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Minisci-type C-H Cyanoalkylation of Heteroarenes via N-O/C-C Bonds Cleavage

Yong Jian,[a] Ming Chen,[b] Chao Yang*[a] and Wu-jiong Xia*[a]

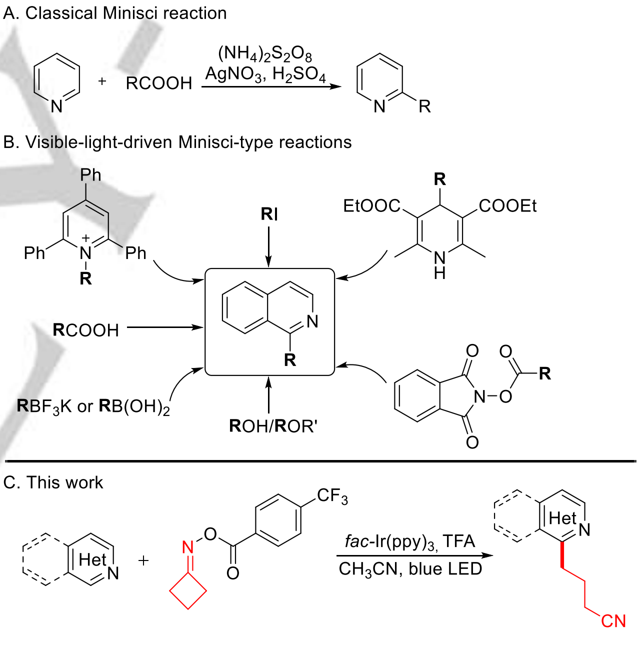
Dedication ((optional))

Abstract: A visible-light-induced C-H cyanoalkylation of heteroarenes was described, in which cycloketone oximes were readily transformed into carbon-centered radicals with a terminal cyano-group via N-O/C-C bonds cleavage in one phtochemical step. This reaction protocol displayed a broad substrate scope of heterocycle compounds, and it provided a promising strategy for the installation of cyanoalkyl groups onto heteroarenes.

Introduction

The alkylation of nitrogen-bearing heterocyclic compounds is always an essential research theme in catalysis and pharmaceutical chemistry.[1] Among numerous synthetic strategies, Minisci-type reaction, which was originally featured with the oxidative coupling of carboxylic acids with heterocycles via a radical process,[2] has evolved to be an applicable and versatile method for this transformation.[3] Over the past decades, with the development of photoredox catalysis,[4] great achievements have been made in the visible-light-promoted Minisci-type reactions by taking advantage of different alkylation reagents (Scheme 1B). Since the first photocatalytic Minisci-type alkylation with peroxides disclosed by Dirocco,[5] other types of compounds, including alcohols,[6] aliphatic carboxylic acids[7] and their derivatives (e.g. *N*-(acyloxy)phthalimides),[8] alkyltrifluoroborates[9] and alkyl boronic acids,[10] pyridinium salts,[11] 1,4-dihydropyridine derivatives,[12] alkyl iodides,[13] even alkanes,[14] have been successively reported to engage in photomediated Minisci-type reactions with different heteroaromatics.

On the other hand, oxime esters, which could be easily accessed from corresponding ketones,[15] have proved to be an elegant N- or C-radical precursor in visible-light catalysis.[16] Mechanistic investigation indicated that radicals were easily delivered from oxime esters through a photocatalyzed reductive single-eletron-tranfer process. Recent works by Wu, Xiao and Leonori et al have extensively demonstrated their high reactivities with unsaturated double/triple C-C bond under the irradiation of visible-light, providing a useful synthetic platform to facilitate molecular diversity and complexity.[17] However, to date, oxime esters have never been used in Minisci-type reaction except the recent nickel-catalyzed cyanoalkylation discovered by Guo and coworkers.[18] Inspired by the above-mentioned works, we wonder if carbon centered radicals bearing a terminal-cyano group could be formed from cycloketone oximes via N-O/C-C bonds cleavage and then took a photomediated Minisci-type reaction to unactivated hetroarenes. Herein we presented our findings on a visible-light-induced C-H cyanoalkylation of heteroarenes by using cycloketone oximes as radical sources, such developed protocol provided a convenient α-alkylation mode to various nitrogen-bearing aromatics.



