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PII: S0040-4039(18)30772-X
DOI: https://doi.org/10.1016/j.tetlet.2018.06.030
Reference: TETL 50068

To appear in: *Tetrahedron Letters*

Received Date: 12 April 2018
Revised Date: 8 June 2018
Accepted Date: 11 June 2018

Please cite this article as: Liu, X., Deng, G., Liang, Y., Selective Synthesis of Benzo[4,5]imidazo[2,1-*a*]isoquinolines via Copper-catalyzed Tandem Annulation of Alkynylbenzonitriles with 2-Iodoanilines, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.06.030

Tetrahedron Letters
journal homepage: www.elsevier.com

# Selective Synthesis of Benzo[4,5]imidazo[2,1-*a*]isoquinolines via Copper-catalyzed Tandem Annulation of Alkynylbenzonitriles with 2-Iodoanilines

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

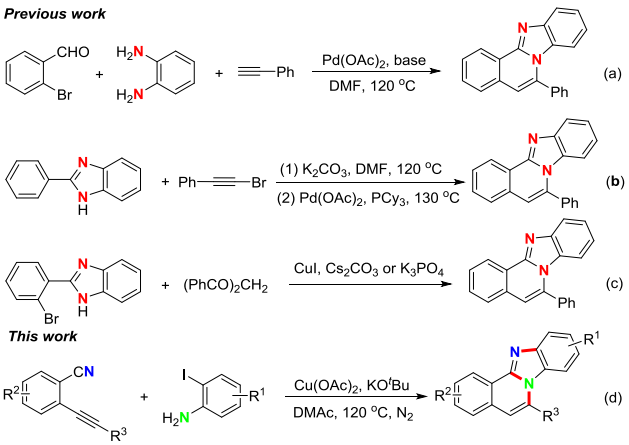
*Keywords:*
2-iodoaniline
*o*-alkynylbenzonitrile
Nitrogen heterocycles
cycloaddition
tandem reaction

ABSTRACT

An efficient copper-catalyzed cascade cyclization reaction for selectively synthesizing a variety of benzo[4,5]imidazo[2,1-*a*]isoquinoline derivatives has been developed. The reaction features the formation of three different C−N bonds in sequence. In the presence of $Cu(OAc)_2$ and KO$^t$Bu, *o*-alkynylbenzonitriles and 2-iodoanilines proceeded smoothly to obtain the corresponding benzo[4,5]imidazo[2,1-*a*]isoquinolines in moderate to good yields.



Isoquinoline-fused benzimidazoles are an important class of heterocycles due to their widespread application in natural products,[1] pharmaceuticals,[2] and synthetic materials.[3] Therefore, great efforts have been made to develop methods for the effective synthesis of this useful structural skeleton in recent years.[4] Benzo[4,5]imidazo[2,1-*a*]isoquinolines[5] are an important member of this tetracyclic heterocycle family and cyclization of the *o*-alkynyladehyde with *o*-phenylenediamine in the presence of various catalysts is the most common method for the preparation of this useful structural core.[6] Beyond that, there are alternative powerful approaches for synthesizing such dominant structural frameworks. For example, Yanada and co-workers have reported a one-pot method for the construction of benzimidazo[2,1-*a*]isoquinolines starting from 2-bromoarylaldehydes, terminal alkynes, and 1,2-phenylenediamines by a microwave-promoted tandem process (Scheme 1 a).[7] Li and co-workers also have developed a one-pot route for the synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines via nucleophilic addition of 2-aryl benzimidazoles to alkynylbromides (Scheme 1 b).[8] More recently, Wang and co-workers have demonstrated that copper-catalyzed C-C coupling and deacylative cyclization can be a powerful tool for the synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines (Scheme 1 c).[9] These methods afford good progress in the synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines. However, two isomers of isoquinoline-fused benzimidazoles were obtained when there are asymmetric substituents on the benzene ring of the benzimidazoles in these previous methods. Therefore, development of novel and expeditious methods for selectively synthesizing benzo[4,5]imidazo[2,1-*a*]isoquinolines is also a big challenge at present. Herein, we describe a copper-catalyzed C–N bond formation reaction for the selective synthesis of substituted benzimidazo[2,1-*a*]isoquinolines using 2-iodoanilines and *o*-alkynylbenzonitriles as substrates.




