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# An environmentally benign and atom-economical protocol for the regioselective synthesis of isoquinolones from *o*-alkynylaldehydes†

Muskan and Akhilesh K. Verma *

**An environmentally benign, transition metal- and base-free, iodine-promoted atom-economical protocol for the synthesis of the privileged isoquinolone scaffold *via* regioselective intramolecular iodoamidation of alkynes under mild conditions has been developed. The present synthetic approach being metal, additive, and solvent-free adheres to the principles of green chemistry, as it tends to minimize waste production. The synthesized product contains an iodo as well as a free –OH group that is readily accessible for subsequent transformation to afford biologically relevant compounds.**

Contemporary synthetic chemistry is witnessing a paradigm shift towards more efficient, sustainable, and environmentally benign protocols for the construction of biologically relevant molecules.[1] A sustainable and environmentally accountable approach in the realm of chemistry signifies a commitment to conduct chemical processes and industrial research in a manner that prioritizes the well-being of the planet, human health, and future generations.[2] One of the most notable developments in this context is the emergence of metal and solvent-free synthesis as a cornerstone of modern organic chemistry.[3] Metal-based catalysts are particularly effective at accelerating chemical reactions, but because of their toxicity and potential for bioaccumulation, they pose significant ecological risks and generate a significant amount of hazardous waste.[4] Solvents not only increase the cost of production, but also some solvents especially volatile organic compounds (VOCs) have adverse environmental effects and can contribute to air pollution.[5] Metal and solvent-free reactions adhere well with green chemistry principles as they typically generate less waste.[6] The reduction in metal and solvent usage directly contributes to a smaller environmental footprint, which is a critical consideration in modern synthetic chemistry.

*Synthetic Organic Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi-110007, India. E-mail: averma@acbr.du.ac.in*

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Isoquinolone, a versatile N-heterocyclic compound, holds a prominent place in the realm of organic chemistry. It serves as a fundamental structural unit in various pharmaceutically relevant as well as naturally occurring compounds, particularly alkaloids (Fig. 1).[7] In order to expand the biological spectrum of isoquinolone, great efforts have been made towards the development of new synthetic protocols for the construction of this privileged motif. The metal-catalyzed annulation reaction between 2-halobenzamide derivatives and alkynes is the most prevalent method for the synthesis of isoquinolone derivatives.[8] While being efficient and versatile, these transformations are accompanied by certain limitations including pricey and toxic metal-based catalytic systems like palladium,[9] rhodium,[10] ruthenium,[11] nickel,[12] copper,[13] *etc.* as well as the use of environmentally hazardous organic solvents. Electrophilic annulation of *ortho*-(1-alkynyl) benzamides is another alternative for the synthesis of isoquinolones.[14]

On the other hand, *ortho*-alkynyl aldehydes as versatile synthons have been well explored for the synthesis of numerous heterocycles and carbocycles (Scheme 1).[15] However, the transformation of *ortho*-alkynyl aldehydes for the construction of isoquinolones is quite rare. Chiba[16] *et al.* achieved the syn-

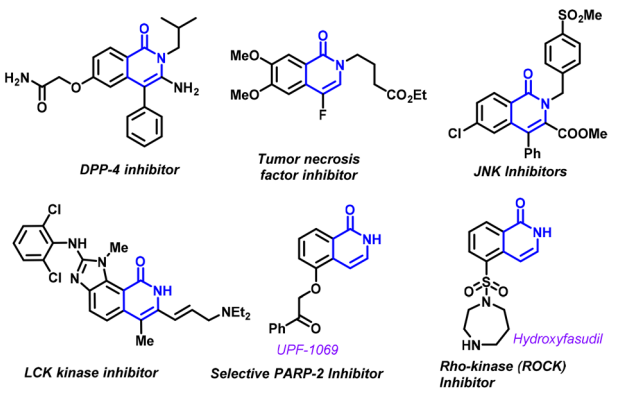
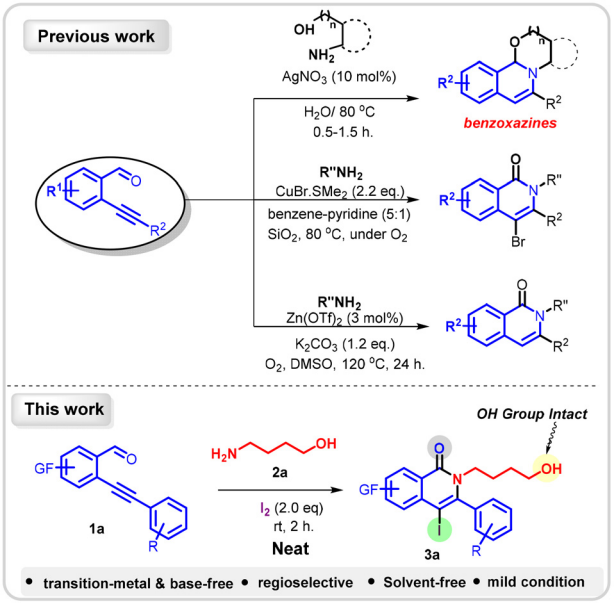