Scheme 1. The development of Minisci-type reactions.

Results and Discussion

To verify our hypothesis, initial investigation was conducted with isoquinoline (**1aa**) and cyclobutanone oxime (**2aa**) in the presence of trifluoroacetic acid (TFA) and photocatalyst under the irradiation of blue LEDs (Table 1). It was delightful that cyanoalkylated product (**3aa**) was obtained in 77% yield when $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was used as photocatalyst after 20 h at room temperature. Encouraged by this result, we evaluated the performance of other photocatalysts (entries 2-5). Among them, *fac*-$Ir(ppy)_3$ was found to be the best catalyst giving **3aa** in 94% yield. Control experiments indicated that blue LEDs irradiation and photocatalyst were essential for the cyanoalkylation (entries 7-8). It is worth noting that air

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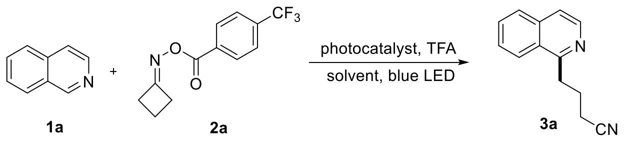
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) atmosphere has a dramatically negative effect on reaction results (94% vs 0%, entry 3 and 6).

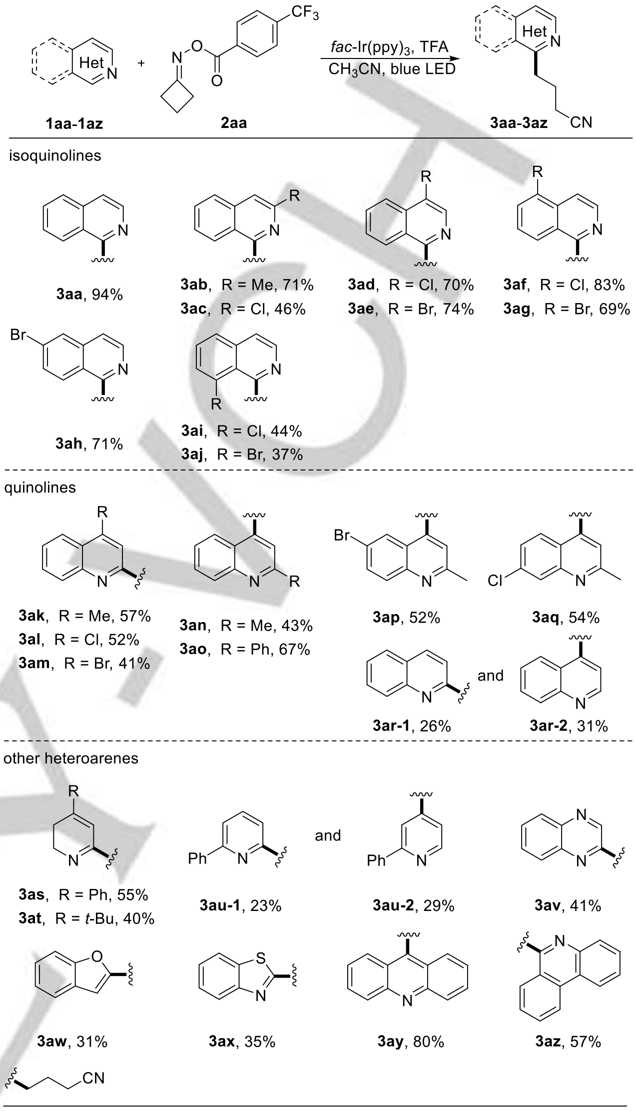
Table 1. Optimization of reaction conditions[a]