**Scheme 1** Synthesis of Benzo[4,5]imidazo[2,1-*a*] isoquinolines

Our investigation began with the reaction of *o*-alkynylbenzonitrile **1a** with 2-iodoaniline **2a** to determine the optimal reaction conditions, and the results are summarized in Table 1. Intriguingly, in the presence of KO$^t$Bu, substrates **1a** and **2a** were converted into the desired product, 6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline **3a,** in 68% yield (entry 1). Subsequently, some copper catalysts, such as CuI, CuBr, CuCl and $Cu(OAc)_2$ were tested (entries 2-5). The result indicated that $Cu(OAc)_2$ was the best catalyst for this cascade cyclization reaction, and desired product **3a** was obtained in 81%

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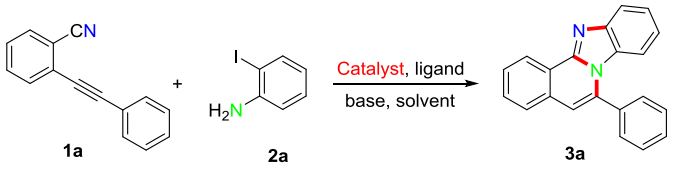
yield (entry 5). To improve the reaction performance, the effects of the ligands were evaluated, however, they all gave slightly lower yield (entries 6-9). Then, reaction conditions were further investigated and the influences of different solvents on the outcome of the model reaction were screened (entries 10-13). We found that DMAc (*N*, *N*-dimethylacetamide) was the best solvent. The yield was decreased significantly when other bases were used (entries 14-16). To our delight, when we increased the amount of **1a** to 1.2 equiv, the yield of **3a** increased to 86% (entries 17). In the end, temperature screening indicated that 120°C was the most suitable temperature for this reaction (entries 17, 18 and 19).

