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铜催化氧化和 Aza-Diels-Alder 反应三组分合成喹啉

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摘要 以苯胺、苯乙烯为原料, 二甲基亚砜(DMSO)为 C1 合成子, 开发了一种铜催化三组分反应合成喹啉衍生物的方法. 机理研究表明, 反应先形成亚胺中间体, 再发生 Aza-Diels-Alder 反应. 该方法具有高效、环境友好和底物适用范围广等特点.

关键词 铜催化; 多组分反应; 喹啉衍生物; Aza-Diels-Alder 反应

Copper-Catalyzed Three-Component Synthesis of Quinolines via Oxidation and Aza-Diels-Alder Reaction

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Abstract A tandem three-component reaction for the synthesis of quinolines from anilines, styrene and dimethyl sulfoxide (DMSO) has been developed. Dimethyl sulfoxide (DMSO) served as one-carbon synthon and solvent. The mechanism studies revealed that imine intermediate was involved and inverse electron demand Aza-Diels-Alder reaction was occurred. This method is featured by environmentally benign, good functional group tolerance and good to excellent yield.

Keywords copper-catalyzed; multi-component reaction; quinoline derivatives; Aza-Diels-Alder reaction

1 Introduction

Quinoline is one of the ubiquitous structural motifs that occur in life, natural products and pharmaceutically active agents. A variety of quinolines exhibit good biological activities, such as antihypertensive, anti-inflammatory, antimalarial and anticancer activities.[1] Recognizing the commercial significance of quinolines, the traditional preparation methods including Skraup synthesis,[2] Friedländer synthesis,[3] Doebner-von Miller reaction,[4] Combes synthesis[5] and Pavorov reaction[6] have been developed to construct quinoline skeletons over the past few decades. However, most of them suffer from some drawbacks, such as high temperature, strong acid, toxic starting reagents and harsh reaction conditions. Therefore, the development of efficient methods for the synthesis of quinoline is of great significance.[7] From the view of green chemistry, recently developed multi-component reactions (MCRs) to construct polysubstituted quinoline derivatives represent an atom- and step-economic strategy. Transition metal, such as Cu,[8] Co,[9] Ag[10] and Pd[11] have been used to catalyze one-pot synthesis of substituted quinolines from arylamines, and metal-free one-pot synthesis of quinolines have also been developed.[12]

More recently, the [3+2+1] Aza-Diels-Alder reaction has become an important supplement to the existing quinoline synthesis method (Scheme 1). Balaraman *et al*.[13] revealed a rhodium-catalyzed C—H activation strategy to build quinoline products, in which anilines and electron-deficient alkynes were employed as reaction substrates and CO gas or CO surrogate was employed as one carbon source (Scheme 1, a). Afterward, paraformaldehyde as the carbonyl source has been explored because it is less expensive, stable, less toxic and simple to operate.[14] Recently, considerable attention has been paid to the development of transition metal catalyzed C—H functionalization by using dimethyl sulfoxide (DMSO) as the versatile reactant in organic synthesis, due to its low toxicity and easy availability.[15] Zhang and Yi group[16] developed a direct synthesis of quinolines via Co(III)-catalyzed and DMSO involved C—H activation/cyclization of amines with alkynes (Scheme 1, b). Singh and Guo *et al*.[17] reported the synthe-

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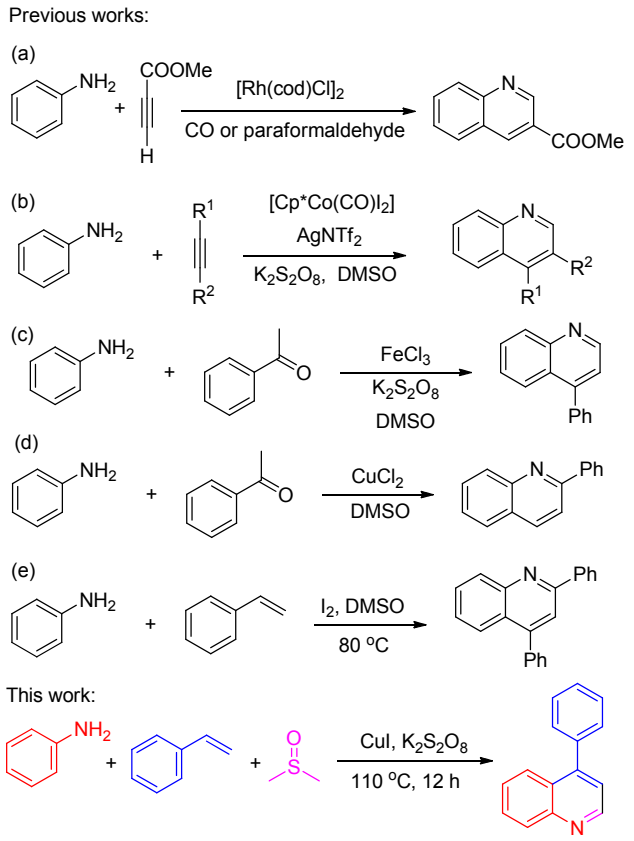
sis of 4-aryl and 2-arylquinolines from oxidative cyclization of anilines, aryl methyl ketones and DMSO, respectively (Schemes 1, c and d).



