# LETTERS

## Synthesis of Polysubstituted Quinolines via Transition-Metal-Free Oxidative Cycloisomerization of *o*-Cinnamylanilines

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**Supporting Information** 

**ABSTRACT:** An efficient synthesis of 2-aryl 4-substituted quinolines from stable and readily available *o*-cinnamylanilines, prepared from anilines and cinnamylalcohols, has been developed. The reaction occurred via a regioselective *6-endo-trig* intramolecular oxidative cyclization using KO<sup>t</sup>Bu as a mediator and DMSO as an oxidant at rt. The reaction showed a broad substrate scope with good to excellent yields.



T he quinoline skeleton is a key structural unit in a large number of natural products, pharmaceuticals, and agrochemicals.<sup>1</sup> Functionalized quinolines are also widely used as materials<sup>2</sup> and catalysts for asymmetry synthesis.<sup>3</sup> For this reason, the development of synthetic protocols for functionalized quinolines has always been an active area of research.<sup>4,5</sup> The most prevalent strategies for constructing quinoline rings are the classic annulation reactions, including the Combes synthesis,<sup>6a-c</sup> Skraup synthesis,<sup>6d-f</sup> Gould–Jacobs reaction,<sup>6g</sup> Conard–Limpach synthesis,<sup>6h,i</sup> Doebner–von Miller reaction,<sup>6j,k</sup> and Povarov reaction,<sup>61–n</sup> where commercially available anilines are still a common substrate.<sup>4</sup> Strategically, in the above cases, N-alkylation of anilines followed by cyclization occurs to provide the corresponding quinolines (Scheme 1a). Recently, consid-

Scheme 1. Strategies for the Synthesis of Substituted Quinolines from Anilines



erable attention has been focused toward the development of strategies concerning the *ortho*-functionalization of anilines followed by a cyclization reaction (Scheme 1b).<sup>7</sup> Despite these significant advances, the synthesis of such starting materials remains a challenging task in many cases. In this context, the development of a new synthetic protocol for the rapid construction of highly functionalized quinolines with high efficiency from easily available *ortho*-functionalized anilines would be a significant contribution.

Driven by the fact that a wide variety of highly substituted *o*cinnamylanilines<sup>8</sup> and their analogues are readily available from cinnamyl alcohols and commercially available anilines, we recently reported a methodology for the synthesis of 2-benzyl indoles from such *o*-cinnamyl anilines (Scheme 2a).<sup>9</sup> In an effort

#### Scheme 2. Oxidative Cyclization of o-Cinnamylanilines



to pursue the diversified application of such *o*-cinnamyl anilines, we have turned our attention toward the possibility of achieving the synthesis of functionalized quinolines from the same (Scheme 2b). Herein, we report a transition-metal-free oxidative cycloisomerization methodology using simple and economical KO<sup>t</sup>Bu in DMSO at room temperature. Functionalized quino-lines were synthesized in high yields and with excellent chemoselectivities. Nevertheless, from the standpoint of sustainability and green chemistry, the development of transition-metal-free reaction conditions has always been an attractive strategy.<sup>10</sup>

The 2-arylquinoline moiety is commonly found in a wide range of bioactive molecules such as antimalarials, antitumor agents, and P-selectin antagonists (Figure 1).<sup>11</sup> On the other hand, 2-styrylquinolines are also important scaffolds having considerable biological significance (Figure 1).<sup>12</sup> However, there are limited methods available for the synthesis of such scaffolds.<sup>13</sup>

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**Figure 1.** Biologically active quinoline skeleton containing a 2-aryl and 2-styryl substitutions.

Our studies began with (E)-2-(1,3-diphenylallyl)-4-methylaniline 1a (Table 1). When a solution of 1a in dimethyl sulfoxide



<sup>a</sup>The reaction was carried out with **1a** (0.2 mmol), base (0.5 equiv), 4 h, 1 mL solvent, under an argon atmosphere. <sup>b</sup>The isolated yields. <sup>c</sup>Carbonates such as Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub> are used.

