Organic LETTERS

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Synthesis of 2-Alkenylquinoline by Reductive Olefination of Quinoline *N*-Oxide under Metal-Free Conditions

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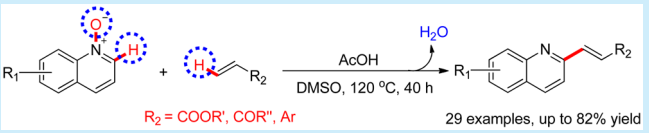
Supporting Information

ABSTRACT: Synthesis of 2-alkenylquinoline by reductive olefination of quinoline *N*-oxide under metal-free conditions is disclosed. Practically, the reaction could be performed with quinoline as starting material via a one-pot, two-step process. A possible mechanism is proposed that involves a sequential 1,3-dipolar cycloaddition and acid-assisted ring opening followed by a dehydration process.



Quinoline derivatives are significant and versatile building blocks in synthetic organic chemistry. Importantly, they have found wide applications in various fields such as pharmaceutical, agrochemical, and dye chemistry.[1] Among them, 2-alkenylquinoline represents one of the typical scaffolds possessing significant bioactivities, as exemplified by compounds shown in Figure 1: Montelukast (A_1, drug for asthma),[2] Chimanine B (A_2, antileishmanial activity),[3] VUF 5017 (A_3, $CysLT_1$ antagonist),[4] and allylic alcohol A_4 (antileishmanial activity).[5]

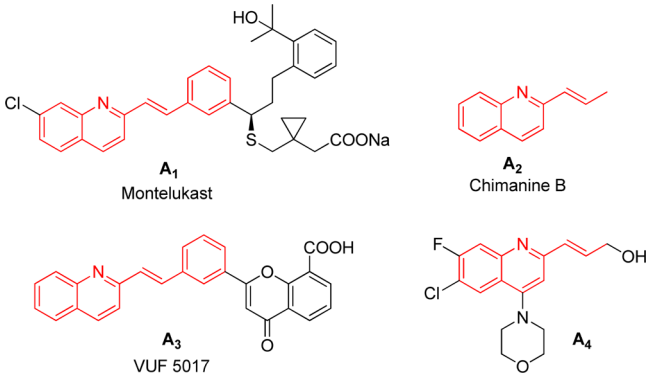
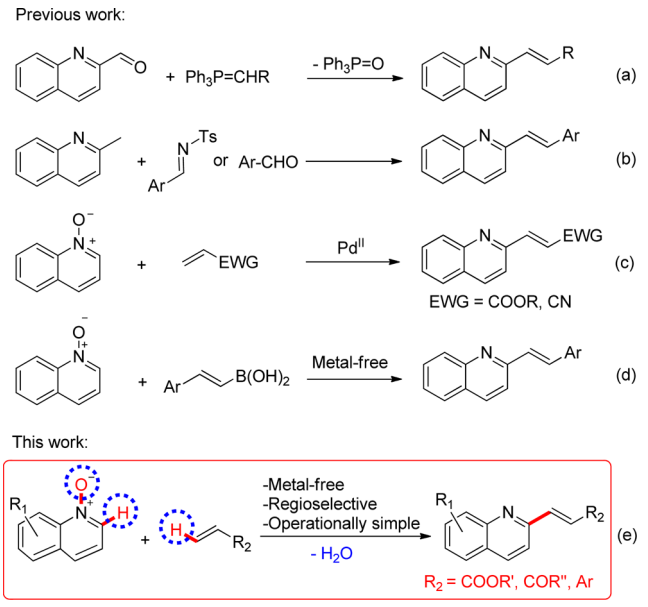


Figure 1. Some examples of bioactive 2-alkenylquinolines.