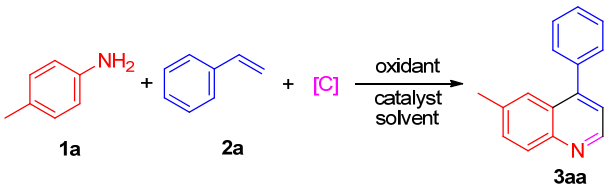
Scheme 1 Quinoline synthesis via multicomponent reaction

However, alkynes are easily oxidized and dimerized and the source of ketone is relatively rare. Therefore, the exploration of a simple MCR for acquisition of substituted quinolines from easily available starting materials such as styrene under mild conditions is highly desirable. Jiang and co-workers[18] described the synthesis of 4-substituted quinolines with vinyl azides as a dual synthon. In addition, Bhahwal *et al.*[19] proposed new methods to acquire quinolines via C—C cleavage of styrene and aniline, mediated by iodine and DMSO (Scheme 1, e). Herein, as continuation of our interest in constructing heterocyclic frameworks, we develop an atom-economical and inexpensive CuI-catalyzed Povarov reaction for synthesis of 4-arylquinolines from easy available aryl amines and styrene in the presence of DMSO.

2 Results and discussion

Initially, *p*-toluidine (**1a**) and styrene (**2a**) were reacted in DMSO in the presence of 10 mol% CuBr and 1.5 equiv. of $K_2S_2O_8$ under air atmosphere at 110 ℃ for 12 h to give the desired quinoline product **3aa** in 67% yield, and the results show that DMSO is more effective than the other C1 synthon such as *N*,*N*′-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA) and *N*-methyl pyrrolidone (NMP) (Table 1, Entries 1～4).

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield[b]/%
1	CuBr	$K_2S_2O_8$	DMF	37
2	CuBr	$K_2S_2O_8$	DMA	23
3	CuBr	$K_2S_2O_8$	DMSO	67
4	CuBr	$K_2S_2O_8$	NMP	nr
5	$Cu(OAc)_2$	$K_2S_2O_8$	DMSO	34
6	$CuCl_2$	$K_2S_2O_8$	DMSO	38
7	$CuBr_2$	$K_2S_2O_8$	DMSO	41
8	CuCl	$K_2S_2O_8$	DMSO	58
9	CuI	$K_2S_2O_8$	DMSO	76
10	—	$K_2S_2O_8$	DMSO	Trace
11[c]	CuI	$K_2S_2O_8$	DMSO	69
12[d]	CuI	$K_2S_2O_8$	DMSO	44
13	CuI	TBHP	DMSO	nr
14	CuI	O_2	DMSO	nr
15	CuI	$(NH_4)_2S_2O_8$	DMSO	36
16	CuI	—	DMSO	nr
17[e]	CuI	$K_2S_2O_8$	DMSO	42
18[f]	CuI	$K_2S_2O_8$	DMSO	63
19[g]	CuI	$K_2S_2O_8$	DMSO	77
20[h]	CuI	$K_2S_2O_8$	DMSO	83
21[i]	CuI	$K_2S_2O_8$	DMSO	<10

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.2 equiv.), catalyst (10 mol%), oxidant (1.5 equiv.), solvent (2.5 mL) at 110 ℃ in air for 12 h. [b] Isolated yield. [c] CuI (20 mol%). [d] CuI (5 mol%). [e] 80 ℃. [f] 140 ℃. [g] 24 h. [h] Under O_2. [i] Under Ar atmosphere.