(DMSO) was stirred at rt in the presence of a catalytic amount of various bases (such as  $Na_2CO_3$ ,  $K_2CO_3$ ,  $CsCO_3$ , LiOH, NaOH, KOH, NaH, and KO<sup>t</sup>Bu, entries 1–6, respectively), it was observed that KO<sup>t</sup>Bu provided the desired 2,4-diphenylquinoline **3a** (entry 6) in 83% isolated yield, which is found to be the best among all the considered bases.

When the same reaction was carried out in other solvents such as DMF,1,4-dioxane, Et<sub>2</sub>O, THF, MeOH, EtOAc, and CH<sub>2</sub>Cl<sub>2</sub>, the reactivity of KO<sup>t</sup>Bu remained less efficient than in DMSO (entries 7–13, respectively). Further, various diamine ligands were added in addition to KO<sup>t</sup>Bu, aimed at increasing the yields of the reaction; however, the desired improvement was not observed (see Supporting Information for details). In any case, we could not observe the formation of the indole **2**.

The results summarized in Scheme 3 demonstrate that the oxidative cyclization protocol is a robust one. We examined the scope of the present reaction of *o*-allylanilines with substitution on the aniline moiety. Electron-donating groups including 6-methyl (**3a**), 6,7-dialkyl (**3b**, **3e**), 6,7-dialkoxy (**3c**, **3f**–**g**), 6,8-dimethoxy (**3d**), 5,6,7-trimethoxy (**3h**), and 6-methylthio (**3i**)

Scheme 3. Variation of Aryl Amine $^{a,b}$ 



<sup>*a*</sup>Reaction conditions: *o*-allyl aniline **1** (0.20 mmol), KO<sup>t</sup>Bu (0.5–1.5 equiv), DMSO (1 mL). <sup>*b*</sup>Isolated yields after column chromatography. <sup>*c*</sup>1.0 equiv of KO<sup>t</sup>Bu was used. <sup>*d*</sup>1.5 equiv of KO<sup>t</sup>Bu was used.

on the aryl moiety were effectively converted to the corresponding 2,4-diphenyl quinoline in good to excellent yields (77-89%). Electron-withdrawing substituents such as 6-nitro (3j), 6-fluoro (3k, 3o), 6-trifluoromethyl (3l), and 6trifluoromethoxy (3m) groups are also compatible with the present reaction conditions and proceeded smoothly to afford the desired quinolines. Even sensitive halogens such as bromoand chloro-substitutions on the aryl ring, which are sensitive to KO<sup>t</sup>Bu, were also nicely tolerated to afford the desired halogenated quinolines (3n-p). Substitution ortho to the NH<sub>2</sub>-group of 2-allyl aniline did not affect the reactivity (for example, in case of 3q). Another type of aryl group, such as 9*H*fluorene-2-allyl-1-amine, was equally applicable to provide a fused tetracyclic 3r quinoline in good yield (70%). In the case of quinolines 3e-g and 3o-p, further addition of KO<sup>t</sup>Bu was required to achieve the complete consumption of the starting material.

In Scheme 4, the oxidative cyclization of *o*-allylanilines containing substitutions on the allyl counterpart is summarized. Various symmetrically substituted 1',3'-diaryl allyls such as *p*-methyl, *p*-chloro-, and *p*-bromo-phenyls attached to anilines at *ortho*-position reacted smoothly to provide the desired quino-lines (**5a**-**c**, respectively) in moderate yields (80%, 76%, and 77%, respectively). Similar reactivity was found with *o*-allylaniline having the 2-thiophenyl as well as 1-naphthyl group as an aryl counterpart on the allyl moiety (**5d** and **5e**, respectively). Additionally, 2-aryl 4-alkyl quinolines (**5f** and **5g**) were also successfully synthesized using the present protocol. Besides, 4-unsubstituted 2-aryl quinoline **5h** was synthesized in 70% yield using the current strategy. Simple 2-allyl aniline is also reacted to