**Fig. 1** Biologically active isoquinolone cores.



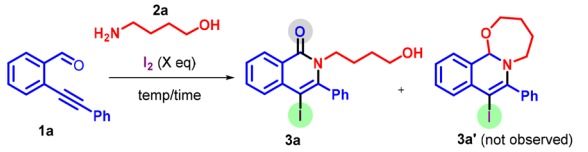

**Scheme 1** Previous and present work.

thesis of isoquinolones *via* cyclocondensation of *ortho*-alkynyl aldehydes and primary amines in the presence of an excess amount of CuBr·$SMe_2$ and $SiO_2$ along with the benzene–pyridine solvent system (Scheme 1b). The group of Wen[17] and co-workers demonstrated the synthesis of isoquinolones through the Cu-salt catalyzed cyclization of 2-(1-alkynyl)benzaldimines under very high-temperature conditions. Hua[18] and colleagues reported $Zn(OTf)_2$ catalyzed cyclocondensation of aryl amines with *ortho*-alkynyl benzaldehydes in the presence of $Zn(OTf)_2$, base (1.2 equiv.) at 120 °C, affording isoquinolones in moderate to good yields (Scheme 1c). Synthetic methodologies available for the synthesis of isoquinolones using *ortho*-alkynyl benzaldehydes have relied on metal-based catalytic systems, additives, and high temperatures and are limited to aryl amines only. Despite having impressive advances, the developed strategies still require advancement, in terms of environmentally benign conditions (metal-free, solvent-free, atom-economical, wide substrate scope with operational simplicity).

The synthesis of isoquinolones from *ortho*-alkynylbenzaldehydes using aliphatic amino alcohols has remained elusive. Considering the notable lack of procedures and in continuation of our ongoing work[19] using *ortho*-alkynyl benzaldehydes, herein we report an environmentally benign, transition metal- and base-free, atom-economical protocol for the synthesis of the privileged isoquinolone scaffold *via* regioselective intramolecular iodoamidation of alkynes under mild conditions. The present methodology is advantageous over the hitherto known strategies as, here, the free-OH group remains intact and is readily accessible for subsequent transformation.

We started our investigation using *o*-alkynyl aldehyde **1a**, 4-amino-1-butanol **2a**, and iodine as our model substrates (Table 1). A reaction of substrate **1a** with amino alcohol **2a** (3.0 equiv.) using 1.0 equiv. of $I_2$ and 2.0 equiv. of $K_2CO_3$ in DCM

