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Direct arylation for the synthesis of 2-arylquinolines from *N*-methoxyquinoline-1-ium tetrafluoroborate salts and arylboronic acids

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ABSTRACT

A rapid and direct arylation reaction of *N*-methoxyquinoline-1-ium tetrafluoroborate derivatives and arylboronic acids with high regioselectivety at room temperature was discovered. The reaction shows exceptional functional group tolerance and broad substrate scope regarding both the quinoline derivatives and the arylboronic acids.

Introduction

Quinoline and their derivates have been extensively proven to own a variety of bioactivities, such as antimicrobial, antiviral and antihypertensive activities.[1] Among them, 2-arylquinolines have aroused great interest and are widely found in bioactive molecules and drug candidates (Fig. 1).[2]

Traditional methods for the synthesis of 2-arylquinolines usually use cross-coupling between arylhalides and organometallics.[3] Recently, the direct coupling of heterocycles with aryl groups by C–H activity has emerged as an economical and ecological alternative,[4] and a series of methods for the direct C–H arylation of heterocycles have been developed.[5] Among these, due to the stable and readily available characteristics, arylboronic acids and their derivatives used as coupling partners for the direct coupling of heterocycles have aroused wide attentions.[6] In 2010, Baran and co-workers applied a mild silver catalytic system to achieve the direct C–H arylation of electron deficient heterocycles with arylboronic acids which afford the desired regioselective products predominantly at C2- and C4- positions (Scheme 1a).[7] In 2012, Yu's group reported a novel iron-mediated direct C–H arylation of quinoline and arylboronic acids with a ratio of 1.4:1 regioselectivity for the 2- and 4 arylation of quinoline (Scheme 1b).[8] Although the poor regioselectivity may limit these methods to more wide application in organic synthesis, it inspired chemists to explore other improved systems to solve this challenging works. Recently, significant improvements have been made for the direct C–H coupling of heterocyclic *N*-oxides.[9] The utilization of heterocyclic *N*-oxides enhanced the reactivity toward nucleophiles on the C2- and C4-positions,[10] thus improve the regioselectivity of direct C–H coupling. In 2015, Antonchick and co-workers developed a transition-metal-free protocol to couple quinoline *N*-oxides with arylboronic acid which features a high regioselectivity on the C2-positions of quinoline *N*-oxides by using DMSO as solvent at 110 °C. Unfortunately, isoquinoline, pyridine and quinazoline *N*-oxides were not compatible with the developed reaction.[11] Our group is interested in the development of novel methods for the synthesis and functionalization of heterocycles.[12] As a part of our ongoing efforts on the introduction of aryl functional groups into heterocycle molecules, we herein report a novel and efficient procedure for the direct and selective synthesis of 2-arylquinoline from arylboronic acids and the readily prepared *N*-methoxy-4-methylquinoline-1-ium tetrafluoroborate salts at room temperature.

Results and discussion

Initially, the reaction of *N*-methoxy-4-methylquinoline-1-ium tetrafluoroborate salts (**1a**) with phenylboronic acid (**2a**) was chosen as a model reaction for optimization. Performing the reaction

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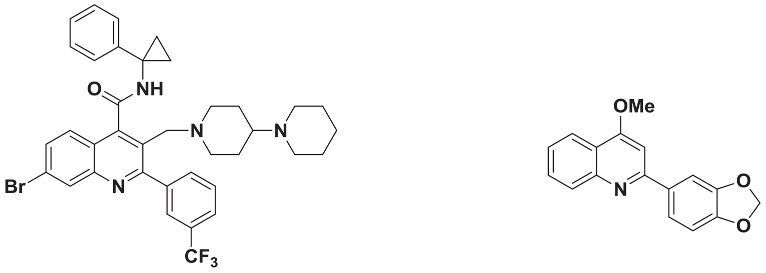
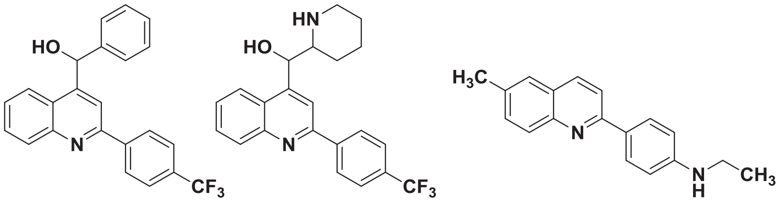


a. GSK2193874 (28)