#### Scheme 4. Variation of Allyl Counterpart<sup>*a,b*</sup>



<sup>a</sup>Reaction conditions: *o*-allyl aniline **1** (0.20 mmol), KO<sup>t</sup>Bu (1.5 equiv), DMSO (1 mL). <sup>b</sup>Isolated yields. <sup>c</sup>Reaction at 80 °C.

provide the desired unsubstituted quinoline (5i), except that a slight increase in reaction temperature ( $80 \,^{\circ}C$ ) was needed. Not only substitutions at the 2- and 4- position of quinolines but also a simultaneous substitution at the 2,3- and 4-position could also be achieved using this approach as shown in the case of 5j and 5k. Notably, 2-styrylquinoline 5l and 5m that are difficult to prepare using other strategies are also synthesized using our methodology.

Further, the reaction of **1a** was scaled 17-fold (1 g, 3.35 mmol) under similar reaction conditions, resulting in a good yield (78%) of the desired product as shown in Scheme 5.

#### Scheme 5. Gram Scale Synthesis



Finally, a one-pot, sequential FC-allylation of anilines with allylalcohols using  $Re_2O_7$  as the catalyst followed by <sup>t</sup>BuOK/DMSO mediated cyclization to provide 2,4-disubstituted quinolines have been demonstrated (see Table 2). Although, moderate yields are obtained, nevertheless, the one-pot methodology is expected to be of high synthetic utility.

A tentative mechanism for the current oxidative cyclization reaction is proposed in Scheme 6. The initial step involves KO<sup>t</sup>Bu/DMSO mediated oxidation<sup>14</sup> of 2-cinnamylaniline 1 to generate intermediate II which undergoes  $6\pi$ -electrocyclization<sup>15</sup> to provide the quinolane III.

Subsequent oxidation of intermediate III using KO<sup>t</sup>Bu/ DMSO afforded product 3 or 5. In general, catalytic KO<sup>t</sup>Bu (0.5 equiv) is sufficient when R is an aryl group (as exemplified in Scheme 3). However, the requirement of excess KO<sup>t</sup>Bu is realized when R is an alkyl or electron-rich aryl group (as exemplified in Scheme 4); otherwise, a prolonged reaction time





<sup>*a*</sup>Reaction conditions: (i) alcohol (0.20 mmol), aniline (0.24 mmol), Re<sub>2</sub>O<sub>7</sub> (5 mol %) in CH<sub>3</sub>CN; (ii) KO<sup>t</sup>Bu (1.2 equiv), DMSO (1 mL). <sup>*b*</sup>Isolated yields after column chromatography.

### Scheme 6. Proposed Mechanism for Current Oxidative Cyclization



is observed. We reasoned that the  $pK_a$  values of the allylic C–H bond (as shown in intermediate I) are responsible for such a display of reactivity.

In summary, we have developed a novel and environmentally benign method for the preparation of 2-arylquinoline and 2styrylquinolines from readily available o-cinnamylanilines using <sup>t</sup>BuOK/DMSO as an economical and commercially available reagent. A sequential synthesis of o-cinnamylaniline, starting from corresponding anilines and substituted cinnamyl alcohols, followed by oxidative cycloannulation has also been demonstrated. The reaction displays a broad substrate scope and good tolerance to a variety of substituents including aryl, alkyl, and heterocyclic groups. 2-Arylquinoline and 2-styrylquinolines are important compounds with potential applications in medicinal chemistry<sup>11,12</sup> that are now accessible via this inexpensive and transition-metal-free approach. Extension of the present reaction demonstrated toward the synthesis of related heterocyclic moieties, and detailed mechanistic investigations are currently in progress in our laboratory.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Experimental procedures, characterization data, and copies of NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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