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Silver-catalyzed regioselective synthesis of benzo[2,7] naphthyridines using *ortho*-alkynyl quinoline carbaldehyde and anthranilic acid derivatives☆

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ABSTRACT

This method represents a significant advancement in the synthesis of Benzo[2,7]naphthyridines. The silver-catalyzed cyclization of *ortho*-alkynyl aldehydes and anthranilic acids proceeds under mild conditions with minimal catalyst loading, providing high yields and excellent regioselectivity. Control experiments and deuteration studies were performed to evaluate the reaction mechanism. The broad substrate scope and scalability make this protocol especially valuable for synthesizing diverse 2,7-naphthyridine derivatives, which are important scaffolds in medicinal chemistry and materials science.

Introduction

2,7-Naphthyridine derivatives constitute a small group of aromatic compounds found in a diverse range of living organisms, including plants, sponges, tunicates, and bryozoans. Two bicyclic examples, neozeylanicine from *Neonauclea zeylanica* (Rubiaceae) [1] and 3-acetyl-2,7-naphthyridine from *Valeriana officinalis* (Valerianaceae), have been known for long time [2]. Additionally, the tricyclic alkaloid perlolidine has been isolated from various plants, such as *Lolium perenne* (Poaceae) as shown in Fig. 1 [3]. The 2,7-naphthyridine core structure is also present in several alkaloids derived from Annonaceae plants, including the antimicrobial compounds sampangine [4] and eupolauridine [5]. Furthermore, numerous pyridoacridone alkaloids, like the cytotoxic pentacyclic ascididemin from the tunicate *Didemnum* sp., share this structural motif as shown in Fig. 1 [6].

Gross et al. reported two new 2,7-naphthyridine metabolites, *lophocladines* A and B, from the red algae *Lophocladia* in Fiji (Fig. 1) [7]. These compounds are rare, with only one other example known from *Valeriana officinalis*. *Lophocladine* B displayed moderate anticancer activity through microtubule disruption, whereas *lophocladine* A was inactive. Beyond these examples, 2,7-naphthyridines are recognized for diverse pharmacological activities, including antitumor, antimicrobial, analgesic, and anticonvulsant effects [8], making them attractive scaffolds in drug discovery.

The literature abounds with reports on Benzo[2,7]naphthyridines, including recent contributions from Neng-Fang She et al. on their application in fluorescent probes [9] and from Anna Wojcicka and collaborators on their synthesis and antitumor evaluation [10] as shown in Fig. 1. Traditional synthesis of these scaffolds has typically involved multiple steps, often resulting in suboptimal selectivity and yield [11]. Consequently, the development of efficient one-pot protocols for their preparation has been a primary objective. While notable advancements have been reported by Franz Bracher and colleagues [12,13], a significant milestone was achieved in 2013 by Nagarajan et al., with the introduction of a metal-catalyzed approach to 2,7-naphthyridine derivatives from *ortho*-alkynyl quinoline carbaldehyde (Fig. 2a-c) [14]. *Ortho*-alkynyl carbaldehydes have established themselves as versatile intermediates in the field of synthetic chemistry, with a proven track record of producing a wide range of compounds that are valuable in the pharmaceutical and medicinal chemistry industries [15]. Although the application of these compounds in the construction of 2,7-naphthyridine structures has not been extensively explored, as evidenced by the limited

