl_3$, cm^{-1}) 3189, 2956, 2925, 1704, 1469; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.43-7.39 (m, 1H), 7.34-7.32 (m, 2H), 7.28-7.25 (m, 3H), 6.60 (d, *J* = 8.4 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 139.4, 138.0, 137.4, 134.5, 132.1, 131.7, 129.8, 129.3, 129.2, 123.7, 123.2, 79.4, 21.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}INO$ 362.0036; Found 362.0025.

(Z)-3-(iodo(m-tolyl)methylene)isoindolin-1-one **(5d):** Yield: (80.4 mg, 89%); White Solid; TLC R_f = 0.65 (30% EtOAc:Hexanes, UV); mp 146-148 °C; IR ($CHCl_3$, cm^{-1}) 3175, 3060, 2891, 1703, 1469; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.78-7.76 (m, 2H), 7.41-7.38 (m, 1H), 7.35-7.31 (m, 1H), 7.26-7.21(m, 3H), 6.53 (d, *J* = 7.6 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 140.7, 138.9, 137.4, 134.5, 132.1, 131.7, 130.0, 130.0, 129.2, 128.9, 126.4, 123.7, 123.2, 79.1, 21.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}INO$ 362.0036; Found 362.0065.

(Z)-3-(iodo(4-methoxyphenyl)methylene)isoindolin-1-one **(5e):** Yield: (49 mg, 52%); Brown Solid; TLC R_f = 0.58 (30% EtOAc:Hexanes, UV); mp 175-177 °C; IR ($CHCl_3$, cm^{-1}) 3196, 2917, 2849, 1708, 1471, 1250; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.43-7.36 (m, 4H), 6.98-6.96 (m, 2H), 6.62 (d, *J* = 7.6 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 160.1, 137.4, 134.5, 133.2, 132.2, 131.7, 131.0, 129.2, 123.7, 123.1, 114.4, 79.4, 55.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}INO_2$ 377.9985; Found 377.9978.

(Z)-3-((4-(dimethylamino)phenyl)iodomethylene)isoindolin-1-one **(5f):** Yield: (65.4 mg, 67%); Brown Solid; TLC R_f = 0.57 (30% EtOAc:Hexanes, UV); mp 192-193 °C; IR ($CHCl_3$, cm^{-1}) 3019, 2917, 2850, 1707, 1466, 1364, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.39 (s,

1H), 8.35-8.33 (m, 1H), 7.99-7.97 (m, 1H), 7.76-7.71 (m, 1H), 7.51-7.47 (m, 1H), 7.41-7.39 (m, 3H), 6.76 (d, *J* = 8.4 Hz, 1H), 3.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.5, 150.9, 143.1, 139.1, 133.7, 131.5, 130.2, 127.6, 126.9, 125.3, 124.5, 111.2, 75.2, 40.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{16}IN_2O$ 391.0302; Found 391.0325.

(Z)-3-((4-fluorophenyl)iodomethylene)isoindolin-1-one **(5g):** Yield: (63 mg, 69%); Yellow Solid; TLC R_f = 0.55 (30% EtOAc:Hexanes, UV); mp 145-147 °C; IR ($CHCl_3$, cm^{-1}) 3193, 3068, 1708, 1471, 1229; ^{1}H NMR (400 MHz, DMSO) δ = 10.27 (s, 1H), 7.70 (d, *J* = 7.44 Hz, 1H), 7.49-7.46 (m, 3H), 7.39-7.31 (m, 3H), 6.35 (d, *J* = 7.88 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 167.9, 163.7, 139.4, 139.1, 139.1, 135.0, 132.7, 132.0, 131.9, 129.8, 123.5, 123.1, 116.8, 116.5, 77.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}FINO$ 365.9786; Found 365.9809.