**Table 1** Optimization of the reaction conditions[a]



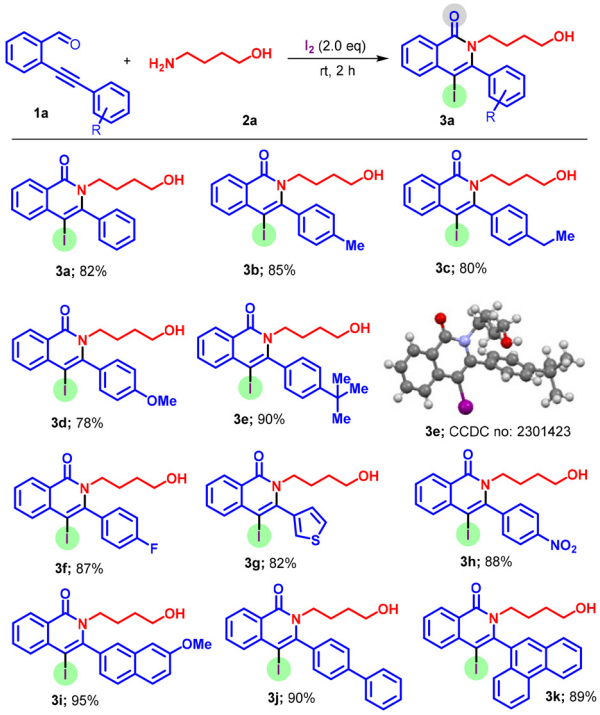

| Entry | Reagent (equiv.) | Solvent | Base | Temp./time (°C)/(h) | Yield[b] (%) **3a** |
|---|---|---|---|---|---|
| 1 | $I_2$ (1.0) | DCM | $K_2CO_3$ | 25/2 | 40 |
| 2 | $I_2$ (2.0) | DCM | $K_2CO_3$ | 25/2 | 60 |
| 3 | $I_2$ (3.0) | DCM | $K_2CO_3$ | 25/2 | 60 |
| 4 | $I_2$ (2.0) | DCM | $K_2CO_3$ | 25/4 | 58 |
| 5 | $I_2$ (2.0) | DCM | $K_2CO_3$ | 50/2 | 35 |
| 6 | $I_2$ (2.0) | DCM | $Cs_2CO_3$ | 25/2 | 52 |
| 7 | $I_2$ (2.0) | DCM | $KHCO_3$ | 25/2 | 35 |
| 8 | $I_2$ (2.0) | DCM | $NaHCO_3$ | 25/2 | 30 |
| 9 | $I_2$ (2.0) | DCM | — | 25/2 | 70 |
| 10 | $I_2$ (2.0) | THF | — | 25/2 | Trace |
| 11 | $I_2$ (2.0) | $CH_3CN$ | — | 25/2 | 55 |
| 12 | $I_2$ (2.0) | Toluene | — | 25/6 | Trace |
| 13 | $I_2$ (2.0) | DCE | — | 25/6 | 60 |
| 14 | $I_2$ (2.0) | Dioxane | — | 25/6 | Trace |
| **15** | **$I_2$ (2.0)** | — | — | **25/2** | **82** |
| 16 | ICl (2.0) | — | — | 25/2 | 40 |

[a] Reaction conditions: reactions were carried out using *o*-alkynyl benzaldehyde **1a** (0.25 mmol), 4-amino-1-butanol **2a** (0.75 mmol), and $I_2$ in an appropriate solvent (2 mL). [b] Isolated yield.

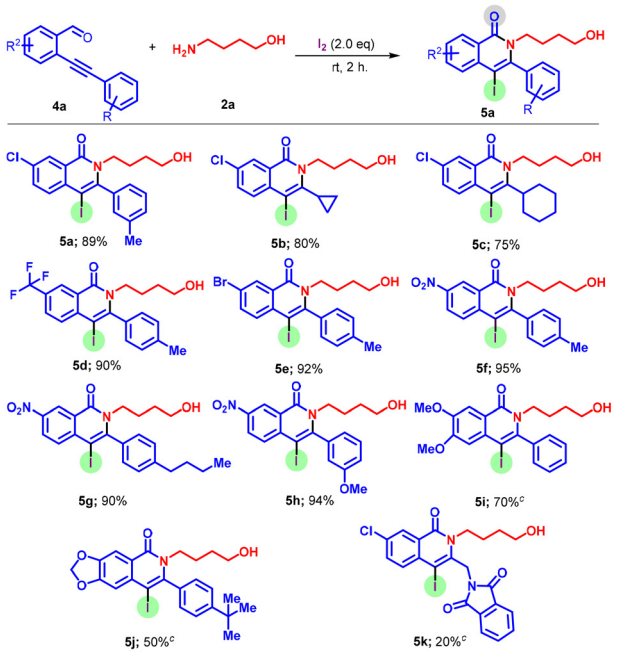
for 2 h at 25 °C gave the product **3a** in 40% yield (entry 1). The use of 2.0 equiv. of iodine provided product **3a** in 60% yield (entry 2); however a further increase of iodine and the time of the reaction did not improve the yield of product **3a** (entries 3 and 4). When the reaction was conducted at an elevated temperature, a sluggish reaction developed, and only 35% yield of product **3a** was formed (entry 5). The use of $Cs_2CO_3$, $KHCO_3$, and $NaHCO_3$ was found to be inferior for the reaction (entries 6–8). A reaction without using a base provided the desired product **3a** in 70% yield (entry 9). Subsequently, we conducted the reaction without any base, and surprisingly, the yield improved. Following this, in our quest to identify the most suitable solvent, we performed a series of reactions under different solvent conditions. Regrettably, no positive impact on the yield of the desired product was observed (entries 10–14). Consequently, we attempted the reaction under neat conditions and observed the product **3a** in 82% yield (entry 15). The use of ICl resulted in a lower yield of the cyclized product (entry 16).