Entry	Solvent	Photocatalyst	Yield[b]
1	CH_3CN	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	77%
2	CH_3CN	$Ir(ppy)_2(dtbbpy)PF_6$	71%
3	CH_3CN	*fac*-$Ir(ppy)_3$	94%
4	CH_3CN	$Ru(bpy)_3(Cl)_2$	n.d
5	CH_3CN	Eosin Y	66%
6	CH_3CN	*fac*-$Ir(ppy)_3$, air	n.d
7	CH_3CN	*fac*-$Ir(ppy)_3$, in the dark	n.d
8	CH_3CN	no photocatalyst	n.d
9	CH_3CN	*fac*-$Ir(ppy)_3$, no TFA	35%

[a] Reaction conditions: isoquinoline **1aa** (0.1 mmol), oxime **2aa** (0.2 mmol), photocalyst (1.0 mol %), TFA (0.15 mmol), CH_3CN (1.0 mL), N_2, 15 W blue LED, rt, 20 h. TFA= trifluoroacetic acid, ppy = 2-phenylpyridine, dtbbpy = 4,4'-di-tert-butyl-2,2'-bipyridine. [b] Isolated yield.

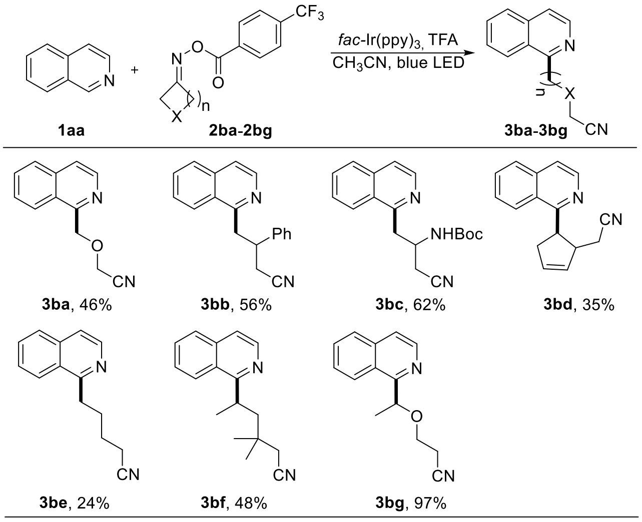
With the optimal reaction conditions in hand, we firstly examined the scope of the hereroarenes. As listed in Scheme 2, a wide range of heterocycle compounds were investigated, among which isoquinolines with methyl or halogen on different poisitions were discovered to afford desired products in good to excellent yields (**3ab**-**3aj**). In addition, in which 4-substituted quinolines effectively transformed into corresponding products in 41-57% yields, yet the electron-withdrawing groups had a slight negative effect on yields (**3ak**-**3am**). When quinolines with a substituent at C2 position, corresponding C4 cyanoalkylated products were obtained in medium yield (**3an**, **3ao**). Importantly, this protocol was tolerant with muti-substituted quinolines, providing target products **3ap** and **3aq** in 52%, 54% yields, respectively. In respect to quinoline that possessed two reactive sites for cyanoalkylation, two regioisomers, **3ar-1** and **3ar-2,** were isolated in a total yield of 57% (26% and 31%, respectively).



Scheme 2. Scope of cyanoalkylation of heteroarenes.[a,b] [a] Reaction conditions: **1aa-1az** (0.1 mmol), oxime **2aa** (0.2 mmol), photocalyst (1.0 mol %), TFA (0.15 mmol), CH_3CN (1.0 mL), 15 W blue LED, rt, 20 h. [b] Isolated yield.