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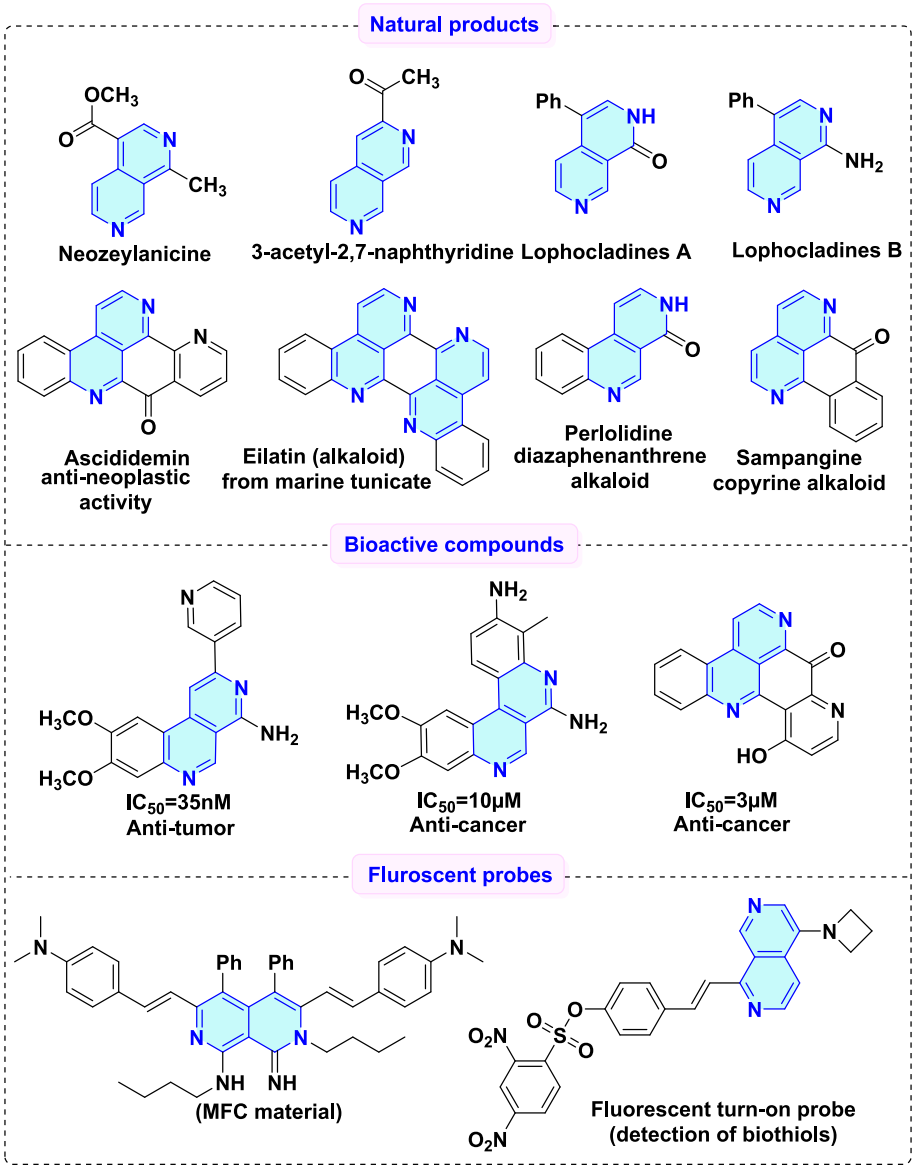


Fig. 1. Various properties of 2,7-naphthyridines.

number of reported examples such as the work of Hiroshi Yamanaka, their potential for this purpose appears promising (Fig. 2d) [16]. Similarly, anthranilic acid, a well-known starting material for the synthesis of various heterocyclic compounds [17] including other types of naphthyridines [18], offers unexplored possibilities for the creation of 2,7-naphthyridine derivatives. Our group have made a significant contribution toward heterocycles [19–22] and naphthyridine derivatives using *ortho*-alkynyl carbaldehyde. To extend this methodology to 2,7-naphthyridines, we adopted a strategy inspired by the work of the Verma group (Fig. 2e) [[23]], employing 4-alkynylquinoline-3-carbaldehyde as the starting precursor, which furnished the desired benzo [2,7]naphthyridines (Fig. 2f).