**Table 1.** Optimization of Reaction Conditions [a]

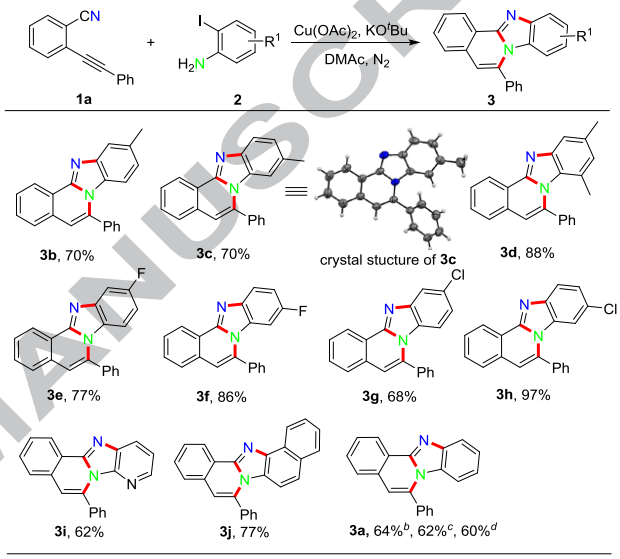



| Entry | Additive | Ligand | Solvent | Base | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 | - | - | DMAc | KO$^t$Bu | 68 |
| 2 | CuI | - | DMAc | KO$^t$Bu | 64 |
| 3 | CuBr | - | DMAc | KO$^t$Bu | 65 |
| 4 | CuCl | - | DMAc | KO$^t$Bu | 70 |
| 5 | $Cu(OAc)_2$ | - | DMAc | KO$^t$Bu | 81 |
| 6 | $Cu(OAc)_2$ | *L*-Proline | DMAc | KO$^t$Bu | 76 |
| 7 | $Cu(OAc)_2$ | TEMED | DMAc | KO$^t$Bu | 73 |
| 8 | $Cu(OAc)_2$ | DEMED | DMAc | KO$^t$Bu | 66 |
| 9 | $Cu(OAc)_2$ | 1,10-Phen | DMAc | KO$^t$Bu | 78 |
| 10 | $Cu(OAc)_2$ | - | DMF | KO$^t$Bu | 43 |
| 11 | $Cu(OAc)_2$ | - | NMSO | KO$^t$Bu | 51 |
| 12 | $Cu(OAc)_2$ | - | NMP | KO$^t$Bu | 70 |
| 13 | $Cu(OAc)_2$ | - | Toluene | KO$^t$Bu | 0 |
| 14 | $Cu(OAc)_2$ | - | DMAc | LiO$^t$Bu | 0 |
| 15 | $Cu(OAc)_2$ | - | DMAc | $Cs_2CO_3$ | 41 |
| 16 | $Cu(OAc)_2$ | - | DMAc | KOH | 35 |
| 17[c] | $Cu(OAc)_2$ | - | DMAc | KO$^t$Bu | 86 |
| 18[d] | $Cu(OAc)_2$ | - | DMAc | KO$^t$Bu | 77 |
| 19[e] | $Cu(OAc)_2$ | - | DMAc | KO$^t$Bu | 72 |

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), [Cu] (10 mmol %), ligand (20 mol%), base (0.9 mmol), solvent (1 mL), under a $N_2$ atmosphere in a sealed Schlenk tube, at 120 °C for 12 h. [b] Isolated yield. [c] **1a** (0.36 mmol). [d] At 100 °C. [e] At 140 °C.

With the optimized reaction conditions in hand, we proceeded to explore the scope of 2-iodoanilines and the results are summarized in Table 2. To our delight, not only were functional groups such as methyl, fluoro and chloro groups compatible with the reaction, but also the corresponding single benzo[4,5]imidazo[2,1-*a*]isoquinolines were selectively obtained in all of those reactions. For example, 4- or 5-methyl substituted *o*-iodoanilines both showed high reactivity and selectively giving **3b** and **3c** both in 70% yield. The absolute configuration of **3c** was unambiguously established by *X*-ray crystallographic analysis (CCDC 1817529). In addition, substrate **2d** with two methyl substituents at the 4- and 6- positions were also viable for producing **3d** in 88% yield. Notably, 4- or 5-chloro substituent on the phenyl ring were well tolerated, affording **3g** and **3h** in 68% and 97% yield, respectively, which gave the chance for futher functionlization through transition-metal-catalyzed coupling reactions. Furthermore, 3-iodopyridin-2-amine was also tolerated under the reaction conditions, affording the corresponding product **3i** in 62% yield. It was noteworthy that 1-iodonaphthalen-2-amine **2j** performed well under the standard conditions, giving the corresponding poly cyclic ring product **3j** in 77% yield, which makes an aryne mechanism in these cases unlikely.[10] Fortunately, when the halogen atom on the aromatic ring was replaced with F, Cl and Br, the reaction proceeded smoothly to obtain the corresponding 6-arylbenzo[4,5]imidazo[2,1-*a*] isoquinoline **3a** in 64%, 62%, 60% yield, respectively.

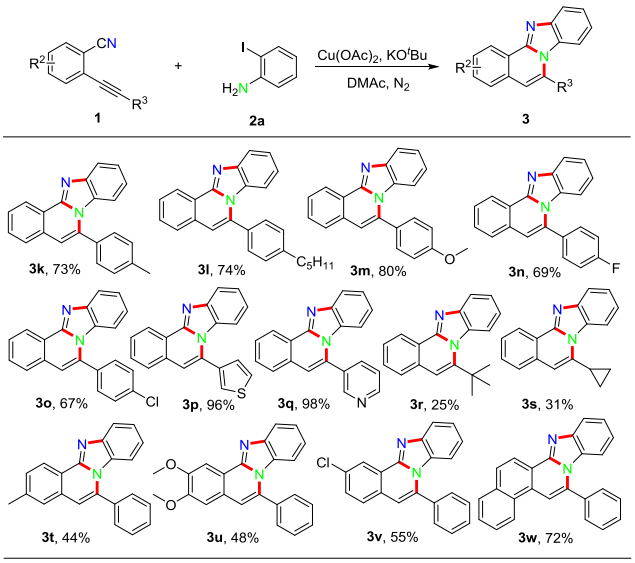
**Table 2.** Substrate Scope of the 2-Halogenoaniline [a]