Due to the importance of 2-alkenylquinolines, considerable efforts have been devoted to developing various methods to construct such motifs. The Wittig reaction was applicable using 2-quinolinecarboxaldehyde as a substrate.[6] However, formation of a stoichiometric amount of phosphane oxide byproduct often complicated the purification process (Scheme 1a). Another well-established strategy involves reacting 2-methylquinolines with aldehydes or imines in the presence or absence of transition metal catalysts (Scheme 1b).[7] However, the limited availability of substituted 2-methylquinolines narrows its range

Scheme 1. Overview of 2-Alkenylquinoline Syntheses



of use. Considering that quinolines are more abundant and obtainable than 2-quinolinecarboxaldehydes or 2-methylquinolines, although still challenging, direct vinylation of quinolines at 2-positions would be extremely attractive and would enrich the structural diversity of the quinoline moiety of 2-alkenylquinoline. In this regard, there are two related reports focusing on the transition-metal-catalyzed C2-selective alkenylation of pyridine, in which one quinoline substrate example was given with moderate yields.[8] It was also revealed that, alternatively, quinoline-derived *N*-iminopyridinium ylide[9] and

Received: February 24, 2016

DOI: 10.1021/acs.orglett.6b00522
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N-oxides[10] could serve as surrogates of quinolines and exhibited higher reactivity. The Wu group found that reaction of quinoline *N*-oxides with acrylates via a palladium(II)-catalyzed C−H activation process synthesized a series of 2-alkenylquinolines in high yields (Scheme 1c).[10a] Recently, Antonchick et al. developed a metal-free cross-coupling reaction of quinoline *N*-oxides with electron-rich aromatic and alkenyl boronic acids to afford various 2-furyl and 2-styryl quinolines (Scheme 1d).[10b] Herein, we describe a convenient protocol to prepare 2-alkenylquinoline by reductive olefination of quinoline *N*-oxide with olefin under metal-free conditions (Scheme 1e). The reaction is operationally simple and easy to scale up to gram scale. Furthermore, a sequential one-pot process involving in situ oxidation of quinoline followed by olefination proved to be very successful, which made the overall protocol even simpler and more convenient.

Initially, we found that quinoline *N*-oxide (**1a**) could react with ethyl acrylate (**2a**) in DMSO to give 2-alkenylquinoline **3aa** in 30% yield (Table 1, entry 1). Screening of different additives indicated that acid assisted the transformation, and among them, acetic acid (AcOH) proved to be the most effective (entries 2−7). Investigation of the reaction temperature showed that the appropriate temperature was 120 °C (entries 8 and 9). Gratifyingly, increasing the amount of AcOH from 1.0 to 3.0 equiv improved the yield from 46 to 56% (entry 10). No further improvement was observed when more AcOH was added (entry 11). Further improvement of the yield to 67% was achieved by increasing the amount of **2a** to 10.0 equiv and extending the reaction time to 40 h (entries 12−14). Moreover, other solvents, such as NMP and sulfolane, were also examined but failed to give better results (entries 15−17).

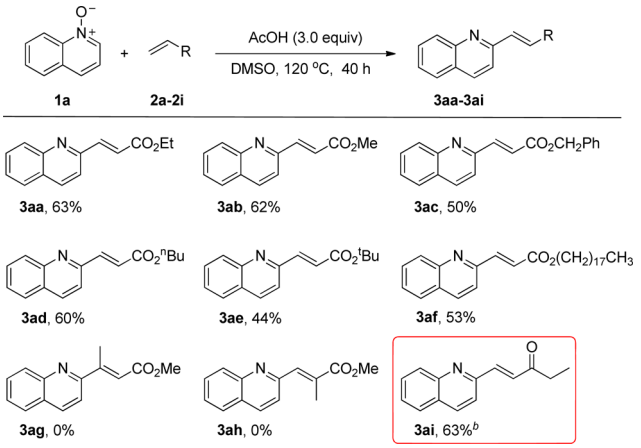
Table 1. Optimization of the Reaction Conditions[a]

entry	additive (equiv)	time (h)	*t* (°C)	yield (%)[b]
1	none	23	130	30
2	AcOH (1.0)	23	130	44
3	pivalic acid (1.0)	23	130	37
4	benzoic acid (1.0)	23	130	37
5	boric acid (1.0)	23	130	27
6	Et_3N (1.0)	48	130	trace
7	^tBuOK (1.0)	48	130	trace
8	AcOH (1.0)	23	120	46
9	AcOH (1.0)	23	110	15
10	AcOH (3.0)	23	120	56
11	AcOH (5.0)	23	120	53
12	AcOH (3.0)	40	120	59
13[c]	AcOH (3.0)	40	120	67 (63)[d]
14[e]	AcOH (3.0)	40	120	53
15[f]	AcOH (3.0)	40	120	37
16[g]	AcOH (3.0)	40	120	21
17[h]	AcOH (3.0)	40	120	17

