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Potassium Hydroxide−Catalyzed Alkynylation of Heteroaromatic N-Oxides with Terminal Alkynes

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Abstract: An efficient potassium hydroxide-catalyzed alkynylation of heteroaromatic N-oxides under transition-metal-free conditions with the assistance of visible-light has been developed. Various C2-alkynylheterocycles were obtained in up to 92% yield with good functional group tolerance. This new method is operational simple, highly efficient, atom economic, and environmental friendly.

Keywords: quinoline N-oxides, alkynylation, visible-light, transition-metal-free, potassium hydroxide-catalyzed.

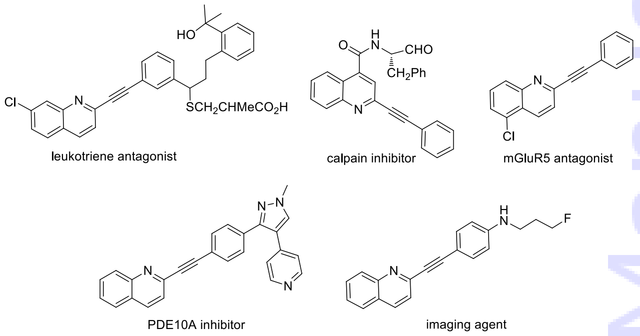
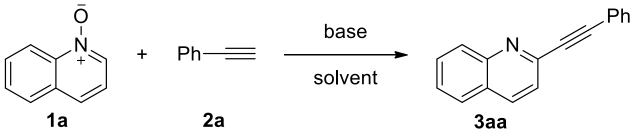


Figure 1. Examples illustrating the importance of 2-alkynylquinolines.

Alkylated arenes have been proven to be ubiquitous structural motifs in organic synthesis, pharmaceuticals and organic materials.[1] Consequently the development of efficient methods to construct this privileged motif is of particular interest. The conventional procedures involve Pd/Cu-cocatalyzed Sonogashira coupling reaction of aryl halides or its analogs with terminal alkynes.[2] Direct alkynylation of (hetero)aromatic compounds has also been developed with various alkynylating reagents, such as alkynyl halides/analogs,[3] hypervalent iodine reagents,[4] arylsulfonylacetylene,[5] and Grignard reagents.[6] From the viewpoint of atom- and step-economy, the direct dehydrogenative cross-coupling reaction of (hetero)arenes with terminal alkynes has appeared as a straightforward and efficient strategy. Following the pioneer work of Nevado and co-workers on the gold-catalyzed ethynylation of electron-rich arenes using electron-deficient alkynes,[7] Su and co-workers reported a Cu-catalyzed direct alkynylation of electron-deficient polyfluoroarenes using terminal alkynes.[8] The heteroarenes with highly acidic (low pK_a) C-H bonds, such as indoles and azoles, were also easily subject to dehydrogenative coupling with terminal alkynes.[9] The groups of Li,[9a] Bobade,[9b] Chang,[9c] Miura,[9d, 9e] and Murai[9f, 9g] had made outstanding contributions in this regard. Recently, Yu[10] and Shi[11] groups demonstrated Cu(II)-mediated and Ni(II)-catalyzed alkynylation of unactivated $C(sp^2)$-H with terminal alkynes using amide-oxazoline and PIP (2-pyridinyl isopropyl) as directing groups. Another representative example was developed by Su and co-workers[12] involving Pd-catalyzed direct alkynylation of thiophenes and furans using terminal alkynes. However, there are still some drawbacks with these procedures, including the undesired homocoupling of alkynes, requirement of transition metal catalysts and stoichiometric oxidants.

Owing to the wide application of 2-alkynylquinolines in advanced functional materials and pharmaceuticals,[13] as exemplified in **Figure 1**, a general method for direct dehydrogenative cross-coupling of quinolines with terminal alkynes under green and efficient conditions is highly desirable. In our continued efforts for the development of direct C-H functionalization of quinoline N-oxides,[14] we have successfully realized the base-promoted heteroarylation of quinoline N-oxides,[14g,14h] in which N-oxide served as a directing group resulting in easy cleavage of the ortho C-H bonds of heteroaryls. We

Table 1. Optimization of the coupling of quinoline N-oxide **1a** with phenylacetylene **2a**[a]



