Regiodivergent ZnO-NP-Catalyzed Decarboxylative Synthesis of Substituted Quinolines and Application of N-Oxide via Late-Stage Diversification

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Article

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Abstract

An efficient regiodivergent ZnO-NP catalyzed decarboxylative protocol for the direct synthesis of 3-arylquinolines and 2,3-diarylquinolines with readily available cinnamic acids and arylazides via C-H functionalization and C-C/C-N bond formation has been developed. In this work, the regioselectivity can be rationally tuned via the perfect choice of reaction solvents; 3-substituted quinolines were obtained when ethylene glycol was used as the solvent, whereas the use of AcOH as solvent afforded 2,3-disubstituted quinolines. The reaction is simple, gram-scale synthesis, environmentally friendly, and proceeds under very mild conditions with a range of functionalities in good to excellent yields. Furthermore, this strategy’s synthetic utility provided a practical approach for the C-H activation of 3-substituted quinoline via N-oxide through the C-C, C-O, C-S, and C-N bond formation and late-stage functionalization (LSF) of drug molecules and natural products were also performed.

Introduction

Quinoline scaffolds are one of the most valuable N-heterocyclic component of natural products1–6 (e.g., Quindoline,4 Cryptolepine,5 and Jusbetonin6). Several quinoline containing synthetic compounds7 as well as important intermediates that display remarkable pharmaceutical and biological activities such as antihypertensive, antidepressant, anticonvulsant, anticancer, anti-inflammatory, antimalarial, anti-thyroid cancer, antifungal, analgesic, antibacterial, antiasthmatic and antiproliferative properties (Fig. 1).1–9

Generally quinoline molecules are synthesized by the typical protocols including the Combes reaction, Skraup reaction, Conrad-Limpach-Knorr reaction, Doebner-Von Miller reaction, Pfitzinger reaction, Povarov reaction and Friedländer reaction (Fig. 2).10–16 In addition, Larock,17 Liang,18 Wang,19 DeShong,20 transition-metal-catalyzed synthetic strategies21–25 and others26–28 reported a facile protocol for forming a variety of quinolines. Among them, the C2 substituted quinolines have been developed through the direct C-C,29,30 C-O,31 C-N,32,33 and C-S34,35 bond formation. Quinoline N-oxides react with lactams/cyclamines,36 primary amides,37 nitriles,38 alklylation,39,40 alkoxylation,41 alkenylation,42,43 arylation,44,45 amination,46 sulfonylation,47,48 phosphonation,49 and thiolation.49 The C3 substituted quinoline have been developed by various protocols such as the palladium catalyzed C3-arylation of quinolines through C-H functionalization,50 Ullmann coupling,51 [4 + 2] hetero Diels-Alder (HDA),52 and Friedlander-type reaction.53

In this regard, a few seminal new methodologies have been reported for the synthesis of substituted quinolines (Scheme 1). For example, in 2012, Zhang et al. have reported iron (III)-promoted tandem reaction for the synthesis of 3-substituted quinoline from anilines and styrene oxides via C-C cleavage and C-H activation.55 Huang and co-workers have developed copper-catalyzed methodology for the synthesis of 3-substituted quinolines from aldehydes and aniline via aerobic oxidative dehydrogenative annulation reaction,56 and Kirchner group’s have also reported regioselective synthesis of substituted quinolines catalyzed by a well-known hydride Mn(I) PNP complex from 2-aminobenzyl alcohols and
secondary alcohols. In 2019, Sortais’s group developed a rhenium-catalyzed (well-defined rhenium complexes bearing a tridentate diphosphinoamino ligand) protocol to synthesize quinolines through the annulation of 2-aminobenzyl alcohol with a variety of secondary alcohols, ketones, aldehydes via sequence of dehydrogenation and condensation process. Recently, Li et al. developed cobalt-catalyzed electrophilic amination with various anthranils and alkenylzinc pivalates, heterocyclic zinc pivalates, or electron-rich arylzinc pivalates produces substituted quinolines. Very recently, Gao et al. (2020), have accomplished Rh-catalyzed synthesis of diverse polysubstituted quinolines via C-H amination/annulation of acrylic acids and anthranils. Interestingly, Zhang and co-workers disclosed the synthesis of substituted quinolin-4-ols/quinolines by the coupling of α-fluoro-β-ketoester or β-ketoester and 2-azidobenzaldehydes via [4 + 2] annulation involving Knoevenagel, aza-wittig, and dehydrofluorination. However, the above mentioned methodologies are associated with several drawbacks, such as expensive transition-metal catalysts, an excess amount of base, hazardous reagents and solvents, and more costly and limited availability of starting materials, prolonged reaction time, low selectivity, and difficulties in recycling the catalyst. Therefore, from an environmental and economic point of view, we have developed a facile and sustainable method to synthesize 3-substituted quinolines and 2,3-disubstituted quinolines from readily available cinnamic acids and arylazides. The ZnO-NP is a heterogeneous catalyst, low-cost, non-toxic, and easily recyclable. It is preferably used for industrial purposes without losing their activity and selectivity. It has been explored as a non-precious and potent metal catalyst for numerous organic transformations.

