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# An efficient synthesis of indol-3-yl benzonaphthyridines via copper(II) triflate-catalyzed heteroannulation

K. S. Prakash, Rajagopal Nagarajan *

*School of Chemistry, University of Hyderabad, Hyderabad 500 046, India*

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ABSTRACT

An efficient and convenient method for the synthesis of indol-3-yl benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines via copper(II) triflate-catalyzed heteroannulation is reported. This method gives new analogues of indole containing benzonaphthyridines from easily accessible starting materials. This reaction proceeds under mild conditions.



Marine sponges are the source of many biologically active nitrogen heterocyclic constituents, which possess a series of 1*H*-benzo[*de*][1,6]-naphthyridines.[1] Aaptamine (**1**) was first isolated in 1982 by Nakamura et al.[2] Naphthyridines and their benzo/hetero fused analogues gained considerable attention due to their wide spectrum of biological activities[3] such as anticancer,[3a,b] anti-HIV-1 integrase inhibitors,[3c] antiproliferative activity,[3d] antimicrobial,[3e] and adrenoceptor blocking activities.[3f] These are reported as allosteric inhibitors of Akt1 and Akt2,[3g] and antagonists of 5-HT4 receptors.[3h] Furthermore, isoaaptamine (**2**), was isolated from sponge in the genus *Suberites* by Fedoreev et al.[4] Later, it was isolated from *Aaptos aaptos*[5a,b] and it has been found to have a PKC inhibitor[5c] and to inhibit growth of cancer cells.[5b,c] Pettit et al. showed that isoaaptamine (**2**) has significant activity against murine P388 lymphocytic leukemia cells ($ED_{50}$ 0.28 μg/mL) and a panel of six human cancer cell lines.[6]

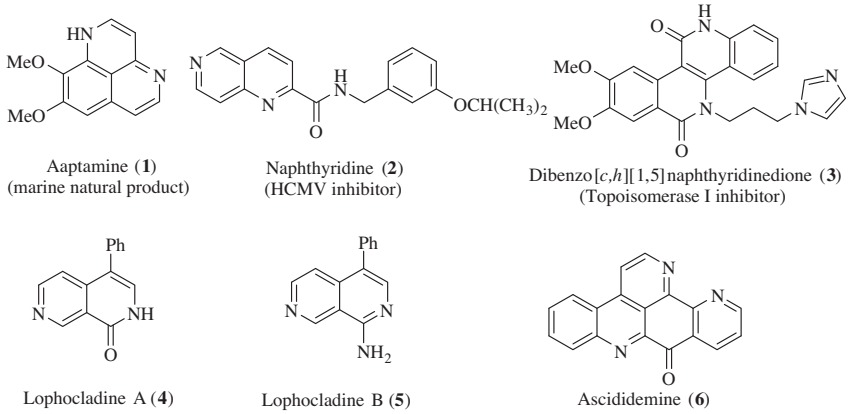


**Figure 1.** Representative structures of related bioactive molecules.

* Corresponding author. Tel.: +91 40 23134831; fax: +91 40 23012460.
*E-mail address:* rnsc@uohyd.ernet.in (R. Nagarajan).

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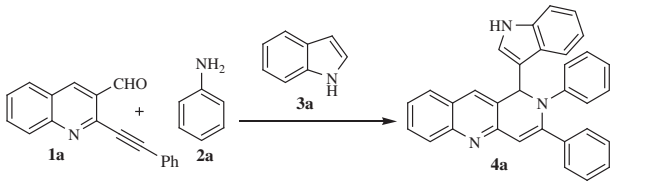
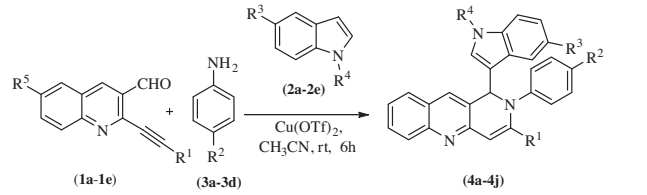
**Table 1**
Optimization of reaction conditions[a]




| Entry | Catalyst | Solvent | Yield[b] (%) | Time (h) |
|---|---|---|---|---|
| 1 | CuI | THF | 35 | 6 |
| 2 | CuBr | THF | 40 | 8 |
| 3 | $Cu(OTf)_2$ | THF | 55 | 6 |
| 4 | Ag(OTf) | THF | 52 | 7 |
| 5 | $AgNO_3$ | THF | 50 | 8 |
| **6** | **$Cu(OTf)_2$** | **$CH_3CN$** | **62** | **6** |
| 7 | $Cu(OTf)_2$ | $CH_3Cl$ | 58 | 6 |
| 8 | $Cu(OTf)_2$ | Dioxane | 56 | 6 |
| 9 | $Cu(OTf)_2$ | Toluene | 30 | 6 |
| 10 | $Cu(OTf)_2$ | DMF | 35 | 6 |
| 11 | — | $CH_3CN$ | — | 6 |

[a] Reaction conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 0.7 mmol of indole (**3a**) catalyst 5 mol %, and 1 mmol of $Na_2SO_4$ as additive at room temperature.
[b] Isolated yields.