Entry	Bases(equiv)	Solvents	Yield [%][b]
1	KOH(1.0)	toluene	66
2	NaOH(1.0)	toluene	17
3	K_2CO_3(1.0)	toluene	ND[l]
4	Cs_2CO_3(1.0)	toluene	ND[l]
5	^{t}BuOLi(1.0)	toluene	ND[l]
6	^{t}BuONa(1.0)	toluene	52
7	^{t}BuOK(1.0)	toluene	Trace
8	KOH(1.0)	xylene	41
9	KOH(1.0)	DCE	Trace
10	KOH(1.0)	CH_3CN	Trace
11	KOH(1.0)	THF	Trace
12	KOH(1.0)	1,4-dioxane	ND[l]
13	KOH(1.0)	DMF	Trace
14	KOH(1.0)	DMSO	Trace
15	KOH(0.5)	toluene	61
16	KOH(0.3)	toluene	60
17	KOH(0.2)	toluene	45
18[c]	KOH(0.3)	toluene	66
19[d]	KOH(0.3)	toluene	74
20[e]	KOH(0.3)	toluene	85
21[f]	KOH(0.3)	toluene	85
22[g]	KOH(0.3)	toluene	59
23[h]	KOH(0.3)	toluene	58
24[i]	KOH(0.3)	toluene	68
25[j]	KOH(0.3)	toluene	85
26[k]	KOH(0.3)	toluene	85

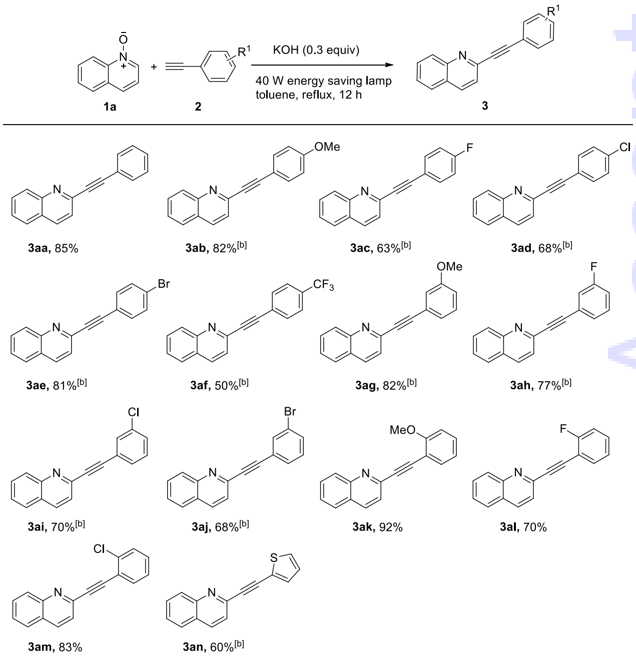
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), solvent (2.0 mL), dark, reflux, 12 h. [b] Isolated yields. [c] 15 W energy saving lamp. [d] 26 W energy saving lamp. [e] 40 W energy saving lamp. [f] two 40 W energy saving lamps. [g] 3 W green LED. [h] 3 W purple LED. [i] 3 W blue LED. [j] 9 W blue LED. [k] 12 W blue LED. [l] ND = not detected. DCE = 1,2-dichloroethane, CH_3CN = acetonitrile, THF = tetrahydrofuran, DMF = N,N-dimethylformamide, DMSO = dimethylsulfoxide.

herein report a highly efficient and transition-metal-free direct dehydrogenative cross-coupling reaction of quinoline N-oxides and terminal alkynes.

With quinoline N-oxide (**1a**) and phenylacetylene (**2a**) as model substrates, various reaction parameters were investigated (**Table 1**). We were pleased to find that the reaction worked smoothly to produce the desired alkynylated product **3aa** in 66% yield using potassium hydroxide (KOH) as the base and toluene as the solvent under reflux (entry 1, **Table 1**). Although sodium hydroxide (NaOH), sodium tert-butoxide (^{t}BuONa) and potassium tert-butoxide (^{t}BuOK) could also promote the reaction, they gave lower yields comparing to KOH (entries 2, 6 and 7 vs entry 1). Other bases, such as potassium carbonate (K_2CO_3), cesium carbonate (Cs_2CO_3), and lithium tert-butoxide (^{t}BuOLi), did not lead to the formation of **3aa** (entries 3-5). We then examined both nonpolar and polar solvents. Toluene gave the highest yield, while only trace amount of **3aa** was observed in DCE, CH_3CN, THF, DMF, and DMSO (entries 9-11, 13, 14). The reaction did not proceed in 1,4-dioxane (entry 12). It is worth noting that the slightly lower yield was obtained when the loadings of KOH were reduced to 0.5 or 0.3 equiv (entries 15-16 vs entry 1). Interestingly, we found that the light could promote the reaction. The desired product **3aa** was isolated in 85% yield under irradiation of a 40 W energy saving lamp (entry 20). Further screening of light source demonstrated that blue LED could also promote this alkynylation (entries 22-26). After surveying the reaction parameters, the optimal reaction conditions were determined as follows: KOH (0.3 equiv), toluene 2.0 mL, 40 W energy saving lamp, refluxing for 12 h.