To the best of our knowledge, this is the first ZnO-NP catalyzed and solvent-controlled decarboxylative regiodivergent protocol for the construction of both 3-substituted quinolines and 2,3-disubstituted quinolines using cinnamic acids and arylazides has not been achieved so far. In chemical processes, solvents are known to play very important role and the considerable effects have been reported in regioselectivity, stereoselectivity, structural control, physical prop-erties, and so on. As a part of our continuing research interest in N-heterocyclic frameworks, we described here the first ZnO-NP catalyzed, and solvent-controlled regiodivergent synthesis of both 3-substituted quinolines and 2,3-disubstituted quinolines via a decarboxylative process.

Results And Discussion

With this working hypothesis in mind, we commenced our studies of the ZnO-NP catalyzed and solvent-controlled decarboxylative reaction by employing 4-azido-1,2-dimethylbenzene (1a) and 4-chlorocinnamic acid (2a) as model substrates under several conditions, and the details are summarized in Table 1. Our initial best results in terms of yield and the corresponding products 3-(4-chlorophenyl)-6,7-dimethylquinoline (3b) and 2,3-bis(4-chlorophenyl)-6,7-dimethylquinoline (4b) were achieved by the reaction of 4-azido-1,2-dimethylbenzene 1a (1.0 mmol) with 4-chlorocinnamic acid 2a (1.2 mmol) in the presence of ZnCl\(_2\) as a catalyst and various solvents system, including DMF, toluene, MeCN, DMSO,
ethylene glycol, lactic acid and acetic acid under an open-air atmosphere at 120 °C for 12 h (Wells A5 and A7, Table 1).

At this stage, the structures of (3b) and (4b) were well characterized by $^1$H and $^{13}$C-NMR and HRMS analysis. Inspired by these result, next, we turned our focus towards the use of different catalysis, such as ZnO, CuO, ZnO-NP, Cu(OTf)$_2$, FeCl$_2$ and Pd(OAc)$_2$ (Table 1). The use of lactic acid proved to be ineffective compared to the acetic acid (Well D6, Table 1). Thus, 3-substituted quinolines (3b) and 2,3-disubstituted quinolines (4b) could be obtained in good to excellent yields and high selectivity by switching solvents (Wells D5 and D7, Table 1) and for more results are summarized in supporting information (see, Table S1 and S2 of the SI). Thus, our best reaction conditions ZnO-NP catalyzed by reaction of 4-azido-1,2-dimethylbenzene 1a (1.0 mmol) and 4-chlorocinnamic acid 2a (1.2 mmol) in ethylene glycol (2 mL) at 120 °C for 12 h (Well D5, Table 1) and also same stoichiometric amount of (1a) and (2a) in acetic acid (2 mL) at 120 °C for 12 h (Well D7, Table 1). The structure of 3-substituted quinolines (3b) was unequivocally confirmed by X-ray crystallographic analysis (Figure 3). Also, the structure of (3j) and (4a) confirmed by F-NMR and DEFT-NMR studies (For detail see in SI).

