

Metal-free C5-H Bromination of Quinolines for One-pot C–X (X=C, O, S) Bond Formations

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Received: March 27, 2017; Revised: May 12, 2017; Published online:

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201700391

Abstract: We developed an efficient and convenient method for metal-free bromination of 8-aminoquinoline scaffolds on the C5 position that is geometrically inaccessible. And this bromination step can be followed in a one-pot manner with five kinds of C–X (X=C, O, S) cross-coupling reactions without any extra workup, such as removal of the solvent or filtration for the separation of intermediate. The reaction tolerates a wide scope of alkyl and aryl amides as well as (hetero)aryl boronic acids, generating the corresponding arylation products in good to excellent yields. Furthermore, the one-pot alkenylation, alkynylation, thiolation and phenoxylation of quinolines on the C5 position can be efficiently realized using this brominated quinoline amide molecular platform. Thus, the method shows high practical potential in industrial organic synthesis.

Keywords: Aminoquinoline; metal-free; one pot; C–H activation; cross-coupling

Introduction

Quinolines are important nitrogen-containing heterocycles widely existed in natural products, bio-active molecules and agrochemicals (Figure 1).^[1] And aminoquinolines have been developed as important bidentate directing groups or ligand auxiliary in various kinds of organic reactions, especially in the area of C–H activation.^[2] Therefore, the synthesis of this kind of motifs, especially those with substituted quinolines, is of great importance.

In the past decade, efforts were put in for this kind of synthesis. Generally, there are two methods. One is the ring-closing reaction of appropriate anilines with carbonyl compounds or alkynes, and the desired products are generated with high efficiency.^[3] However, there are limitations and drawbacks. For example, the reaction conditions are usually harsh and expensive multi-substituted anilines are required as starting materials for the synthesis of multi-substituted quinolines.

The other method is the direct late-stage and siteselective C–H functionalization of quinoline frameworks that is suitable for straightforward synthesis of complex molecules with a quinoline scaffold. Exam-



Figure 1. Representative molecules that contain quinoline scaffolds.

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ples of the modification of quinoline scaffolds are mainly on the C2,^[4] C3,^[5] C4^[6] and C8^[7] positions that are easily accessible. As for the C5 position that is geometrically inaccessible,^[8] it was not until 2013 that Stahl et al. reported the first chlorination of quinoline framework via a Cu(I)-catalyzed single electronic transient (SET) mechanism using LiCl as chloride source.^[9] Since then, several methods efficient for C5 modification have been disclosed, such as the reactions of allylation (Zeng^[10]), chalcogenation (Zhu,^[11a] Baidya^[11b] and Xu^[12]), halogenation (Xie^[13] and many others^[14]), sulfonylation (Wei^[15] and many others^[16]), amination (Baidya^[17] and others^[18]), azidation (Zhu^[19]), fluoroalkylation (Huang^[20] and others^[21]), nitration (Ribas^[22] and others^[23]), esterification (Xia^[24] and others^[25]), methoxylation (Shi^[26] and You^[27]), homo-coupling (Watkins^[28]) and alkylation (Song^[29a,b] and others^[29c]). Although great progresses on remote C5-H functionalization of quinoline have been made, there are still drawbacks: (1) The reaction conditions are different, and it is not easy to extend a particular system to another by simple modification, and that developed by Zhang et al.^[16c] for sulfonalyation is the only exception. Therefore, it is desirable to develop a general and simple method to realize the transformations. (2) A number of direct remote C-H functionalization on C5 position of quinoline have not been demonstrated, including arylation, alkynylation, alkenylation, etc. (3) The harsh reaction conditions for remote C5-H functionalization of quinoline, such as those adopted in thiolation, [11a] should be replaced by some milder ones. (4) Recently, Baidva et al.^[14d] disclosed an efficient two-step transformation combined with metal-catalyzed remote C5-H iodination followed by a traditional cross-coupling process. However, in the method the iodide produced in the first step has to be isolated. And the protocol is not appropriate for one-pot synthesis, because the metal for the first step might have negative effect on the transformation that follows. As a result, there is a need for the isolation of the halogenation intermediate (vide infra).

Compared to analogs such as iodoarene (less stable and with heavier molecular weight) and chloroarene (less active), bromoarene is more stable and reactive, making it a good intermediate for the generation of various kinds of functional molecules that are widely used in organic synthesis.^[30] Herein, we report an efficient protocol that combines fast and efficient metal-free^[31] bromination on C5 position of quinolines with traditional C–X (C, O, S) cross-coupling reactions, including arylation, alkynylation, alkenylation, phenoxylation, and thiolation. Without the need for intermediate isolation, materials that were previously inaccessible by metal-catalyzed halogenation process can be synthesized in a one-pot manner.