[a] Reaction conditions: **1a** (0.36mmol), **2** (0.3 mmol), $Cu(OAc)_2$ (10 mmol %), KO$^t$Bu (0.9 mmol), DMAc (1 mL), under the $N_2$ atmosphere in a sealed Schlenk tube, at 120 °C for 12 h. [b] The substrate = 2-fluoroaniline, [c] The substrate = 2-chloroaniline, [d] The substrate = 2-bromoaniline.

Inspired by the above results, we turned our attention to exploring the scope of the 2-(phenylethynyl)benzonitriles in the presence of *o*-iodoaniline **2a** (0.3 mmol), $Cu(OAc)_2$ (10 mol%) and KO$^t$Bu (0.9 mmol) in DMAc (1 mL) under $N_2$ atmosphere at 120 °C for 12 hours. The results are summarized in table 3. First, we investigated the scope of substituents on the aryl ring of the terminal alkyne. The results showed that substrates bearing either electron-donating (R = Me, $^n$amyl, OMe) or electron-withdrawing groups (R = F, Cl) furnished the transformation, producing the desired benzo[4,5]imidazo[2,1-*a*]isoquinolines in good to excellent yields (**3k**-**3o**). Notably, thiophen-3-yl-substituted alkyne and pyridine-3-yl-substituted alkyne were also suitable for the tandem cyclization reaction, affording the corresponding products in 96% and 98% yields, respectively (**3p** and **3q**). As for low activity aliphatic alkyne substituted substrate **1r** and **1s**, the corresponding product **3r** and **3s** could also successfully be obtained, albeit in a low yield. Next, substrates with Me, two OMe or Cl on the aryl ring linked to cyano group were compatible with the standard conditions, producing **3t**, **3u** and **3v** in moderate yield. Finally, we examined the substrate 1-(phenylethynyl)-2-naphthonitrile **1w**, affording the poly-cyclic ring product in 72% yield.

**Table 3.** Substrate Scope of the *o*-Alkynylbenzonitrile [a]




[a] Reaction conditions: **1** (0.36 mmol), **2a** (0.3 mmol), $Cu(OAc)_2$ (10 mmol %), KO$^t$Bu (0.9 mmol), DMAc (1 mL), under the $N_2$ atmosphere in a sealed Schlenk tube, at 120 °C for 12 h.

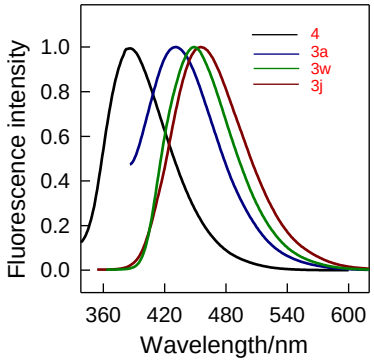
Spectroscopic properties of benzo[4,5]imidazo[2,1-*a*]isoquinolines were further investigated by measurements of three representative compounds **3a**, **3w**, and **3j**. Photochemical data shown in Table 4 revealed that, due to structure hybrid characteristic, typical absorption of both isoquinoline and benzimidazoles could not be found in the absorption spectra, but they possessed absorption bands centered at about 338-375 nm. Moreover, as depicted in Figure 1, in comparison with the maximum emission peaked at 386 nm of isoquinoline in DCM solution, the bathochromic-shift fluorescence appeared for these derivatives, which would be attributed to their improved conjugate structure.