[a]**1a** (0.1 mmol), **2a** (0.5 mmol), and additive in DMSO (0.5 mL). Because **1a** is hydroscopic, it was stored and used in a glovebox. [b]Determined by ^1H NMR (internal standard: dimethyl terephthalate). [c]**2a** (1.0 mmol). [d]Isolated yield. [e]**2a** (2.0 mmol). [f]NMP as solvent. [g]Sulfolane as solvent. [h]DMF as solvent.

Under the optimized reaction conditions, we explored a series of acrylic esters (Scheme 2). Among them, ethyl, methyl, and *n*-butyl acrylates reacted smoothly to give the desired product in good yields. However, more sterically demanding acrylates, including *t*-butyl, benzyl, and octadecyl esters, only gave corresponding products in moderate yields. Interestingly, no desired products were detected when a methyl group was positioned at the *α*- or *β*-site of methyl acrylate, which might be attributed to the steric effect. It is worth noting that vinyl ketone could also serve as a good reactant for this transformation to give the corresponding product **3ai** in 63% yield.

Scheme 2. Evaluation of a Series of Acrylic Esters[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (1.0 mmol), and AcOH (0.3 mmol) in DMSO (0.5 mL) at 120 °C. Isolated yields are given. [b]Reacted for 5 h.

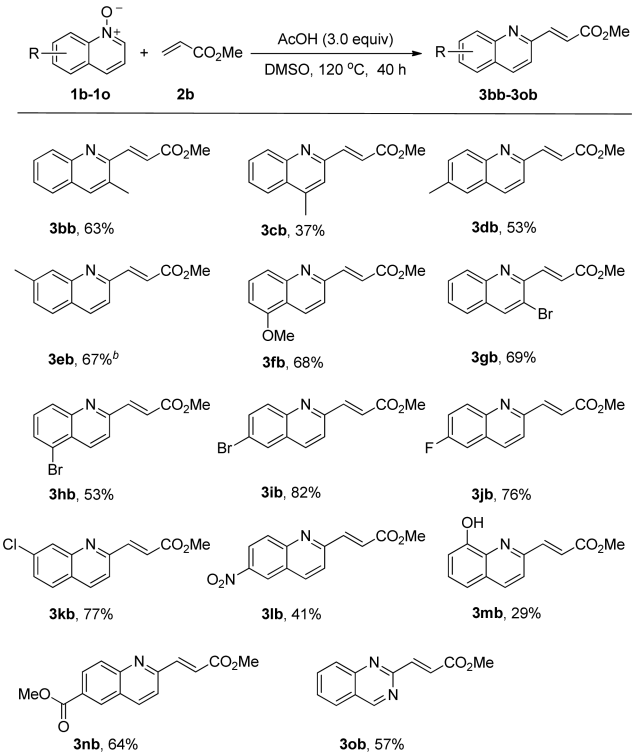
Subsequently, we investigated the reaction with different quinoline *N*-oxides (Scheme 3). It was found that methyl quinoline *N*-oxides with different substitution patterns reacted well and gave moderate to good yields. The same was true for the bromine-substituted quinoline *N*-oxides. Interestingly, a substituent on the C3-position of quinoline *N*-oxide was well-tolerated, although the steric congestion possibly affects the reaction. In addition, the presence of a halogen substituent, such as bromine, offered a great opportunity for further transformation. Meanwhile, many functional groups such as nitro (**3 lb**), hydroxyl (**3mb**), and ester (**3nb**) were very compatible with the present reaction conditions, which would enhance the synthetic utility of the current protocol. Quinazoline *N*-oxide could also be applied, furnishing the desired product in 57% yield (**3ob**).