Having established the optimal conditions, we then probed the scope of substrates with respect to readily available *ortho*-alkynyl aldehydes **1** using 4-amino-1-butanol **2** for the synthesis of the corresponding quinolones **3a–k** (Scheme 2). The reaction does not show any profound electronic effect, and both electron-rich **1b–d**, **5a**, **5g** (4-Me, 4-OMe, 4-Et, 3-Me, 4-*n*Bu) and electron-deficient **1f**, **1h** (4-F, 4-$NO_2$) substituents on the phenyl/aryl ring attached to the alkyne were found to be suitable to afford the desired products in good to excellent yields (78%–90%). Next, a diverse array of starting substrates

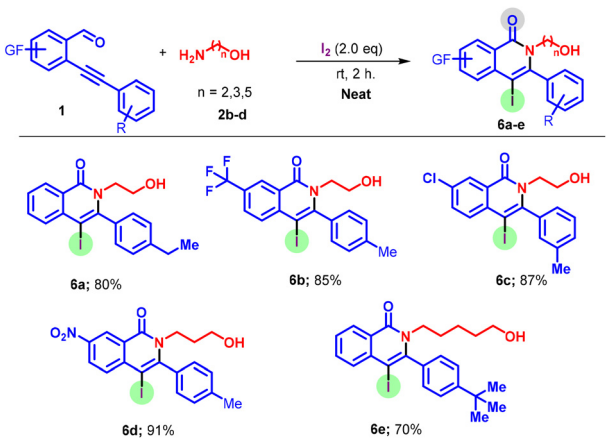
 




**Scheme 2** Scope of *ortho*-alkynylaldehydes. Reactions were performed using **1a** (0.25 mmol), **2a** (0.75 mmol), and $I_2$ (0.50 mmol) at 25 °C for 2 h. Isolated yield.




**Scheme 3** Scope of arylsubstituted *ortho*-alkynylaldehydes. Reactions were performed using **4a** (0.25 mmol), **2a** (0.75 mmol), and $I_2$ (0.50 mmol) at 25 °C for 2 h. Isolated yield. [a] For 4 h.