Results and Discussion

We first attempted the synthesis of C5-arylated quinoline **4a** by treating 8-aminoquinoline amide (**1a**) with any reagent directly via C5-H arylation similar to that of C5-H chalcogenation reported by us (Table 1, entries 1-3).^[11a] The result was that there is no formation of 4a. Nonetheless, unexpected C5-brominated quinoline 2a was obtained when CuBr₂ was used. To investigate whether a cascade Suzuki cross coupling^[32] can proceed in a one-pot manner after bromination, we combined the bromination with a Pdcatalyzed Suzuki cross-coupling reaction without any workup for 2a isolation. To our delight, 4a could be obtained in 27% yield (entry 4) using $Pd(PPh_3)_4$ as catalyst. The use of PdCl₂ or Pd(PPh₃)₂Cl₂ as catalyst resulted in low efficiency (entries 5-6). We then turned our attention to metal-free halogenation using NXS (X = Cl, I, Br) (entries 7–9) and found that Suzuki coupling proceeded with high efficiency. The results imply that the metal salts from the bromination process have a negative effect on the Suzuki cross coupling that follows. And we found that NBS is the best choice for the formation of 4a (entry 8), while DMF is the best among the solvents tested (entries 10–12). Further optimization of reaction conditions resulted in 90% yield of 4a when bromination was conducted at 50°C for 1 h (entries 13–18). Note that the second step was performed with simple addition of the required chemicals into the mixture obtained at the end of the metal-free brominating reaction. And there is no need of solvent removal or material isolation. Such convenient transformation cannot be realized in the metal-catalyzed halogantion processes. For example, we performed a number of metalcatalyzed/mediated bromination that were reported to be efficient,^[14a,d,h] and had the Suzuki cross coupling reaction followed as shown in Scheme 1. It was found that Suzuki cross coupling failed to proceed in such an approach.

With the optimized reaction conditions in hand, we explored the applicability of the protocol and examined a series of aryl boronic acids (Table 2). It was found that aryl boronic acid bearing electron-donating or electron-withdrawing groups on the benzene ring are well tolerated (4a-4s). With electron-donating (4b-4i) and electron-withdrawing groups (4j-4p), the corresponding products are obtained in moderate to good yields. The para, meta or ortho substitution of aryl rings with a methyl group does not significantly affect the arylation reaction (4b, 4h and 4i). 1-Naphthylboronic acid could react smoothly to give 4q in 75% yield. When a methyl group is on the C2 (4r)or a methoxyl group on the C6 position (4s), the corresponding product can be obtained in good vield. However, alkyl boronic acid (3t) is less reactive in this catalytic system, but it can be successfully synthesized

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Table 1. Optimization of reaction conditions.^[a]

	H Cataly Tem	[X] yst. Solv. p, t, N ₂	X NH 2a lation and work	[Pd] (10 mo [Ar] (2 equi Na ₂ CO ₃ (2 ec DMSO (1.0 140 °C, 6 h	l%) iv.) mL) n, N2	Ph NH 0 4a
entry	[X] (equiv.)	Temp./ time	Solv. (1 mL)	[Ar]	[Pd]	Yield of 4a [%] ^b
1	CuBr ₂ (1.5)	120 ºC / 12 h	DMF	PhI	-	NR
2	CuBr ₂ (1.5)	120 ºC / 12 h	DMF	Bpin	-	NR
3	CuBr ₂ (1.5)	120 °C / 12 h	DMF	PhB(OH) ₂	-	NR
4	CuBr ₂ (1.5)	120 ºC / 12 h	DMF	PhB(OH) ₂	Pd(PPh ₃) ₄	27
5	CuBr ₂ (1.5)	120 °C / 12 h	DMF	PhB(OH) ₂	PdCl ₂	23
6	CuBr ₂ (1.5)	120 °C / 12 h	DMF	PhB(OH) ₂	Pd(PPh ₃) ₂ C	Cl ₂ 20
7	NCS (1.1)	120 °C / 12 h	DMF	PhB(OH) ₂	$Pd(PPh_3)_4$	trace(55% ^c)
8	NBS (1.1)	120 °C / 12 h	DMF	PhB(OH) ₂	$Pd(PPh_3)_4$	91
9	NIS (1.1)	120 °C / 12 h	DMF	PhB(OH) ₂	$Pd(PPh_3)_4$	21
10	NBS (1.1)	120 °C / 12 h	Toluene	PhB(OH) ₂	$Pd(PPh_3)_4$	70
11	NBS (1.1	120 °C / 12 h	THF	PhB(OH) ₂	Pd(PPh ₃) ₄	57
12	NBS (1.1)	120 ºC / 12 h	1,4-Dioxane	PhB(OH) ₂	$Pd(PPh_3)_4$	50
13	NBS (1.1)	80 ºC / 12 h	DMF	PhB(OH) ₂	$Pd(PPh_3)_4$	93
14	NBS (1.1)	50 °C / 12 h	DMF	PhB(OH) ₂	$Pd(PPh_3)_4$	91
15	NBS (1.1)	25 °C / 12 h	DMF	PhB(OH) ₂	Pd(PPh ₃) ₄	92
16	NBS (1.1)	50 °C / 6 h	DMF	PhB(OH) ₂	Pd(PPh ₃) ₄	90
17 ^d	NBS (1.1)	50 °C / 1 h	DMF	PhB(OH) ₂	Pd(PPh ₃) ₄	92 (90)
18	NBS (1.1)	50 °C / 10min	DMF	PhB(OH) ₂	Pd(PPh ₃) ₄	55