(Z)-3-((4-bromophenyl)iodomethylene)isoindolin-1-one **(5h):** Yield: (43.6 mg, 41%); Yellow Solid; TLC R_f = 0.60 (30% EtOAc:Hexanes, UV); mp 164-166 °C; IR ($CHCl_3$, cm^{-1}) 3204, 3015, 1708, 1470; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80-7.78 (m, 1H), 7.74 (s, 1H), 7.60-7.56 (m, 2H), 7.45-7.42 (m, 1H), 7.33-7.28 (m, 3H), 6.60 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.1, 139.9, 138.0, 134.2, 132.4, 131.7, 131.2, 130.7, 129.5, 123.9, 123.5, 123.1, 86.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}BrINO$ 425.8985; Found 425.8978.

(Z)-3-((3-chlorophenyl)iodomethylene)isoindolin-1-one **(5j):** Yield: (70.6 mg, 74%); Brown Solid; TLC R_f = 0.59 (30% EtOAc:Hexanes, UV); mp 148-150 °C; IR ($CHCl_3$, cm^{-1}) 3192, 2961, 1709, 1471; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80-7.77 (m, 2H), 7.46-7.44 (m, 2H), 7.42-7.40 (m, 2H), 7.34-7.29 (m, 2H), 6.57 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 142.5, 138.3, 134.7, 134.2, 132.4, 131.7, 130.4, 129.7, 129.5, 129.4, 127.8, 123.9,

123.1, 75.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}ClINO$ 381.9490; Found 381.9475.

(Z)-3-(1-iodoheptylidene)isoindolin-1-one **(5k):** Yield: (66.6 mg, 75%); Yellow Solid; TLC R_f = 0.69 (30% EtOAc:Hexanes, UV); mp 88-89 °C; IR ($CHCl_3$, cm^{-1}) 3191, 2955, 2927, 2856, 1700, 1471; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.86-7.84 (m, 1H), 7.80-7.78 (m, 1H), 7.68 (s, 1H), 7.66-7.60 (m, 1H), 7.55-7.51 (m, 1H), 1.75-1.67 (m, 2H), 1.46-1.43 (m, 2H), 1.36-1.34 (m, 6H), 0.92-0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8, 135.9, 134.0, 132.5, 132.2, 129.0, 124.2, 123.0, 89.9, 40.1, 31.5, 29.5, 28.3, 22.5, 14.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{19}INO$ 356.0506; Found 356.0541.

(Z)-3-(cyclohexyliodomethylene)isoindolin-1-one **(5l):** Yield: (83 mg, 94%); White Solid; TLC R_f = 0.66 (30% EtOAc:Hexanes, UV); mp 118-119 °C; IR ($CHCl_3$, cm^{-1}) 3186, 2927, 2853, 1697, 1471; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.87-7.79 (m, 3H), 7.65-7.58 (m, 1H), 7.54-7.50 (m, 1H), 2.76-2.72 (m, 1H), 1.90-1.88 (m, 2H), 1.78-1.71 (m, 2H), 1.54-1.48 (m, 4H), 1.29-1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8, 134.7, 134.1, 132.5, 132.3, 129.1, 124.3, 123.0, 102.1, 42.7, 34.5, 25.8, 25.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{17}INO$ 354.0349; Found 354.0371.

(Z)-3-(cyclohex-1-en-1-yliodomethylene)isoindolin-1-one **(5m):** Yield: (50 mg, 57%); White Solid; TLC R_f = 0.65 (30% EtOAc:Hexanes, UV); mp 165-167 °C; IR ($CHCl_3$, cm^{-1}) 3159, 3015, 2932, 2854, 1711, 1652, 1465; ^1H NMR (400 MHz, $CDCl_3$) δ = 10.8 (s, 1H), 8.35-8.33 (m, 1H), 7.93-7.91 (m, 1H), 7.74-7.70 (m, 1H), 7.51-7.47 (m, 1H), 5.96-5.94 (m, 1H), 2.34-2.32 (m, 2H), 2.26-2.24 (m, 2H), 1.88-1.83 (m, 2H), 1.78-1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.4, 145.3, 138.9, 136.6, 133.6, 132.5, 131.2, 127.4, 126.9, 124.6, 74.5, 27.6, 25.0, 22.4, 21.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}INO$ 352.0193; Found 352.0175.