Encouraged by the result, different Cu catalysts like CuCl, CuI, $Cu(OAc)_2$•H_2O, $CuBr_2$ and $CuCl_2$ were next screened. Among these tested copper sources, CuI was found to be superior and resulted in 76% yield (Table 1, Entries 5～9). Only a trace amount of product was formed in the absence of copper salt (Entry 10). It was observed that the product yield was decreased to 44% in the presence of 5 mol% catalyst, whereas no significant increment was observed using 20 mol% catalyst (Entries 11, 12). Moreover, various oxidants such as *t*-butyl hydroperoxide (TBHP), $(NH_4)_2S_2O_8$, $K_2S_2O_8$ and O_2 were tested, and the results showed that $K_2S_2O_8$ is the most effective oxidant (Entries 13～15). The absence of oxidant failed to generate the desired products (Entry 16). When the temperature was decreased from 110 to 80 ℃, the product yield decreased to 42%. However, when the temperature increased to 140 ℃, the yield is slightly reduced (Entries 17, 18). In addition, when the reaction time is extended to 24 h, and the yield is not further improved (Entry 19). In contrast, the similar yield could be obtained in the oxygen atmosphere, and **3aa** was obtained in very low yield under argon atmosphere, indicating that oxygen was essential in the reaction (Entries 20, 21).

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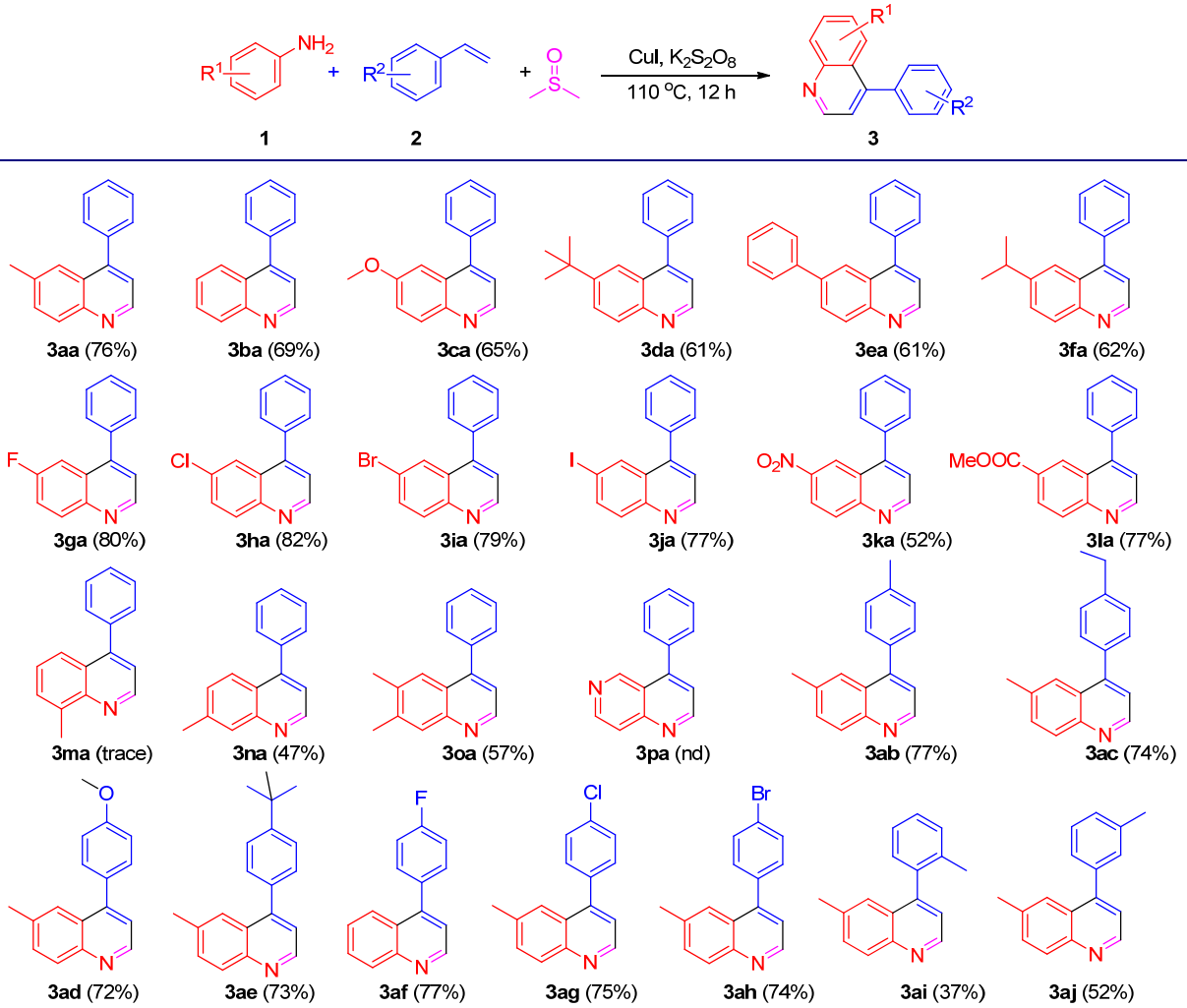
With the reaction conditions optimized, the scope and limitations of this reaction were examined. Firstly, the scope of the reaction with respect to aniline substrates was explored, and the results are showed in Table 2. This protocol was compatible with a wide range of functional groups, such as alkyl, methoxy, aryl, fluoro, chloro, bromo, iodo and nitro groups on the *para*-position of aryl ring (**3aa** ～ **3la**). In general, anilines bearing electron-withdrawing groups exhibited higher reactivity than those bearing electron-donating groups. A good yield could be obtained using a halogen-bearing substrate, which can be used for further transformation. Moreover, the steric hindrance has obvious effect on the reaction. Anilines with methyl group at the *para*-position afforded better yields than those at the *ortho*- and *meta*-positions (**3ma** and **3na**). The reaction is suitable for polysubstituted anilines, when 3,4-dimethylaniline was used as substrates, the target product **3oa** could be obtained in 54% yield.