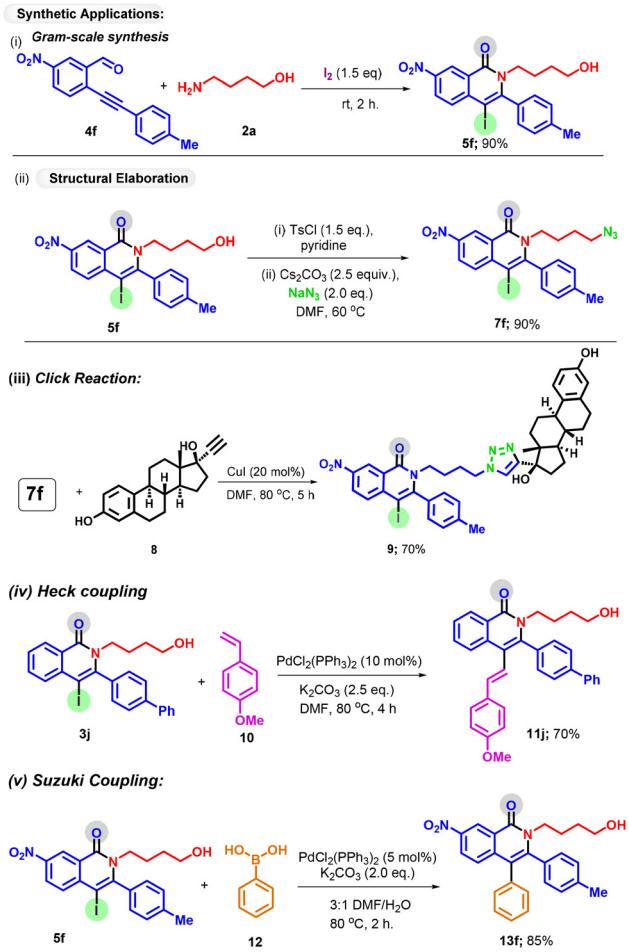

**Scheme 4** Scope of amino alcohols. Reactions were performed using **1a** (0.25 mmol), **2a** (0.75 mmol), and $I_2$ (0.50 mmol) at 25 °C for 2 h. Isolated yield.

possessing the sterically hindered alkynyl group **1i–k** were examined. To our delight, steric effects did not appear to impact the iodo-cyclization, as we obtained the respective products **3i–k** in appreciable yields. The X-ray crystal structure[20] of **3e** confirmed that the product formed is exclusively a 6-*endo-dig* cyclized product. Incredibly, a thienyl heterocyclic motif was also tolerated to afford **3g** in 75% yield.

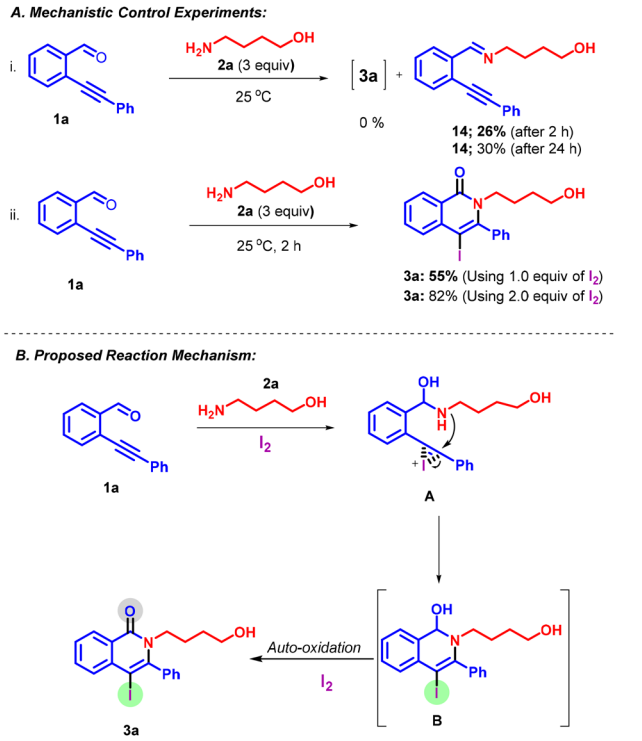
Next, we investigated how substituents on the alkyne-tethered phenyl ring influenced the reaction (Scheme 3). Substrates bearing 5-Cl, 5-Br, and 5-$CF_3$, 5-$NO_2$ groups on the phenyl were all compatible with this conversion, giving the corresponding products **5a–k** in 87%–95% yields. It is noteworthy that substrates with –$NO_2$ and –$CF_3$ at the C-5 position, with respect to the phenyl ring, delivered products with slightly high yields. Furthermore, cycloalkyl substituted *o*-alkynyl aldehyde **4b–c** also worked well and afforded the desired product **5b** and **5c** in 80% and 75% yields, respectively. The substrate-bearing methoxy at the 4- and 5-positions of the ring afforded the desired product **5i** in 70% yield. Even more challenging functional handles such as **4j** and **4k** were tolerated and provided the desired products albeit in lower yields.