After having ZnO-NP catalyzed, and solvent-controlled decarboxylative regiodivergent optimal reaction conditions in hand, a series of reactions using different organic azides (1a) and substituted cinnamic acids (2a) were employed to explore 3-substituted quinoline derivatives, as revealed in Scheme 2. We first surveyed the reaction in ethylene glycol using a variety of substrates (1a) that were treated with different cinnamic acids (2a). The arylazides (1a) bearing both electron-donating groups (EDGs) as well as electron-withdrawing groups (EWGs) at different positions of the benzene ring readily delivered the corresponding 3-substituted quinolines in good to excellent yields. For example, arylazides (1a) containing electron-withdrawing groups such as 3,5-dichloro (3c), 3,4-dichloro (3e), 4-chloro (3s, 3u, 3w and 3x) and electron-donating groups as well as electron-neutral (H), such as 3,4-dimethyl (3a, 3b, 3f, 3g, 3h, and 3v), 3,5-dimethyl (3i, 3j, 3k, 3l, 3o, 3q, and 3r), and (3d, 3m, 3n, 3p, and 3t) were tolerated in this reaction, affording the corresponding products in good to excellent yields. Then, the cinnamic acids having substituents on the aryl ring were further examined. The substrates (2a) containing electron-donating groups (EDGs) such as 4-Me (3f, 3l, 3t, and 3u), and 4-OMe (3q, 3v, and 3x), and electron-neutral (H) as well as electron-withdrawing groups (EWGs) such as (3a, 3c, 3e, 3o, 3p, and 3s), and 4-NO$_2$ (3r), 4-F (3h, 3j, and 3n), 4-Cl (3b, 3d, 3i, and 3w), and 4-Br (3g, 3k, and 3m), the reaction proceeded well, it provided the corresponding products (3-substituted quinolines) in good to excellent yields (65-82%), and selectivity of (3b) (Scheme 2).

Subsequently, the success of our optimized reaction conditions was investigated by synthesizing a library of 2,3-disubstituted quinolines using acetic acid as a solvent. A variety of arylazides (1a) and cinnamic acids (2a) were studied, and the results are summarized in Scheme 3.

The reaction of arylazides (1a) with substrates (2a) containing both electron-donating groups such as alkyl (e. g., 4-Me; 4k, 4l, 4n, and 4o), and alkoxy (e. g., 4-OMe; 4d, 4j, and 4q), and electron-withdrawing
groups such as 4-NO₂ (4c), 4-F (4a, 4h, and 4r), 4-Cl (4b and 4p), and 4-Br (4e and 4g) substituents afforded the corresponding products (65-75%) in good to excellent yields (Scheme 3).

On the other hand, a series of organic azides (1a), which also bears electron-donating groups (3,5-di-Me, and 3,4-di-Me) and electron-neutral (H) or an electron-withdrawing groups (4-Cl) on the benzene ring, underwent the reaction with cinnamic acids (2a) using our optimized reaction conditions to afford the desired products (4a-4r) in satisfactory yields (Scheme 3).

Moreover, to evaluate the practicality of the ZnO-NP catalyzed and solvent-controlled decarboxylative methodology in a gram-scale synthesis by using 10.0 mmol of 4-azido-1,2-dimethylbenzene (1a), and 12.0 mmol of 4-chlorocinnamic acid (2a) under standard conditions. The 3-substituted quinolines (3b) and 2,3-disubstituted quinolines (4b) were obtained in 77% and 70% yield, indicating that the reaction is scalable and its potential industrial applications in the future (Scheme 4).

The synthetic applications of our developed protocol were investigated, we performed experiments using 3-(4-chlorophenyl)-6,7-dimethylquinoline (3b) as a starting material for the functionalization at 2-position of compound 3b as displayed in Scheme 5. Initially, 3b were treated with m-CPBA in dichloromethane at room temperature under air to give 3-(4-chlorophenyl)-6,7-dimethylquinoline N-oxide intermediate (5) in 90% yields. The intermediate 5 was then treated with p-toluenebenzenesulfinic acid sodium salt and 4-methylbenzenesulfonylhydrazide in the presence of I₂/TBHP in DMF at room temperature and NaI/TBHP in DMF/H₂O at 100 C to give 3-(4-chlorophenyl)-6,7-dimethyl-2-tosylquinoline (6) in good yield.