Result and discussion

In order to determine the ideal reaction circumstances, a series of experiments were carried out as detailed in Table 1. Among the various catalysts examined, silver nitrate ($AgNO_3$) exhibited superior efficacy. In contrast, CuI, Ag_2O, and $Pd(OAc)_2$ and demonstrated unsatisfactory outcomes (see ESI). Continuing with silver nitrate as the catalyst, we investigated the influence of additional parameters such as temperature, reaction duration, and atmospheric conditions. When dichloromethane (DCM) was initially used as the solvent with $AgNO_3$ as the catalyst, the reaction of **1a** and **2a** afforded product **3aa** in 60 % yield (Table 1, entry 1). Subsequently, switching to DCE as the solvent resulted in an enhanced yield of 65 % (entry 2). Further experimentation with a variety of solvents, including DMF, THF, and water, failed to produce significant improvements in product yield (entries 3–5). To potentially augment productivity, mixed solvent systems were explored. Among these combinations, a mixture of DCE and EtOH proved most effective, delivering a product yield of 76 % (entry 6). Subsequent optimization of the solvent ratio within this mixture identified a 3:1 ratio of DCE to EtOH as optimal, leading to a product yield of 88 % (entry 7). An increase in catalyst loading to 10 mol% resulted in a diminished product yield of 75 % (entry 8). Conversely, elevating the reaction temperature also led to a decrease in product formation (entry 9). Finally, the most favorable conditions for this reaction involve compound **1a** (0.2 mmol), compound **2a** (0.2 mmol), a DCE: EtOH solvent mixture (3:1) (1.5 mL, 0.5 mL) and a reaction temperature of 25 °C.

The substrate scope of *ortho*-alkynyl aldehydes (**1**) and anthranilic acids (**2**) was explored under optimized reaction conditions Scheme 1. Initially, quinoline carbaldehyde (**1a**) was coupled with various

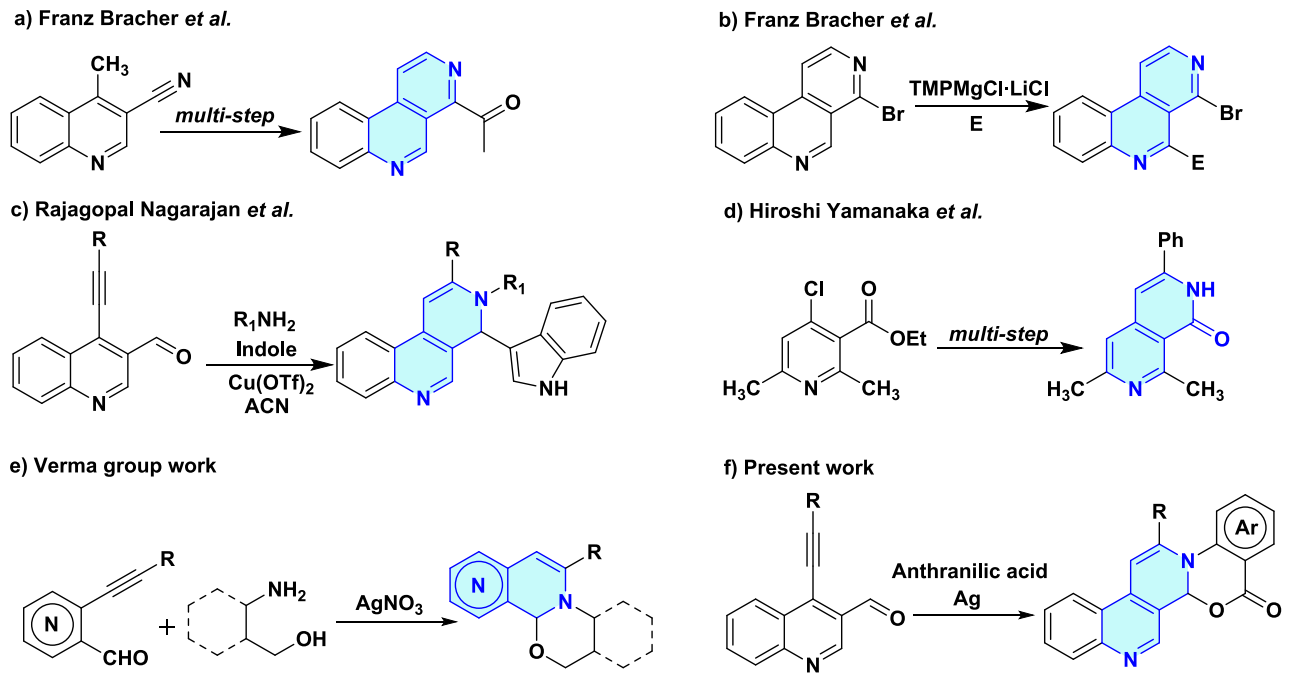
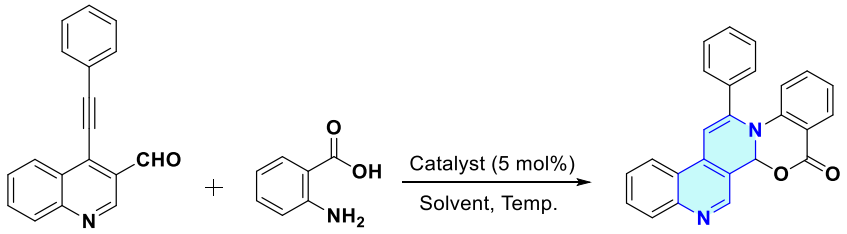