^[a] **1a** (0.2 mmol), [X] (equiv.), [Ar] (**3**, 0.4 mmol), solvent (1.0 mL), N₂;

^[b] GC yield, using *n*-tridecane as internal standard; the number in parentheses is isolated yield;

^[c] at 160 °C;

^[d] in this run, **2a** can be isolated in 96% yield at the end of the brominating step.

via a two-step manner by isolating 2a with EtMgBr in Et₂O at room temperature for 24 h (4t, 41%). None-theless, heterocyclic boronic acid such as thienyl-, furyl-, and pyridinyl-boronic acids are all compatible, giving the target products in excellent yields (4u-4y).

Then the scope of 8-aminoquinoline amides was explored under the adopted reaction conditions (Table 3). A number of aliphatic amides give the products in moderate to good yields (5a-5d). Moreover, the system could be applied to a variety of benzamides, generating the desired products in good yields (5e-5i). The result is in sharp contrast with that of our thiolation system in which only a mixture of thiolated products (on benzamides or quinoline motif) can be obtained.^[11a] Herein, the bromination of quinoline ring is favored over the metalation-deprotonation (CMD) process at the *ortho*-position of benzamide.^[14b] Furthermore, arylated product in moderate yield can be obtained in the two cases of heterocyclic amides (**5h** and **5i**).

To demonstrate the synthetic utility of this method, we carried out the reaction on 5 mmol scale, and the desired product was obtained in 78% yield (1.186 g of 4a) (Scheme 2a). The amide bond could be readily cleaved without damaging the C–C bond that is newly formed to obtain 83% yield of **6**. Followed by sulfonylation of amino group (85% yield of **7**), a drug candidate for inhibiting ubiquitination was synthesized in a "one-pot" manner to give **7** in a yield of 55%. The approach is superior to the procedures patented by

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Scheme 1. Suzuki cross coupling following reported bromination methods.

Rigel Pharmaceuticals Inc.,^[33] thereby providing a feasible protocol for concise synthesis of biologically relevant arylated substances. Furthermore, by using this platform molecule, one can realize one-pot remote alkenylation (C-H bromination and Heck reaction^[34]), alkynylation (C-H bromination and Sonogashira cross-coupling reaction^[35]), and phenoxylation (C-H bromination and Ullmann-type C-O crosscoupling reaction^[36]) of 8-aminoquinoline scaffolds on the C5 position (Scheme 2b), with the desired products 8, 9 and 10 obtained in 80%, 83% and 67% yield, respectively. It is worth pointing out that to the best of our knowledge there are no reports on direct C5-H functionalization for the synthesize of 8, 9, 10.

To further demonstrate the advantage of using this one-pot method, we attempted the Ullmann-type C-S cross-coupling^[37] using the recently reported approach of metal-free bromination of quinolines under aqueous condition,^[14k] and obtained no C-S cross coupling product (Scheme 3a, Condition A). However, using our one-pot protocol, desired product 11 and 12 can be obtained in 85% and 90% yield, respectively (Scheme 3a, Condition B). The above results indicate that the solution of the first reaction has a significant effect on the Ullmann-type C-S bond cross coupling reaction that follows, and the DMF in the solution can be directly used in the cross coupling reaction without any workup processes such as isolation and evaporation that are essential if the reaction were performed in aqueous solution. Compared to our work on C-H direct thiolation of quinolines on C5 position (12, 88%, in the presence of 1.5 equivalents of CuBr₂ at 160 °C for 24 h) (Scheme 3b),^[11a] the present protocol exhibits higher yield (12, 90%) with lower metal loading (0.2 equivalent of CuI) and under milder reaction conditions (bromination at 50°C for 1 h, followed by C–S cross-coupling at 100°C for 18 h) (Scheme 3a, Condition B).