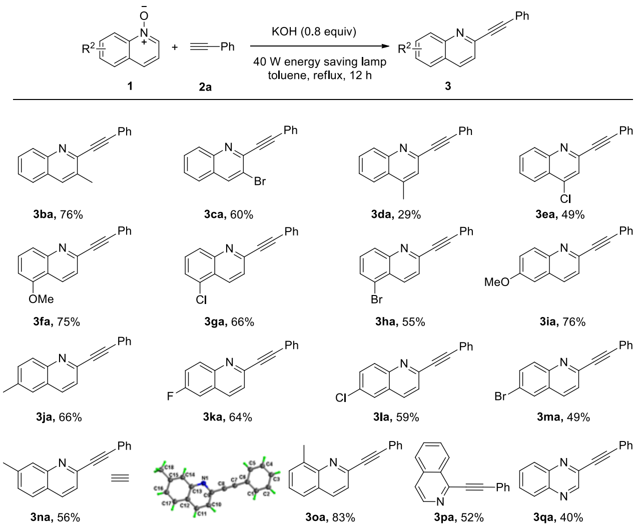
With the optimal conditions in hand, we turned our attention to explore the scope of the substrates. The results are shown in **Table 2** and **Table 3**. A series of representative alkynes were tested with quinoline N-oxide **1a** in **Table 2**. It was found that both electron-rich and electron-deficient aryl substituted alkynes were tolerated and afforded the corresponding products in good yields. Generally, arylacetylenes with electron-donating groups on their phenyl rings gave higher yields than that with electron withdrawing groups (**3ab, 3ag, and 3ak** vs **3af**). *Meta*-substituted phenylac etylenes also worked well and gave the desired products **3ag-3aj** in good to excellent yields (68-82%). Steric hindrance on the

Table 2. KOH-catalyzed alkynylation of quinoline N-oxides with terminal alkynes[a],[c]

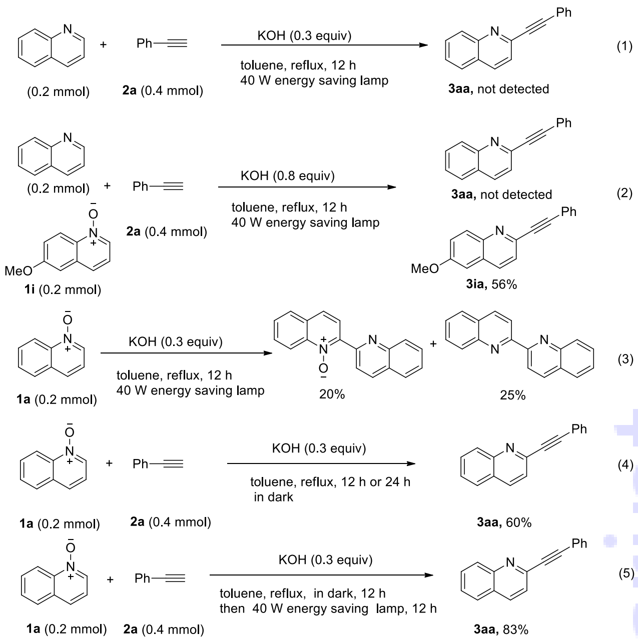


[a] Reaction conditions:**1a** (0.2 mmol), **2** (0.4 mmol), KOH (0.3 equiv), toluene (2.0 mL), reflux, 12 h, 40 W energy saving lamp, 12 h. [b] KOH (0.5 equiv). [c] Isolated yields.

Table 3. KOH-catalyzed alkynylation of quinoline N-oxides with terminal alkynes [a],[b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), KOH (0.8 equiv), toluene (2.0 mL), reflux, 12 h, 40 W energy saving lamp. [b] Isolated yields.

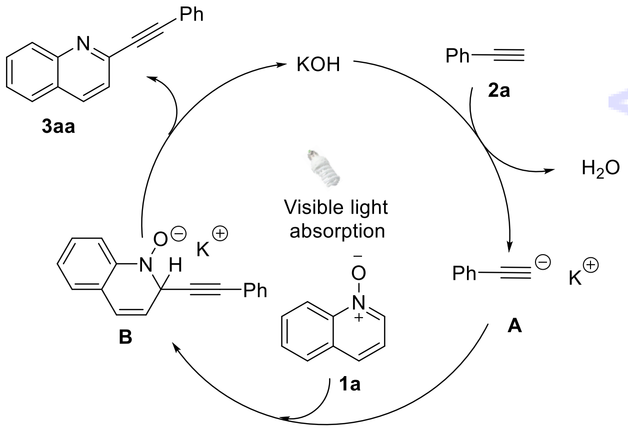


Scheme 1. Controlled experiments

aryl group of phenylacetylene had no significant influence on this transformation, e.g. the coupling reaction of *o*-methoxy-phenylacetylene (**2k**) with quinoline N-oxide (**1a**) gave the desired product in an excellent yield of 92%. In addition, heteroarylacetylene, for example 2-ethynylthiophene was also tested, affording the corresponding product **3an** in 60% yield. While, this catalytic system was not applied to alkylacetylenes. When cyclohexylacetylene and trimethylsilylacetylene were used as the substrates, the corresponding products were not obtained.