Fig. 2. Various synthetic approaches toward naphthyridine.

Table 1
Optimization of reaction conditions.[a]

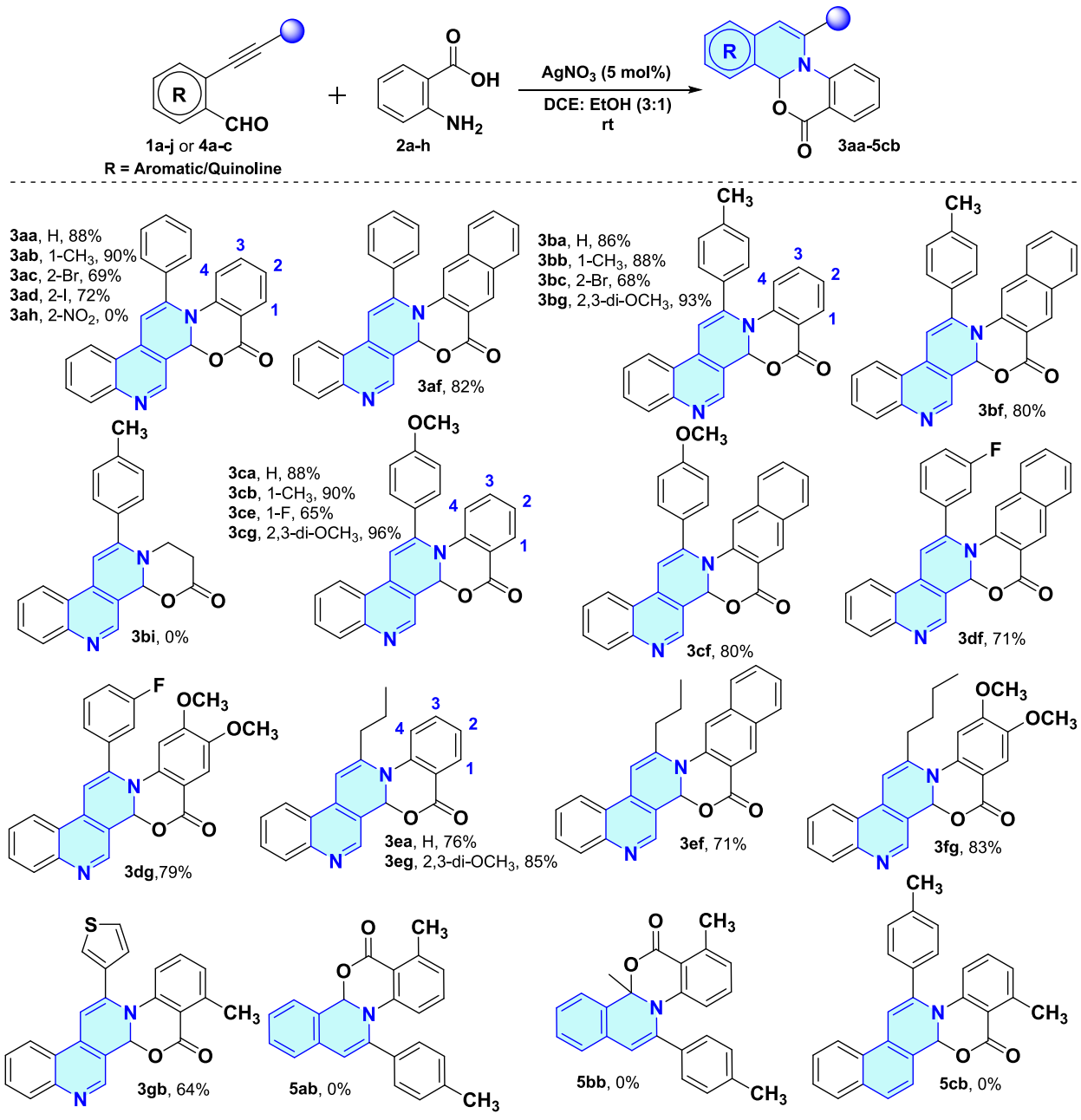


1a 2a 3aa

Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]
1	$AgNO_3$	DCM	Rt	60
2	$AgNO_3$	DCE	Rt	65
3	$AgNO_3$	DMF	Rt	40
4	$AgNO_3$	THF	Rt	22
5	$AgNO_3$	H_2O	Rt	NR
6	$AgNO_3$	DCE: EtOH (2:1)	Rt	76
7	$AgNO_3$	DCE: EtOH (3:1)	Rt	88
8	$AgNO_3$	DCE: EtOH (3:1)	Rt	75[c]
9	$AgNO_3$	DCE: EtOH (3:1)	80	79

[a] Reaction was performed using **1a** (0.2 mmol), **2a** (0.2 mmol) and solvent (2 mL) in presence of catalyst (5 Mol%) for 12 h.
[b] Isolated yields by column chromatography.
[c] Catalyst (10 Mol%), rt. = room temperature, NR = no reaction.

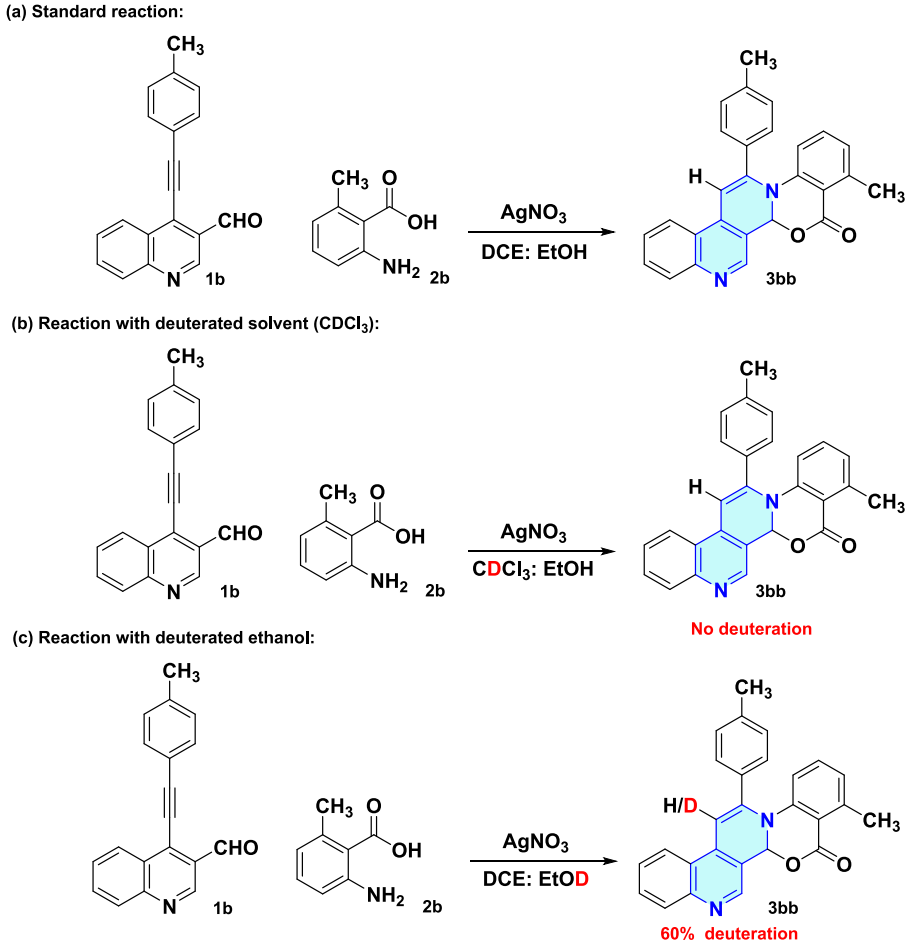
anthranilic acid derivatives, yielding the desired products **3aa-ad** in excellent yields of up to 90 %. Notably, electron-donating groups on the anthranilic acid moiety enhanced product formation, while electron-withdrawing groups (e.g., Br, I) diminished yields. A naphthyl-substituted anthranilic acid also afforded the corresponding product (**3af**) in 82 % yield. Unfortunately, NO_2 bearing anthranilic acid was failed to yield **3ah**. To further investigate the reaction scope, a quinoline aldehyde bearing a *p*-tolyl group (**1b**) was reacted with different anthranilic acids, producing compounds **3ba-bg** in high yields. The introduction of methoxy groups at the 2 and 3 positions of the anthranilic acid led to an excellent yield of 93 % for product **3bg**. A naphthyl-substituted anthranilic acid again provided the desired product (**3bf**) in good yield. To confirm the regioselectivity of the molecule, we analyzed the NOESY spectrum of **3bb**, which clearly displays the expected proton–proton correlations, as presented in the Supporting Information (See SI). The impact of electron-donating groups on the quinoline aldehyde was examined using compound **1c**, which possesses a methoxy substituent. This substrate reacted efficiently with various anthranilic acids to give products **3ca-cg** in good yields. A combination of electron-donating groups on both the quinoline and anthranilic acid