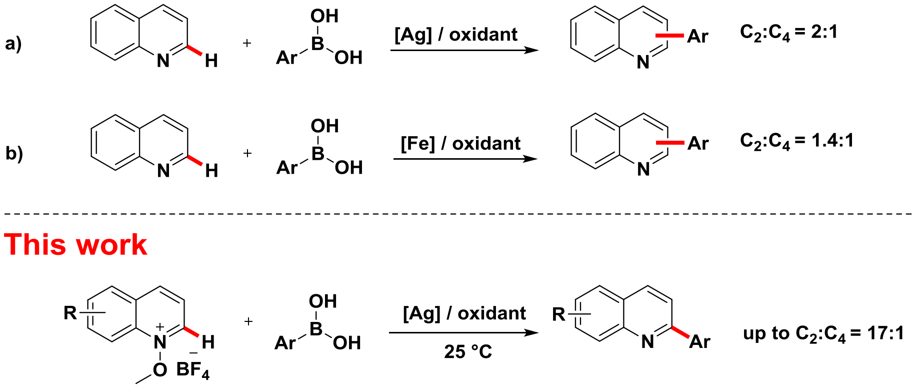
b. Graveolinine



c. Biofilm inhibitor

d. Potential anticancer agent

Fig. 1. Bioactive compounds containing 2-arylquinolines.



Scheme 1. Direct 2-arylation of quinoline derivatives with arylboronic acids.

in the presence of $AgNO_3$ (0.15 mmol), oxidant (1 equiv) at room temperature for 6 h give the desired product **3aa** in 41% yield. (Table 1, entry 1). Dramatic decline was observed by decreasing the amount of $AgNO_3$ to 0.1 mmol (32%, entry 2). Next, obvious increase of the yield of **3aa** was found when the amount of **1a** and **2a** was adjusted to 3 equiv and 1 equiv (entries 4–5). The $Na_2S_2O_8$ was slightly better than $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ (entries 5–7). The screening of the amount of the TFA showed that a good yield (75%) of **3aa** was obtained when 1 equiv TFA was employed. Increasing or decreasing the amount of the additive caused the decrease of the yields (entries 8–10). Finally, the reaction time was optimized as 30 min (entries 10–14).

With the optimized conditions in hand, we then explored a range of *N*-methoxyquinoline-1-ium tetrafluoroborate salts derivatives for the arylation reaction (Table 2). Both C-2 and C-4 arylation products were detected. To our delight, the C-2 arylation products were formed with high regioselectivity. This synthetic method was compatible with both electron-donating and electron-withdrawing groups. The reaction of *N*-methoxyquinoline-1-ium tetrafluoroborate salts **1b** with phenylboronic acid **2a** gave the coupling product **3ba** in 62% yield. Substrate with an electron-withdrawing group on C4 position, such as cyano gave higher yield (**3ea,** 86%) than that with electron-donating one (**3ja**, 37%). In the case of substrate with phenyl, **3da** were obtained in 65% isolated yield. Especially, the substrate with –Cl group at the 4-position could readily converted to the corresponding product in good yield (**3ka**). The bromine-substituted substrates were tolerated as well, resulting the desired products in 63%, 60%, and 67% yields (**3fa, 3ga** and **3ha**), respectively. Importantly, the arylation reactions go smoothly with substrates derived from isoquinoline and pyridine, and the desired products **3ia** and **3la** were obtained in moderate to good yields.

In light of these encouraging results, we further examined the substrate scope for arylboronic acids. The results are summarized in Table 3. The results demonstrate that arylboronic acids bearing electron-donating, electron-neutral, or electron-withdrawing groups on the benzene ring are all well tolerated in this reaction, and the desired products can be obtained in moderate to good yields (**3ab**–**3an**). Substrates containing an electron-donating group gave the coupling products in slightly higher yields. For example, when benzene ring possessed electron-donating groups (e.g., –Me and –OMe), the target products were obtained in 54%, 70%, 57%, 62%, 53% and 57% yields, respectively (**3ab**–**3ag**). A slightly decrease of the yields was found from a substrate with