**Table 2**
Synthesis of benzo[*b*][1,6]naphthyridines and substrate scope[a]



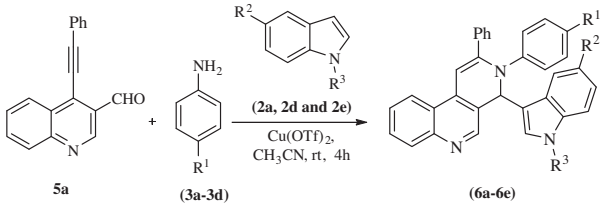

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Product | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | Ph | H | H | H | H | **4a** | 62 |
| 2 | Ph | Me | H | H | H | **4b** | 60 |
| 3 | Ph | Cl | H | H | H | **4c** | 64 |
| 4 | Ph | OMe | H | H | H | **4d** | 68 |
| 5 | Ph | Br | H | H | H | **4e** | 70 |
| 6 | Ph | H | H | Me | H | **4f** | 72 |
| 7 | Ph | H | OH | H | H | **4g** | 74 |
| 8 | Ph | H | OMe | H | H | **4h** | 73 |
| 9 | *p*-Tolyl | H | H | H | H | **4i** | 68 |
| 10 | *n*-Hexyl | H | H | H | H | **4j** | 58 |
| 11[c] | TMS | H | H | H | H | — | — |
| 12 | Ph | H | H | H | OMe | **4k** | 72 |

[a] Unless otherwise noted, all reactions were carried out in 5 mL of $CH_3CN$ under optimized reaction conditions. 0.5 mmol of quinoline alkynylaldehydes, 0.5 mmol of anilines, and 0.7 mmol of indoles were stirred at room temperature. 5 mol % of $Cu(OTf)_2$ was used
[b] Isolated yields after column chromatography.
[c] Complex mixture found in TLC.

Most recently, 5-(3-chlorophenylamino)-benzo[*c*][2,6]naphthyridine-8-carboxylic acid (CX-4945), found to be the first clinical stage inhibitor of protein kinase CK2 for the treatment of cancer[7] and dibenzo[*c*,*h*][1,5]naphthyridinediones were reported as topoisomerase I (Top1) inhibitors.[8] Lophocladine A (**4**) and Lophocladine B (**5**) are 2,7-naphthyridine alkaloids, in which, **4** exhibited affinity for NMDA receptors and it was found to be a δ-opioid receptor antagonist. Lophocladine B (**5**) showed cytotoxicity to NCI-H460 human lung tumor and MDA-MB-435 breast cancer cell lines.[9]

Very recently, bis-aaptamine alkaloids (suberitine A–D) were isolated from the marine sponge *Aaptos suberitoides* and showed that they have potent cytotoxicity against P388 cell lines.[10] These remarkable biological applications of naphthyridine molecules prompted us to synthesize benzonaphthyridine derivatives.

**Table 3**
Synthesis of benzo[*c*][2,7]naphthyridines and substrate scope[a]




| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H | H | H | **6a** | 92 |
| 2 | Me | H | H | **6b** | 90 |
| 3 | Cl | H | H | **6c** | 94 |
| 4 | H | OMe | H | **6d** | 90 |
| 5 | H | H | *n*-Butyl | **6e** | 92 |

[a] Unless otherwise noted, all reactions were carried out in 5 mL of $CH_3CN$ under optimized conditions. 0.5 mmol of quinoline alkynylaldehyde, 0.5 mmol of anilines, and 0.7 mmol of indoles were stirred at room temperature. 5 mol % of $Cu(OTf)_2$ was used.
[b] Isolated yields after column chromatography.