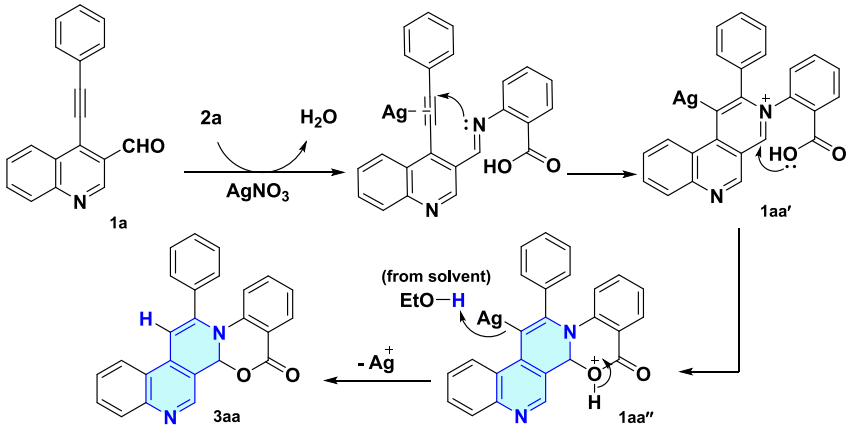
Scheme 1. Substrate scope of Benzo[2,7]naphthyridines. *Reagents and conditions:* reaction was performed using **1** or **4** (0.2 mmol), **2** (0.2 mmol) and DCE: EtOH (3:1) (2 mL) in presence of $AgNO_3$ (5 mol%) for 12 h at rt.

components resulted in an impressive yield of 96 % for the corresponding product **3cg**. A naphthyl-substituted anthranilic acid coupled with **1c** afforded product **3cf** in 80 % yield. To assess the influence of electron-withdrawing groups, quinoline aldehydes bearing such substituents were employed. These substrates successfully reacted with anthranilic acids to yield the desired products **3df** and **3dg** in good yields of up to 79 %. Interestingly, aliphatic alkyne-bearing quinolines (**1e** and **1f**) were also explored and successfully furnished the desired products (**3ea-fg**) in high yields. For example, compound **3ef** was obtained in 71 % yield, while **3 fg** showed a higher yield of 83 %. Following the establishment of substrate scope, the reaction's scalability was assessed by conducting it at a 1.8 mmol scale, as outlined in Scheme 4. While a slight decrease in yield to 62 % was observed, the reaction proceeded smoothly. Furthermore, we evaluated the reaction feasibility using aliphatic amino acid **2i**; however, it did not afford the desired product **3bi**. Additionally, while screen heteroaromatic alkynes, we tested thiophene derived starting material **1 g**, which successfully afforded desired product **3gb**. Conversely, when ortho-alkynyl ketone (**4a**), benzaldehyde (**4b**), and naphthaldehyde (**4c**) were tested, none of them yielded the desired products **5ab-cb**.