Quinoline N-oxide (5) reacted with MsCl in an aqueous solution at room temperature to produce 3-(4-chlorophenyl)-6,7-dimethylquinolin-2(1H)-one (7). The reaction of quinoline N-oxide (5) with 3,4-dimethylaniline/4-bromophenol/5,5-dimethylcyclohexane-1,3-dione and 2,2-dimethyl-1,3-dioxane-4,6-dione in the presence of K₂CO₃, diethylphosphite, and CCl₄ in DMF for 3 h at room temperature, affording the corresponding products (8), (10), (11), and (13) in good yields. KOH-promoted alkynylation of N-oxides via reaction of quinoline N-oxide intermediate (5) with phenylacetylene in toluene under reflux conditions to give 3-(4-chlorophenyl)-6,7-dimethyl-2-(phenylethynyl)quinoline (9). Intermediate 5 react with diethylphosphite to provided the phosphonylated desired product (12) in good yield (See in supporting information).

Late-stage functionalization (LSF) is emerging as one of the most powerful tool for the drug discovery. LSF can modify an existing bioactive molecule into a closely related analog and hence speed up the drug discovery program. Several drugs and bioactive natural products such as taxol, quinine, celecoxib, tenofovir, camptothecin, artemisinin, rifamycin, and alpha-tocopherol have been transformed into their novel analog via the late-stage transformation approach. Owing to the medicinal importance of late-stage functionalization, we have also utilized our standardized protocol for the late-stage transformation of some important drugs such as paracetamol, and metronidazole, and bioactive natural products for example, alpha-tocopherol, ferulic acid, p-coumaric acid, and vanillin (Scheme 6) and experimental procedure incorporated in supporting information.
In an effort to gain insight into the mechanistic pathway, we performed a series of control experiments, and the results were elucidating under the standard conditions, as shown in Scheme 7. Initially, the reaction of 4-azido-1,2-dimethylbenzene (1a) with 4-chlorocinnamic acid (2a) in the presence of ZnO-NP (3 mol %) catalyst under neat conditions at 120 °C for 24 h, did not found any product (Scheme 7, eqn (1)). We have explored the amine (3,4-dimethylaniline) (1a) as a substrate for the nitrogen source to react with 4-chlorocinnamic acid (2a) under the standard conditions, and no desired product was furnished (Scheme 7, eqn (2)). Further, cinnamaldehyde (2a) was used as a starting material to react with 4-azido-1,2-dimethylbenzene (1a) under standard conditions, the reaction was unsuccessful, which indicates that the cinnamaldehyde species do not participate in this reaction system (Scheme 7, eqn (3)).

On the basis of the above-mentioned mechanistic control experiments and literature reports,55-57,95-101 a plausible mechanism for the regiodivergent synthesis of both 3-substituted quinolines and 2,3-disubstituted quinolines has been outlined in Scheme 8. Initially, the reaction of arylazides (1a) with arylcinnamic acids (2a), afforded the intermediate (A), and (B) via Schmidt type rearrangement process.95 Subsequently, intermediate (A) dimerized with intermediate (B) or followed by Michael addition reaction, which undergoes intramolecular cyclization, after that elimination of amine to furnish dihydroquinoline intermediate (D).55-57,100 Then intermediate (E)55,101 was generated through dehydrogenation of intermediate (D), and radical species (F) from quinoline intermediate (E) in the presence of air. Moreover, the quinoline radical intermediate (F) reacted with hydroperoxide radical to furnished reactive quinoline hydroperoxide intermediate (G). Finally, the 3-substituted quinoline 3(a-x) is provided by the decomposition of hydroperoxide intermediate (G) via C-C bond cleavage. For the 2,3-disubstituted quinoline, the quinoline-2-phenylmethanone (H)96-101 is produced by the elimination of water from the quinoline hydroperoxide intermediate (G). The concerted dearomatization of intermediate (H) generates delocalized quinoline cyclopropanone intermediate (I) and (J) (Wheland intermediate)98,99 which underwent aromatization-induced decarbonylation (CO) to deliver the corresponding product 2,3-disubstituted quinolines 4(a-r) (Scheme 8).