Encouraged by the successful cyanoalkylation of isoquinolines and quinolines, other heteroarenes were also examined. Gratifyingly, pyridine compounds were observed to smoothly participated in the cyanoalkylation with **2aa**. For examples, **3as** and **3at** were respectively synthesized from 4-phenylpyridine and 4-tert-butylpyridine in yields of 55% and 40%. Similar to the behavior of quinoline **1ar**, 2-phenylpyridine, whose derivatives are commonly used as key ligands in photocatalyst,[19] could be transformed to **3au-1** and **3au-2** in 23% and 29% yield, respectively.

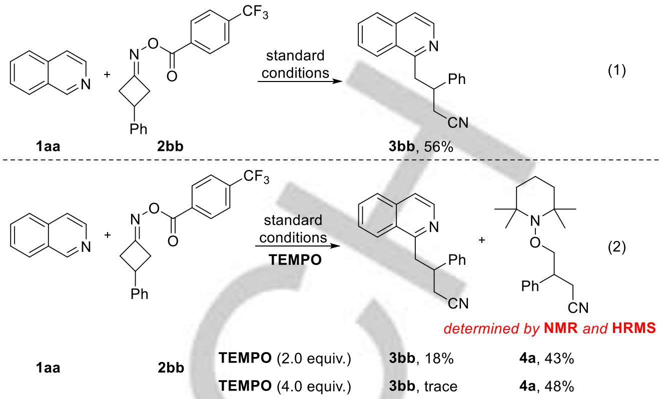
Besides, the current reaction conditions were also compatible with quinoxaline, benzofuran and benzothiazole, affording corresponding cyanoalkylated **3av**, **3aw** and **3ax** in moderate yields. Finally, other fused heterocycles, such as acridine and phenanthridine, were exposed to the irraditions of blue LED to deliver **3ay** and **3az** in yields of 80% and 57%, respectively.



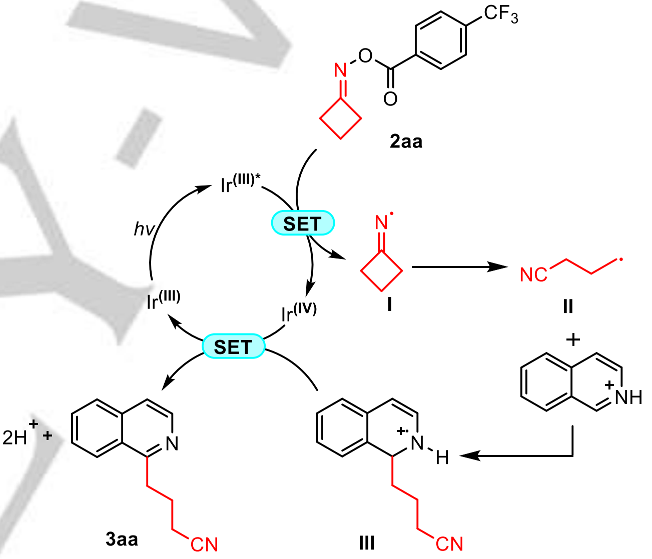
Scheme 3. Scope of cycloketone oximes.[a,b] [a] Reaction conditions: **1aa** (0.1 mmol), oxime **2ba**-**2bg** (0.2 mmol), photocalyst (1.0 mol %), TFA (0.15 mmol), CH_3CN (1.0 mL), 15 W blue LED, rt, 20 h. [b] Isolated yield.

Subsequently, the scope of cycloketone oximes was investigated as shown in Scheme 3. The reactions of oxetan-3-one oxime and substituted cyclobutanone oxime proceeded smoothly with **1aa**, affording corresponding products **3ba**, **3bb** and **3bc** in 46%, 56% and 62% yield, respectively. It's interesting to find that **3bd,** which is difficult to be synthesized by traditional methods, could be easily obtained from bicyclo[3.2.0] oxime **2bd**. The experiment results also proved ether, amide and alkenyl were good tolerant groups. To increase the diversity of oxime scope, reactions were conducted by using cyclopentanone oxime and substituted cyclopentanone oximes as reaction partners which were found to be amenable by this protocol. More remarkably, cycloketone oximes with multi-substituents could be successfully converted into corresponding carbon radicals through selective C-C bonds cleavage, such as the cases of **3be**, **3bf** and **3bg**. In addition, we further investigated the reactivity of six-, seven-, eight- and twelve-membered ring ketoximes, disappointedly, no desired product was detected under the optimal conditions.