Furthermore, to gain insight into the reaction mechanism, a series of control experiments were carried out (Scheme 2; additional details are

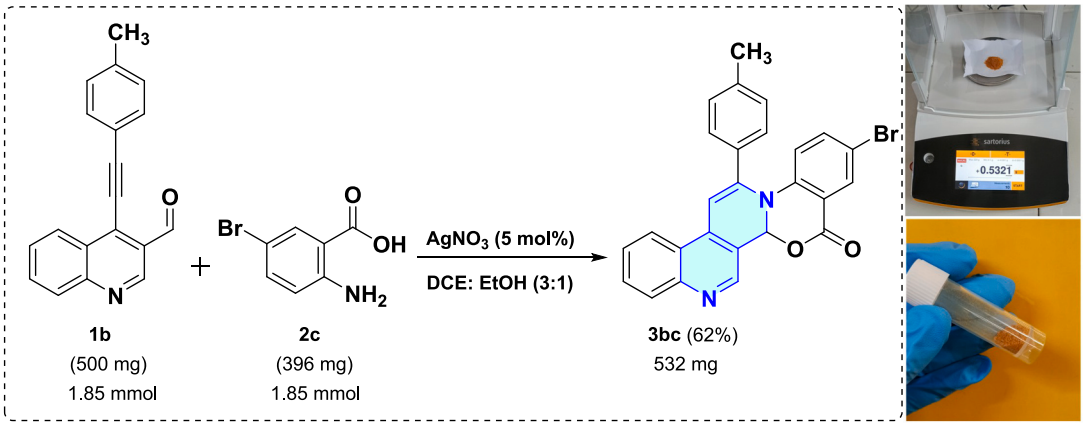


Scheme 2. Control experiments.



Scheme 3. Plausible mechanism.

provided in the Supporting Information). For instance, to trace proton transfer, reactions were performed in deuterated solvents (ethanol-d_1 and $CDCl_3$). No deuterium incorporation was observed in $CDCl_3$; however, in deuterated ethanol, approximately 60 % deuterium incorporation was detected at the C-1 position of the molecules. This observation indicates that ethanol not only serves as the reaction medium but also acts as a proton source to facilitate the transformation. Based on these control experiments and previous literature reports [18], we propose the plausible mechanism outlined in Scheme 3. The reaction begins with the condensation of quinoline aldehyde and the anthranilic acid derivative to form an imine intermediate. Subsequently, silver promotes the cyclization of the alkyne moiety, generating the cyclic intermediate **1aa′**. The highly reactive imine subsequently undergoes a second cyclization, wherein nucleophilic attack by the benzoic acid moiety affords intermediate **1aa″**. Finally, protonation from the solvent completes the transformation, yielding the desired product **3aa**.



Scheme 4. Scale-up experiment.

Conclusion

In summary, a highly efficient and regioselective silver-catalyzed approach has been established for the synthesis of Benzo[2,7]naphthyridines. This method leverages readily available *ortho*-alkynyl aldehydes and anthranilic acids as starting materials and proceeds under mild conditions with low catalyst loading. The protocol consistently delivers the desired products in excellent yields, surpassing existing methodologies in terms of selectivity and operational simplicity. The versatility of this approach is underscored by its broad substrate scope and scalability, enabling the construction of a diverse array of Benzo [2,7]naphthyridines derivatives. This work provides a valuable platform for the development of novel benzo[2,7]naphthyridines -based compounds with potential applications in various fields.

CRediT authorship contribution statement

Kapil Chahal: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Ravikumar Badhavath:** Visualization, Validation, Methodology, Investigation, Data curation. **K. Velangini Sunidhi Reddy:** Visualization, Validation, Investigation, Data curation. **Kirti Vashishtha:** Data curation, Investigation, Visualization, Writing – review & editing. **K. Rajender Reddy:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

The supporting information contains comprehensive details, including the experimental procedures, physical constants of products, and characterization of representative compounds (^{1}H, ^{13}C and HRMS). Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2025.155835.

Data availability

Data will be made available on request.

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