Conclusion

In summary, we have disclosed the first ZnO-NP catalyzed, and solvent-controlled regiodivergent synthesis of both 3-substituted quinolines and 2,3-disubstituted quinolines from cinnamic acids and arylazides via the decarboxylative process. In this protocol, the ZnO nanoparticles catalyst has been shown to be superior to the other readily/commercially available metal catalysts, and it could be recycled. The present synthetic strategy also furnishes the advantageous features such as the practically simple, cheap, and readily accessible starting materials, the valuable structures of the substituted quinolines, highly regioselectivity and excellent substrate scope/functional group tolerance, mild and environmentally benign reaction conditions and the discharging CO\textsubscript{2} and CO as traceless by-products. We have also accessed the synthetic utility of present protocol via late-stage functionalization (LSF) of drug molecules for example, paracetamol, metronidazole, and bioactive natural products, such as alpha-tocopherol (vitamin E), ferulic acid, p-coumaric acid, and vanillin. We believe that other researchers in
medicinal chemistry and molecular synthesis, in general, will be as generous as we have been able to apply the chemistry because of its wide scope and broad applicability.

**Experimental Section**

**Representative experimental procedure for the synthesis of 3-Substituted Quinolines 3(a-x):** Arylazides 1a (1.0 mmol), and arylcinnamic acids 2a (1.2 mmol) and ZnO-NP catalyst (3 mol %) were taken in a 25 mL round bottom flask containing ethylene glycol (2 mL) as a solvent under open air atmosphere condition, the reaction mixture was stirred at 120 °C. The completion of reaction was monitored by TLC; the reaction mixture was allowed to cool at room temperature. Then reaction mixture was diluted with ethyl acetate and water. The extracted layer was dried over anhydrous sodium sulphate and solvent was evaporated under vacuum. The crude product was purified by 100-200 mesh silica gel by column chromatography with hexane/ethyl acetate (6:4) to afford 3-substituted quinolines.

**Representative Experimental Procedure for the Synthesis of 2,3-Disubstituted Quinolines 4(a-r):** Arylazides 1a (1.0 mmol), and arylcinnamic acids 2a (1.2 mmol) and ZnO-NP catalyst (3 mol %) were taken in a 25 mL round bottom flask containing AcOH (2 mL) as a solvent under open air atmosphere condition, the reaction mixture was stirred at 120 °C. The completion of reaction was monitored by TLC; the reaction mixture was allowed to cool at room temperature. Then reaction mixture was diluted with ethyl acetate and water. The extracted layer was dried over anhydrous sodium sulphate and solvent was evaporated under vacuum. The crude product was purified by 100-200 mesh silica gel by column chromatography with hexane/ethyl acetate (8:2) to afford 2,3-disubstituted quinolines.

**Declarations**

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: XX.XXXX/acssuschemeng.XXXXXXX.

General remarks, optimization of experiment conditions, general experimental procedure, characterization data for compounds, $^1$H and $^{13}$C-NMR spectra of compounds, $^{19}$F-NMR-Spectra of Compound (3j) and (4a), DEPT-NMR-Spectra of Compound (3j) and (4a), and $^{31}$P-NMR-Spectra of Compound (12) and X-Ray-data of Compound (3b) (PDF).

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Authors declare no competing financial interest.

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**Table**

Table 1 is available in the Supplementary Files section

**Schemes**

Schemes 1 to 8 are available in the Supplementary Files section.

**Figures**
Figure 1

Biologically Active Molecules Containing Substituted Quinoline Scaffolds and Our Target Molecules

Figure 2

Synthesis of Substituted Quinolines (Well-Known Reactions)
Traditional Protocols and Our Strategy for the Synthesis of Functionalized Quinolines

Figure 3

ORTEP diagram of compound (3b)

Supplementary Files

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- Supporting.docx
- Table1.docx
- Scheme1.png
- Scheme2.png
- Scheme3.png
- Scheme4.png
- Scheme5.png
- Scheme6.png
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- Scheme8.png