To our delight, styrenes were also found to be applicable for this reaction. From the results shown in Scheme 4, substitution at the *ortho*-, *meta*-, or *para*-position of the styrene benzene ring with either electron-rich or electron-withdrawing groups was well-tolerated, but no product was detected when a non-terminal olefin such as **4f** was used.

The reaction could be performed on a gram scale. Treatment of 3-bromoquinoline *N*-oxide (**1g**, 15.0 mmol, 3.4 g) with methyl acrylate (**2b**) gave the desired product **3gb** in 75% yield (3.3 g) (Scheme 5). Furthermore, a sequential one-pot process involving in situ oxidation of quinoline followed by olefination with styrene was explored to synthesize 2-styryl quinoline **5aa**. This proved to be successful, and the desired product was obtained in 80% yield (Scheme 6). It should be mentioned that,

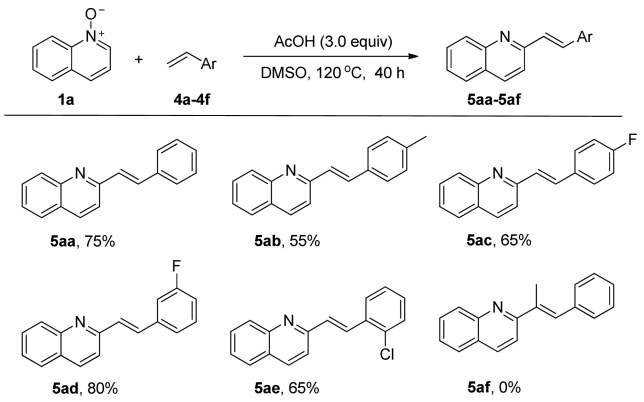
DOI: 10.1021/acs.orglett.6b00522
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Investigation of Various Substituted Quinoline *N*-Oxides[a]



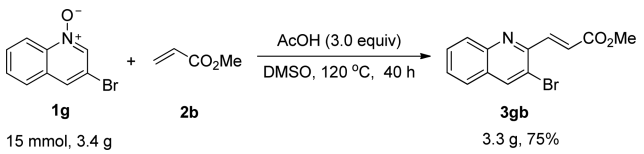
[a]Reaction conditions: **1** (0.1 mmol), **2b** (1.0 mmol), and AcOH (0.3 mmol) in DMSO (0.5 mL) at 120 °C. Isolated yields are given. [b]Because **1e** is hydroscopic, it was stored and used in a glovebox.

Scheme 4. Reaction of Quinoline *N*-Oxide with Various Styrenes[a]



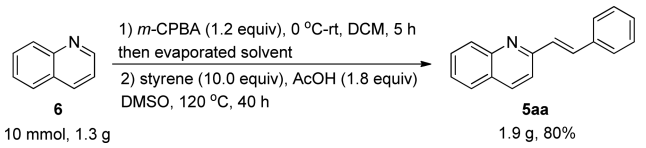
[a]Reaction conditions: **1a** (0.1 mmol), **4** (1.0 mmol), and AcOH (0.3 mmol) in DMSO (0.5 mL) at 120 °C. Isolated yields are given.

Scheme 5. Reaction of 3-Bromoquinoline *N*-Oxide with Methyl Acrylate on a Large Scale



due to the formation of a stoichiometric amount of 3-chlorobenzoic acid byproduct in the oxidation step, addition of

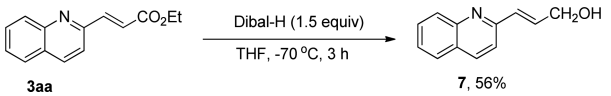
Scheme 6. One-Pot, Two-Step Process Involving in Situ Oxidation of Quinoline Followed by Olefination with Styrene



1.8 equiv of AcOH was sufficient to achieve high yield in the olefination step. However, only 58% yield was obtained if no AcOH was added.