(Z)-3-(iodomethylene)isoindolin-1-one **(5o):** Yield: (56 mg, 82%); White Solid; TLC R_f = 0.33 (10% EtOAc:Hexanes, UV); mp 191-193 °C; IR ($CHCl_3$, cm^{-1}) 3019, 2880, 1709, 1467; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.80 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 1H), 7.84-7.79 (m, 1H), 7.68-7.64 (m, 1H), 7.61-7.56 (m, 1H), 6.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 140.7, 135.3, 132.5, 132.3, 130.2, 124.3, 123.8, 54.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for C_9H_7INO 271.9567; Found 271.9563.

(Z)-3-(iodo(thiophen-3-yl)methylene)isoindolin-1-one **(5p):** Yield: (66.3 mg, 75%); Yellow Solid; TLC R_f = 0.58 (30% EtOAc:Hexanes, UV); mp 162-164 °C; IR ($CHCl_3$, cm^{-1}) 3208, 2928, 1708, 1471; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 4.0 Hz, 1H), 7.72 (s, 1H), 7.48-7.42 (m, 3H), 7.34-7.30 (m, 1H), 7.15 (d, *J* = 4.8 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0, 140.7, 138.4, 134.6, 132.3, 131.4, 129.4, 128.3, 126.8, 125.8, 123.8, 122.9, 72.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_9INOS$ 353.9444; Found 353.9426.

(Z)-3-(iodo(phenyl)methylene)-5,6-dimethoxyisoindolin-1-one **(5q):** Yield: (79.4 mg, 78%); Yellow Solid; TLC R_f = 0.48 (50% EtOAc:Hexanes, UV); mp 206-207 °C; IR ($CHCl_3$, cm^{-1}) 3220, 3019, 2838, 1701, 1496, 1217; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.46-7.45 (m, 4H), 7.41-7.39 (m, 1H), 7.17 (s, 1H), 5.86 (s, 1H), 3.88 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 152.3, 150.5, 141.1, 137.8, 129.7, 129.1, 129.0, 128.5, 124.6, 105.2, 104.7, 76.0, 56.1, 55.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{15}INO_3$ 408.0091; Found 408.0079.

N-((E)-3-(iodo(phenyl)methylene)isobenzofuran-1(3H)-ylidene)methanamine **(5r):**[45] Yield: (42.4 mg, 47%); White Solid; TLC R_f = 0.27 (30% EtOAc:Hexanes, UV); mp 121-124 °C; IR ($CHCl_3$, cm^{-1}) 3017, 2877, 1708, 1217; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.76 (d, *J* = 8.4

Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.58-7.53 (m, 3H), 7.49-7.45 (m, 1H), 7.33-7.29 (m, 1H), 7.22-7.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.7, 147.1, 140.5, 135.9, 131.6, 131.1, 130.5, 130.1, 128.2, 127.9, 124.9, 122.9, 73.4, 34.9.

Procedure for the Synthesis of (*Z*)-2-benzyl-3-(iodo(phenyl)methylene)isoindolin-1-one (6): To the ice cooled suspension of NaH (60 % dispersion in oil) (1.2 equiv) in DMF was added **5b** (0.25 mmol). After 15 min, Benzyl bromide (1.1 equiv) was added slowly. Reaction was stirred for 2 h. After completion, 1 mL methanol was added and the reaction mixture was diluted with EtOAc, and washed with satd. aq. NH_4Cl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using Hexanes-EtOAc as the eluent. Yield: (92.2 mg, 87%); White Solid; TLC R_f = 0.66 (30% EtOAc:Hexanes, UV); mp150-152°C; IR ($CHCl_3$, cm^{-1}) 3068, 3029, 2928, 1709, 1470; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76-7.74 (m, 1H), 7.31-7.05 (m, 13H)(solvent peak included), 5.89 (d, *J* = 8.0 Hz, 1H), 5.61 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =169.5, 145.0, 139.4, 137.6, 137.4, 132.1, 129.3, 129.1, 129.0, 128.9, 128.4, 128.1, 126.9, 126.4, 123.8, 122.9, 87.1, 44.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{17}INO$ 438.0349; Found 438.0363.