Studies were performed to obtain insight into the reaction mechanism (Scheme 4). The addition of a 2,6-diisopropyl-4-methylphenol radical inhibitor, (BHT) or (2,2,6,6-tetramethyl-piperidin-1-yl)oxidanyl (TEMPO), resulted in inhibition of reaction (Scheme 4a), indicating the involvement of a radical step. We found that the arylation reaction is of low efficiency with N-(naphthalen-1-yl)pivalamide 1b or N-protected amide 1b', yielding the corresponding product with no regioselectivity (Schemes 4b). When analog N,O-bidentate directing group 1c is used, the quinoline is hydrolyzed and no desired product is obtained (Schemes 4c), which confirms the indispensable role of the 8-aminoquinoline skeleton for this reaction. The protocol is also ineffective with 1d, giving 1da in low yield and poor regioselectivity (Schemes 4d), plausibly due to the low efficiency and poor regioselectivity of the first bromination step. Thus, the acyl group is important in the control of regioselectivity. In Scheme 4e, the two-step reaction is of high efficiency, giving 2a and 4a in 96% and 96% yield, respectively. The molecular structure of 2a has been unambiguously confirmed by single crystal X-ray diffraction study (Figure 2) (CCDC 1497054).^[38]

On the basis of the results of the control experiments and those of literatures,^[9,13-14] we propose a

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Reaction conditions: **1** (0.2 mmol), NBS (0.22 mmol), DMF (1.0 mL), 50 °C, 1 h, N₂; then RB(OH)₂ (**3**, 0.4 mmol), Pd(PPh₃)₄ (10 mol%), Na₂CO₃ (2 equiv.), DMSO (1.0 mL), 140 °C, 6 h, N₂, isolated yield; ^{*a*} in a two-step manner followed by treatment of isolated **2a** with EtMgBr in Et₂O at room temperature for 24 h.

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Reaction conditions: **1** (0.2 mmol), NBS (0.22 mmol), DMF (1.0 mL), 50 °C, 1 h, N₂; then PhB(OH)₂ (**3a**, 0.4 mmol), Pd(PPh₃)₄ (10 mol%), Na₂CO₃ (2 equiv.), DMSO (1.0 mL), 140 °C, 6 h, N₂, isolated yield.



Figure 2. X-ray of 2a

pathway for arylation on the C5 position of quinolines (Scheme 5). First, Br• radical is generated from NBS upon heating. Then the quinoline ring is brominated to generate 2a. After Suzuki coupling, the desired product 4a is obtained.

Conclusion

In summary, we developed an efficient method for the synthesis of 5-(hetero)arylated quinoline motifs via a cascade reaction of metal-free radical C5–H bromination and Suzuki-coupling reaction without isolation of the intermediate bromide. The system is applicable to a variety of boronic acids and amides, giving the target products in good yields. Furthermore, through this platform molecule, the alkenylation, alkynylation and thiolation, and phenoxylation of quinolines on the C5 position can also be efficiently realized. Thus, this protocol shows high practical potential in industrial orgnanic synthesis.

Experimental Section

General Procedure for One-Pot Arylation of Quinolines

To a 10 mL screw capped vial equipped with a magnetic stirring bar was added 8-aminoquinolines amide (1) (0.2 mmol), *N*-bromosuccinimide (0.22 mmol), and DMF (1.0 mL) under N₂ atmosphere. The reaction mixture was placed in a pre-heated oil bath at 50 °C and vigorously stirred





Scheme 2. Gram-scale and synthesis application.



Scheme 3. Comparison of Ullmann-type C-S cross-coupling performed under the different conditions.

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Scheme 4. Control experiments.



Scheme 5. Possible pathway.

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for 1 h to generate brominated quinoline **2**. Afterward the reaction mixture was cooled down to ambient temperature and added boronic acid derivatives (0.4 mmol), sodium carbonate (0.4 mmol), Pd(PPh₃)₄ (0.02 mmol), and DMSO (1.0 mL) under N₂ atmosphere. The mixture was placed in an oil bath pre-heated at 140 °C and vigorously stirred for 6 h. Subsequently it was cooled down to room temperature, filtered through a plug of celite and then washed with saturated brine and extracted with ethyl acetate (3×5.0 mL). The solvents were removed under reduced pressure and the crude reaction mixture was purified by chromatography on silica gel using PE/EtOAc as eluent to obtain the desired product **4** or **5**.

Acknowledgements

We thank the National Natural Science Foundation of China (Nos. 21373003 and 21676076), the Natural Science Foundation of Hunan Province (2016JJ3034), and Hunan Youth Talent (2016RS3023) for financial support. C.T. Au thanks the Hunan University for an adjunct professorship. We thank Prof. Nobuaki Kambe and Prof. Takanori Iwasaki (Osaka University), Prof. Akihiro Orita (Okayama University of Science), and Prof. Li-Biao Han (AIST, Tsukuba, Japan), and Prof. Wai-Yeung Wong (Hong Kong Polytechnic University) for helpful discussion.

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UPDATES

Metal–free C5-H Bromination of Quinolines for One-pot C–X (X=C, O, S) Bond Formations

Adv. Synth. Catal. 2017, 359, 1-11

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