**Table 4.** Spectroscopic Properties of 6-Phenylbenzo[4,5]-imidazo[2,1-*a*]isoquinolines [a]

| Compd | $Abs_{max}$ (nm) | $\varepsilon\times10^3$(L·mol$^{-1}$·cm$^{-1}$) | Emission $_{max}$(nm) | Stokes shift(nm) | φf[b] |
|---|---|---|---|---|---|
| **3a** | 308 | 6.90 | 431 | 83 | 0.584 |
| | 348 | 6.77 | | | |
| **3w** | 375 | 6.10 | 449 | 74 | 0.778 |
| | 290 | 6.52 | 455 | | 0.578 |
| **3j** | 309 | 8.29 | | 117 | |
| | 338 | 8.14 | | | |
| **4** | 237 | 6.82 | 386 | - | - |
| **5** | 241 | 7.03 | - | - | - |

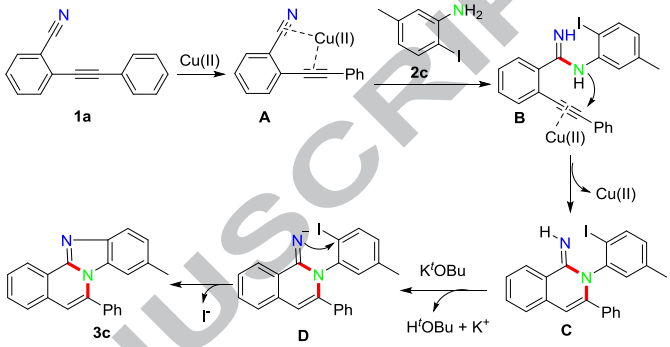
[a] Measured in DCM. [b] Measured with quinine sulphate as a standard. **4** (isoquinoline), **5** (benzimidazole).

**Figure 1.** Normalized Fluorescence (bottom) Spectra




**4** (black), **3a** (blue), **3w** (green) and **3j** (red) measured in DCM.

According to the literature,[10] a plausible reaction mechanism is outlined in Scheme 2. First, the alkynylbenzonitrile **1a** is activated by copper catalyst to form the Cu(Ⅱ) complex **A**. Then, 2-iodo-5-methylaniline **2c** reacts with the activated alkynylbenzonitrile to produce the intermediate **B** *via* nucleophilic addition reaction.[11] The intermediate **B** undergoes an intramolecular nucleophilic addition on the copper-activated triple bond, giving rise to the cyclic intermediate C. Finally, the intermediate **C** undergoes a KO$^t$Bu-initiated deprotonation to generate carbanion **D**,[12] which leads to the desired product **3c** via a nucleophilic aromatic substitution reaction.




**Scheme 2.** Plausible Mechanism

In summary, we have demonstrated a novel copper-catalyzed method for the synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines from *o*-alkynylbenzonitriles and 2-iodoanilines. In this reaction, three different C–N bonds are sequentially formed through the cleavage of one C-I bond and two N-H bonds. Notably, this project can selectively synthesize a series of isoquinoline-fused benzimidazoles, which make it appealing for application to the synthesis of important natural products, pharmaceuticals, and functional materials.

## Acknowledgments

This work was supported by the Natural Science Foundation of China (21572051, 21602057), Education Department of Hunan Province (15A109), Opening Fund of Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research (Ministry of Education of China), Hunan Normal University (KLCBTCMR201707, KLCBTCMR201708), Hong Kong Scholars program (XJ2017009) for financial support.

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**Supplementary Material**

Supplementary data (experimental procedures and characterization data for all new compounds and copies of NMR spectra) associated with this article can be found, in the online version.

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## Graphical Abstract

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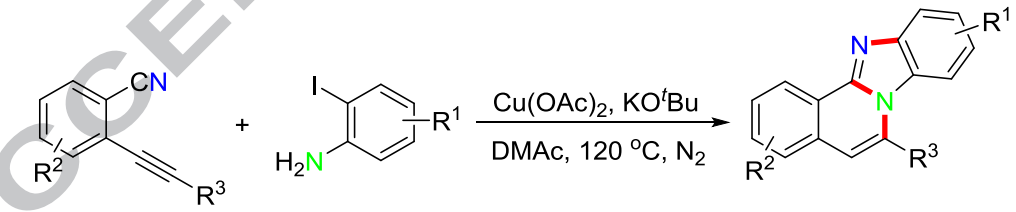


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Highlights

- Broad substrate scope.
- Simple operation and mild conditions.
- Selective synthesis of a series of benzo[4,5]imidazo[2,1-*a*]isoquinoline derivatives in moderate to good yields.