Upon completion of the study of the *o*-alkynyl aldehyde scope, we then looked to examine the tolerance of the system to an array of amino alcohols for the synthesis of diverse products **6a–e** (Scheme 4). It was observed that all amino alcohols (**2b–d**) provided the required products in yields ranging from 65–82%. It is worth mentioning here that long-chain nucleophiles were also amenable to the reaction conditions which provided a diminished reaction yield.

Furthermore, to illustrate the practical utility of the reaction, we performed a gram-scale reaction, and to our delight, the desired isoquinolone was obtained in 76% yield (Scheme 5i). The robustness of the protocol was further reflected by synthetic elaboration and late-stage modification of drugs. Product **5f** bearing a free OH group was easily transformed into azide **7f** in 90% yield (Scheme 5ii). A further reaction of azide substrate **7f** with alkyne **8** afforded the triazole




**Scheme 5** Synthetic utility of products.




**Scheme 6** Control experiments and a plausible reaction pathway.

hybrid **9** in 70% yield by a click reaction. Considering the synthetic versatility of alkene and aryl groups, the synthetic utility of the iodo handle was further explored by conducting the Heck (Scheme 5iv) and Suzuki coupling (Scheme 5v) reactions, resulting in the formation of coupling products **11j** and **13f** in good yields.

To validate the mechanism of the regio- and chemoselective iodine-mediated 6-*endo-dig* ring closure, several control experiments were performed. In our first control experiment, we carried out the reaction of *ortho*-alkynyl aldehyde **1a** with amino alcohol **2a** in the absence of iodine at room temperature for 2 h and 24 h. The desired iodocyclized product **3a** was not observed, instead the formation of an imine **14** was observed only in 26% (after 2 h) and 30% (after 24 h) yields (Scheme 6a(i)), as verified by crude NMR (see the ESI† for details). This result suggests that the formation of the product proceeds *via* aminol formation. Next, to confirm the use of 2.0 equiv. of iodine, we performed two sets of reactions using 1.0 and 2.0 equiv. of iodine under standard reaction conditions (Scheme 6a(ii)). On using 1.0 equiv. of iodine, we observed the formation of product **3a** in 55% yield; however, on using 2.0 equiv. of iodine, product **3a** was observed in 82% yield. This control experiment suggests the use of the second equiv. of iodine for the autooxidation of intermediate **B** into product **3a**.

On the basis of control experiments and literature studies, we presented a plausible mechanistic pathway for the regio- and chemoselective formation of product **3a** along with the free OH group in Scheme 6b. The reaction was initiated by the nucleophilic attack of the amine **2a** to the CHO group of **1a** to give the unstable species (hemiaminal) **A**. Subsequently, hemiaminal **A** undergoes a regioselective intramolecular 6-*endo-dig* iodoamidation with an electrophilically activated alkyne, leading to the generation of iodo species **B** (Scheme 6b). The presumed intermediate **B**, upon subsequent oxidation, yielded the desired product **3a**. $I_2$ serves dual purposes in this context, acting as the catalyst for N–C bond-forming cyclization as well as the oxidant (species **B** to product **3a**) under the current reaction conditions.

## Conclusions

In conclusion, we have unveiled a straightforward transition-metal, additive, and solvent-free strategy for the synthesis of the pharmaceutically important isoquinolone motif *via* regioselective intramolecular iodoamidation of alkynes. Synthetically, the strategy appears to hold much promise as this protocol provides an environmentally benign and atom-economical route for the facile construction of functionalized isoquinolones that have not been easily accessible. Notably, it is the first report that involves the use of amino alcohols as the

coupling partner with *ortho*-alkynyl aldehydes to synthesize diverse isoquinolones. The incorporation of the free-OH group opens the gateway for a more sustainable and efficient synthesis of diverse isoquinolone derivatives, fostering the development of novel drug candidates and expanding the scope of chemical synthesis in the pharmaceutical industry.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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20 Crystallographic data for compound **3e** has been deposited with the Cambridge Crystallographic Data Centre. CCDC deposit number for compound **3e** is 2301423.†