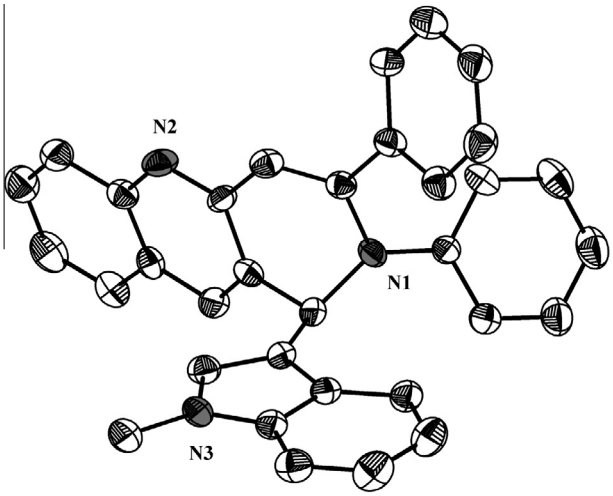
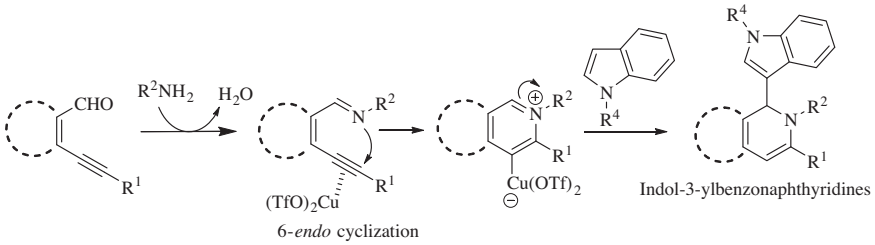



**Figure 2.** ORTEP diagram of **4f**. Hydrogen atoms are omitted for clarity.

Representative molecules of related naphthyridine are shown in Figure 1.

We envisioned that benzonaphthyridines can be synthesized by 6-*endo* mode iminoannulation of quinoline alkynyl aldehydes. Electrophilic activation of alkynes followed by annulation toward intramolecular addition reactions of heteronucleophiles has become a useful tool for the synthesis of new heterocyclic compounds.[11] Recently, there has been immense synthetic interest in the 6-*endo*-mode cyclization of 2-(1-alkynyl)arylaldimine using various transition metals and Lewis acid catalysis for the synthesis of isoquinolines and 1,2-dihydroisoquinolines motif.[12] A wide variety of functionalized terminal acetylenes participate in this metal-catalyzed and Lewis acid catalyzed cyclization process to afford the desired nitrogen heterocycles.[13]

Recently, our group reported the synthesis of benzo[*b*]-, indolo[2,3-*b*]-, carbazolo[2,3-*b*]carbazole derivatives,[14a] ellipticinium, ellipticine derivatives,[14b] and benzimidazoellipticine derivatives[14c] by 6-*endo*-mode type cyclization of carbazole alkynyl aldehydes. In continuation of our research interest in heteroannulation,[14] herein we report a convenient synthesis of indol-3-yl benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines via copper(II)-triflate catalyzed heteroannulation (Tables 2 and 3).




**Scheme 1.** Possible mechanism for formation of benzonaphthyridines.

At the outset, we optimized the reaction condition using various catalysts and solvents. The results are summarized in Table 1. Initially, we started with CuI in THF solvent at room temperature (Table 1, entry 1) and the expected product was obtained in 35% yield. Hence, we screened other catalysts and solvents as shown in Table 1. CuBr gave a low yield of 40% in THF (Table 1, entry 2). Other catalysts, such as $Cu(OTf)_2$, AgOTf, and $AgNO_3$ gave moderate yield of 55%, 52%, and 50% in THF (Table 1, entries 3–5). Without catalyst no reaction was observed (Table 1, entry 11). For all the above optimization, we used 5 mol % catalyst loading. Increasing the amount of catalyst also did not improve the yield of the product. So 5 mol % $Cu(OTf)_2$ was used for further solvent optimization. We screened other solvents such as, toluene, dioxane, chloroform, and DMF (Table 1, entries 7–10). Here, the best result was obtained in acetonitrile as solvent (Table 1, entry 6). Under optimized conditions, within 6 h complete conversion of starting material was observed in TLC.

Having optimized reaction conditions in hand, we focused our attention on the exploration of the substrate scope. With other substrates, such as various anilines and indoles, the corresponding products were isolated successfully (Table 2, entries 2–8). Similarly, other quinoline alkynylaldehyde substrates could be handled without any trouble and also gave the corresponding benzo[*b*][1,6]naphthyridines in good yields (Table 2, entry 9, 10, and 12).

When we attempted the reaction with $R^1$ as the trimethyl silyl group, an inseparable mixture of products was obtained (Table 2, entry 11). The structure of the product **4f** was unambiguously confirmed by the single crystal X-ray diffraction analysis.[15] The ORTEP diagram is shown in Figure 2.