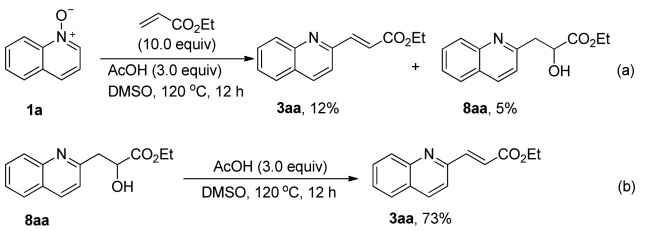
2-Alkenylquinolines **3** could be easily reduced to various quinoline allylic alcohols **7**,[11] which possess potential antileishmanial properties (Scheme 7).[5,12] Their syntheses used to require six steps starting from various substituted anilines.[5]

Scheme 7. Synthetic Application



To gain insight into the reaction mechanism, control experiments were carried out. In view of the fact that a similar reaction was realized by Wu's group with a Pd-catalyzed reaction, to rule out the possibility that traces of metals may promote the reaction, the reagents in this study were all checked by ICP to determine whether they are free from metal contaminants. The results showed that no metal elements including Pd, Cu, Ni, and Co were detected. When the reaction of quinoline *N*-oxide **1a** with ethyl acrylate was stopped after 12 h, it was found that in addition to the desired product **3aa**, unexpectedly, alcohol **8aa** was isolated in 5% yield (Scheme 8a). Moreover, when alcohol **8aa**[13] was subjected to the

Scheme 8. Control Experiments



optimized reductive olefination reaction conditions, 2-alkenylquinoline **3aa** was obtained in 73% yield (Scheme 8b). Accordingly, **8aa** was believed to be the key intermediate in this reaction.

Based on the above findings, a probable mechanism is proposed in Scheme 9. It is assumed that the reaction might first proceed via 1,3-dipolar cycloaddition of quinoline *N*-oxide **1a** with ethyl acrylate to form the five-membered isoxazolidine intermediate **A**.[14] Subsequent acid-assisted cleavage of the N–O bond with rearomatization of the quinoline ring generates alcohol **C**, which is further converted to the final product **3aa** by acid-promoted dehydration.

In conclusion, we have developed a convenient and regioselective syntheses of 2-alkenylquinolines by reductive olefination of quinoline *N*-oxides under metal-free conditions.

DOI: 10.1021/acs.orglett.6b00522
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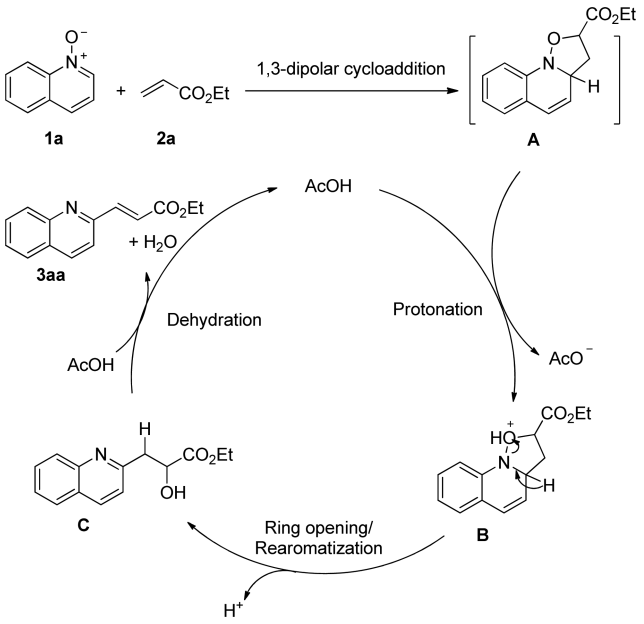
Scheme 9. Proposed Reaction Mechanism



The substrate scope is wide, and good yields are obtained even on a gram scale. Practically, a one-pot, two-step process involving in situ oxidation of quinoline followed by reductive olefination has been developed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00522.

Experimental procedures, characterizations, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Grant No. 21402244), Foundation for the Author of National Excellent Doctoral Dissertation of P. R. China (Grant No. 201425), the "Start-up Funding from Sun Yat-Sen University", and the "One Thousand Youth Talents Plan" for financial support. We thank Hui Liu (Sun Yat-Sen University) and Teng Li (Sun Yat-Sen University) for their valuable suggestions during preparation of this manuscript.

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DOI: 10.1021/acs.orglett.6b00522
Org. Lett. XXXX, XXX, XXX−XXX