Encouraged by the results obtained with alkynes, this catalytic system was applied to other N-oxides under optimized reaction conditions. The desired products was provided in lower yields. N-oxides could be employed as suitable substrates using 0.8 equivalent of KOH, giving the corresponding products **3ba**-**3qa** in good yields for most cases (**Table 3**). When the pyridine ring of quinoline N-oxide was substituted by methyl and halogen groups, the products were isolated in 29-76% yields (**3ba**-**3ea**). The reactions also provided the desired products in moderate to good yields when the substituents were on the benzene ring of quinoline N-oxides (**3fa**-**3oa**). This method could also be applied to alkynylation of isoquinoline N-oxide and quinoxaline N-oxide, giving the products **3pa** and **3qa** in 52% and 40% yields. When pyridine N-oxide was used as the substrate, the corresponding product was not obtained. The molecular structure of **3na** was confirmed by single crystal X-ray diffraction analysis,[15] and is shown in Figure S1 in the Supporting Information.

To gain insights into the mechanism of this transformation, some control experiments were carried out (**Scheme 1**). The desired product **3aa** was not obtained when the condensation of quinoline with **2a** was processed under standard reaction conditions, which indicated that N-oxide moiety was necessary for this transformation (eq 1). A 1:1 mixture of 6-methoxyquinoline N-oxide (**1i**) and quinoline had been added to the reaction system under standard reaction conditions, and compound **3ia** was obtained in 56% yield, while **3aa** was not observed. This result demonstrated that quinoline was not a reaction intermediate (eq 2). Dimerization of **1a** was found in the absence of **2a** (eq 3). However, no homo-coupling product of either the terminal alkynes or the N-oxides was observed in the model reaction, which suggested that quinoline N-oxide could react as both electrophile and nucleophile. To clarify the role of light, two parallel reactions were conducted under the standard conditions. In dark, **3aa** was obtained in 60% yield (eq 4), and quinoline N-oxide was not detected. Furthermore, the yield of **3aa** was not improved after prolonging the reation time to 24 h.



Scheme 2. Proposed reaction mechanism.

Another reaction proceed in dark for 12 h, and then proceed in 40 W energy saving lamp, **3aa** was obtained in 83% yield (eq 5). These results indicated that quinoline N-oxide could be first afforded as an electrophilic reagent which was further converted into the corresponding alkynylation quinoline *via* the assistance of visible light, but the reason why light promotes the reaction is still unknown in this case.

On the bases of the results obtained above and previous literatures,[16] a tentative nucleophilic addition-elimination process was proposed (**Scheme 2**). First, phenylacetylene **2a** was deprotonated byKOH to generate a phenylacetylene carbanion **A**, which further attacked the *ortho*-position of quinoline N-oxide **1a** and gave intermediate **B**. Finally, product **3aa** was produced through [1,3]-hydrogen migration assisted by visible light, and the catalyst KOH re-entered the next catalytic cycle.

In conclusion, we have developed a KOH-catalyzed alkynylation of heteroaromatic N-oxides under transition-metal-free conditions with the assistance of visible-light. A series of *ortho*-alkynylated heterocycles were synthesized in up to 92% yield. This reaction features atom economy, environmental friendliness, high efficiency, additive-free, and good functional group tolerance. The present protocol provides an important approach to synthesize *ortho*-alkynylated heteroaromatic compounds, which would be useful to build multitudinous biologically active molecules and functionalized materials.

Experimental Section

Typical Procedure

The mixture of quinoline N-oxides (29.0 mg, 0.2 mmol), phenylacetylenes (44 uL, 0.4 mmol) and KOH (3.4 mg, 0.06 mmol, 30% mol) in anhydrous toluene (2.0 mL) was stirred and refluxed conditions under 40 W energy saving lamp for 12 hours. When the reaction was completed, the crude mixture was cooled to room temperature. The mixture was purified by column chromatography on silica gel. (Elute: petroleum ether-EtOAc) to give the desired product **3aa** as a yellow oil; yield: 38.6 mg (85%).

Acknowledgements

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[15] CCDC 1486069 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; deposit@ccdc.cam.ac.uk].

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