Considering the biological importance of 2,7-naphthyridine core (Fig. 1), we planned to synthesize 3,4-dihydro-4-(1*H*-indol-3-yl)-2,3-diphenylbenzo[*c*][2,7]naphthyridine (**6a**), by performing the reaction with 4-(2-phenylethynyl)quinoline-3-carbaldehyde (**5a**), aniline, and indole derivatives under the same optimized condition. The requisite precursor **5a** was prepared from the Sonogashira coupling of 4-chloroquinoline-3-carbaldehyde and phenylacetylene.[16a,b] In this case, the expected product is formed in excellent yield (92%) with lesser reaction time (Table 3, entry 1). Then, we examined the scope of this reaction by changing the substrates such as various substituted anilines and indoles. These substrates were well tolerated and excellent yield was obtained. The results are summarized in Table 3.

Mechanism for the formation of benzonaphthyridines is shown in Scheme 1. As depicted in Scheme 1, initial step is the formation of an imine. Subsequent activation of alkyne by $Cu(OTf)_2$ and then 6-*endo*-*dig* type annulation lead to the formation of a six-membered ring. Then, nucleophilic addition of indole delivers the product benzonaphthyridines.

In summary, we have developed an efficient methodology for the synthesis of new indol-3-yl benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines in moderate to excellent yields via copper(II) triflate-catalyzed heteroannulation. On the other hand, all of the synthesized compounds have yet another vital nucleus, indole, which is known to be part of many biologically important molecules. This approach is general and an efficient method for the construction of diverse indol-3-yl benzonaphthyridine skeletons under mild reaction conditions[17]. Moreover, generality and biological significance of naphthyridine motif make it highly valuable.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.106.

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15. CCDC-908173 contains 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; Molecular formula: $C_{33}H_{25}N_3$, $a = 15.190(4)$, $b = 10.3275(17)$, $c = 16.424(4)$, $\beta = 108.46(3)$, space group $P21/n$.
16. Preparation of starting materials, see: (a) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691; (b) Amaresh, R. R.; Perumal, P. T. *Indian J. Chem. Sect. B* **1997**, *36*, 541. Reported procedure was followed for the Sonogashira coupling reaction for preparing quinoline alkynylaldehydes (**1a–e** and **5a**).
17. *General procedure for the synthesis of benzonaphthyridines:* An oven-dried 10 mL round-bottomed flask equipped with a teflon coated magnetic stirring bar is charged with 0.5 mmol of 2-(2-phenylethynyl)quinoline-3-carbaldehyde, 0.5 mmol of amine and 1 mmol of $Na_2SO_4$, 5 mL of acetonitrile. Then, 0.7 mmol of indole and copper(II) triflate (5 mol %) added to the reaction mixture. The reaction mixture is allowed to stir until complete conversion was observed by TLC. The reaction mass is poured into crushed ice slowly and extracted with ethyl acetate. The organic layer is washed with water, dried over anhydrous sodium sulfate and the solvent is removed under vacuum. The crude product is purified using column chromatography (eluent: 30% ethyl acetate in hexanes). The product is eluted in 30% eluent as a light yellow solid. We followed the same procedure for synthesis of other benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines (**4a**–**4k** and **6a**–**6e**).
*1,2-Dihydro-1-(1H-indol-3-yl)-2,3-diphenylbenzo[b][1,6]naphthyridine* (***4a***): Yield: 62%; mp 156–158 °C. IR (KBr): 3052, 1600, 1577, 1434, 1403, 1386, 1263, 1094, 749 $cm^{-1}$. $^1H$ NMR (400 MHz, TMS, $CDCl_3$): 8.24 (br s, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 7.93 (s, 1H), 7.71–7.69 (m, 1H), 7.64–7.58 (m, 3H), 7.41–7.36 (m, 2H), 7.26–7.21 (m, 5H), 7.19–7.11 (m, 5H), 6.95–6.93 (m, 2H), 6.63 (s, 1H). $^{13}C$ NMR (100 MHz, TMS, $CDCl_3$): 151.9, 148.9, 147.9, 147.0, 137.3, 136.4, 131.9, 129.3, 128.8, 128.7, 128.5, 128.3, 128.2, 127.6, 127.5, 127.4, 125.1, 125.0, 122.9, 122.8, 122.3, 120.1, 118.9, 117.9, 112.0, 111.7, 102.6 (aromatic C), 62.1 (aliphatic C). HRMS (ESI-MS) calcd for $C_{32}H_{23}N_3$; 450.1970 (M+H), found: 450.1970.