Procedure for the Synthesis of (*Z*)-3-(3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-ylidene)isoindolin-1-one (7): To a solution of the **5b** (0.25 mmol) in DMF (2 mL) were added $PdCl_2(PPh_3)_2$ (4 mol %) and CuI (3 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. TEA (4.0 equiv) was added by a syringe. The reaction mixture was heated to 80 °C. A solution of the 4-Ethynylanisole (1.2 equiv) in DMF (1 mL) was added dropwise over 5 min, and the mixture was allowed to stir at 80 °C for 2 h (the reaction progress was monitored by TLC). After cooling, the reaction mixture was diluted with EtOAc, and washed with satd. aq. NH_4Cl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude

product, which was purified by column chromatography on silica gel using Hexane-EtOAc as the eluent. Yield: (68.5 mg, 78%); Yellow Solid; TLC R_f = 0.67 (30% EtOAc:Hexanes, UV); mp 194-195°C; IR ($CHCl_3$, cm^{-1}) 3183, 3019, 2928, 2184, 1703, 1471, 1249; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.74(s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.58-7.55 (m, 2H), 7.51-7.46 (m, 5H), 7.42-7.38 (m, 1H), 7.30-7.27 (m, 1H), 6.90-6.86 (m, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 160.0, 138.0, 135.7, 135.0, 133.2, 131.8, 130.6, 129.7, 129.2, 128.9, 128.6, 123.6, 114.6, 114.1, 105.4, 99.7, 86.5, 55.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{18}NO_2$ 328.1332; Found 328.1355.

Procedure for the Synthesis of (*Z*)-3-(phenyl(thiophen-2-yl)methylene)isoindolin-1-one (8): To a suspension of **5b** (0.25 mmol) and thiophen-2-ylboronic acid (1.2 equiv) in DMF:H_2O (4:1) 2 ml was added $PdCl_2$ (5 mol %) and Cs_2CO_3 (1.4 equiv). The reaction was heated to 80°C for 2 h (the reaction progress was monitored by TLC). After cooling, the reaction mixture was diluted with EtOAc, and washed with satd. aq. NH_4Cl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using Hexanes-EtOAc as the eluent. Yield: (65.2 mg, 86%); White Solid; TLC R_f = 0.47 (30% EtOAc:Hexanes, UV); mp 158-160 °C; IR ($CHCl_3$, cm^{-1}) 3196, 3081, 1700, 1607, 1472, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.50-7.47(m, 3H), 7.41-7.35 (m, 4H), 7.24-7.20 (m, 1H), 7.08-7.06 (m, 1H), 7.03-7.02 (m, 1H), 6.35 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.9, 142.8, 138.8, 136.8, 131.9, 131.7, 130.4, 130.1, 129.0, 128.8, 128.6, 128.3, 127.7, 127.2, 123.7, 123.4, 117.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{14}NOS$ 304.0791; Found 304.0810.

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ASSOCIATED CONTENT

Supporting information

Supplementary data including the Table S1 (Aminocyclization of 2-Phenylethynyl-benzamide: Optimization Studies) and Table S2 (Preparation of 2-(1-alkynyl)benzamides), NMR spectra, and analytical data (for compounds 4a-4t and 5a-5t, 6-8) is available free of charge via the Internet or from the author. Also, the crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1561244. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223 33603; e-mail: deposit@ccdc.cam.ac. uk).

AUTHOR INFORMATION

Corresponding Author

Tel.: +91-8800665868; E-mail: saurabh.mehta@dtu.ac.in

Notes

The authors declare no competing financial interest.

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