To gain more insights into the mechanism of this protocol, a series of control experiments were conducted as shown in scheme 4. By employing isoquinoline **1aa** and oxime **2bb** as model substrates, the standard conditions delivered **3bb** in 56% yield (scheme 4, eq (1)). The reaction system was almost completely suppressed in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (4.0 equiv.), suggesting a radical process might be involved (eqn (2)). Further investigation showed that the alkyl radical with a terminal cyano- was trapped by TEMPO, giving **4a** in 48% yield (for details, see Supporting information), implying a cascade N-O, C-C bonds cleavage sequence might be involved in the process of radical formation.



Scheme 4. Control experiments.



Scheme 5. The proposed reaction mechanism.

In the previous reports, Xiao and other groups have already described analogous mechanisms about alkyl radicals generated from cyclobutanone oxime derivatives though photocatalytic process. Based on the experimental results and literatures, a possible mechanism was proposed as depicted in Scheme 5. The Minisci reaction was initiated with the excitation of photocatalyst *fac*-$Ir(ppy)_3$ by visible light irradiation. Then the excited $^*Ir^{III}$ was oxidized to Ir^{IV} ($E_{1/2}{}^{*III/IV}$= -1.73 V vs. SCE)[4a] by oxime **2aa** (E_{red} = -1.64 V vs. SCE)[17g]. Meanwhile, the obtained radical intermediate **I** underwent a ring-opening event to deliver radical **II** which subsequently attacked protonated isoquinoline to afford radical cation **III**. Through the reduction of **III** by Ir^{IV}, the final product **3aa** was afforded in 94% yield via a SET process and the catalyst was regenerated.

Conclusions

In conclusion, in the report we developed a Minisci-type C-H cyanoalkylation of heteroarenes via visible light photoredox catalysis under mild conditions. This photochemical method provided a convenient access to cyanoalkyl substituted heteroarenes, which had great meaning in drug discovery. Besides, the developed protocol was applicable with a broad substrate scope of heteroarenes. Finally, we clarified a possible visible-light induced photoredox pathway by series of mechanistic studies.

Experimental Section

Isoquinoline (**1aa**, 0.1 mmol), oxime ester (**2aa**, 0.2 mmol), TFA (0.15 mmol) and 1.0 mmol % photocatalyst *fac*-Ir(ppy)$_3$ in CH$_3$CN (1.0 mL) were placed in a dry glass tube, the system was degassed using three freeze-pump-thaw cycles with nitrogen, and then stirred at room temperature under the irradiation of 15 W blue LED till the reaction finished (monitored by TLC). Remove the solvent in vacuo, residues were purified by silica gel column chromatograph using petroleum/ethylacetate elutent (5:1-2:1) to afford the desired Minisci alkylation products.

Acknowledgments ((optional))

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Keywords: Cyanoalkylation • Heteroarenes • Oximes • Photocatalysis • C-C Bond

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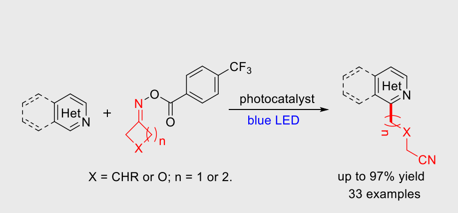

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Minisci Reactions

Yong Jian, Ming Chen, Chao Yang and Wujiong Xia**

Page No. – Page No.

Minisci-type C-H Cyanoalkylation of Heteroarenes via N-O/C-C Bonds Cleavage

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