However, the reaction does not work well when 4-aminopyridine was used as the substrate. It is possible that 4-aminopyridine's electronic cloud density is lower than aniline.

The scope of styrene was next investigated. The results show that styrene have excellent substrate adaptability. No significant substitute effect was observed on styrene, various substrates bearing different substitution groups including CH_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, F, Cl and Br were found to be well tolerated and gave the desired products in good yields (Table 2, **3ab** ～ **3ah**). Similar to aromatic amine, the steric hindrance of styrenes has a great influence on the reaction. It was observed that the product yield was decreased to 52% and 37% when styrenes bearing a methyl group on the *meta*- and *ortho*-positions (**3ai**～**3aj**) were used. However, aliphatic olefin had no reactivity for the reaction.

Since the consideration of quinolines were mainly applied in pharmaceutical intermediates, gram-scale synthesis was tried. To our satisfaction, 73% isolated yields of **3aa** were obtained when the reaction amount was increased up to 8 mmol scales by controlling reaction conditions in longer reaction time for their completion (Scheme 2).

Table 2 Scope of the synthesis of quinoline[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), CuI (10 mol %), $K_2S_2O_8$ (1.5 equiv.), DMSO (2.5 mL) at 110 ℃ in air for 12 h.

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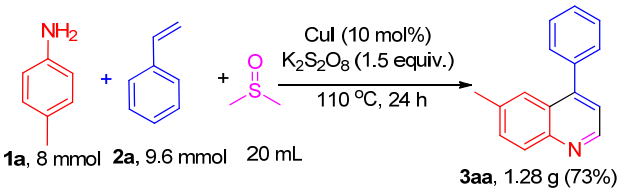


Scheme 2 Gram scale experiment

To gain insight into the possible mechanism of this reaction, a series of experiments were carried out, as shown in Scheme 3. Firstly, when DMSO was replaced by DMSO-d_6, 2-*D*-4-phenyl quinoline was obtained in 73% yield, which not only proved that DMSO participated in the reaction, but also provided a good strategy for the synthesis of 2-deuterized quinoline (Scheme 3a). Secondly, the desired product **3aa** could be obtained in 69% yield when radical inhibitor 2,2,6,6-tetramethyl piperidine-*N*-oxide (TEMPO, 2 equiv.) was added to the standard reaction, and ruling out the possibility of a radical pathway (Scheme 3b). Thirdly, the intermolecular competition experiments between electronically differentiated substrates were conducted. In the intermolecular competition reaction of styrene with *p*-methylaniline (**1a**) and *p*-chloroaniline (**1h**) under the optimized conditions, the products **3aa** and **3ha** were obtained in 17% and 52% yield (Scheme 3c), indicating that the electron-deficient anilines reacted preferentially. Additionally, a scrambling test of styrenes bearing an electron-donating and electron-withdrawing group (**2b** and **2g**) with aniline was conducted, and **3ab** was isolated in 37% yield along with 41% of **3ag**, indicating that there is no significant electronic effect on the styrenes (Scheme 3c).

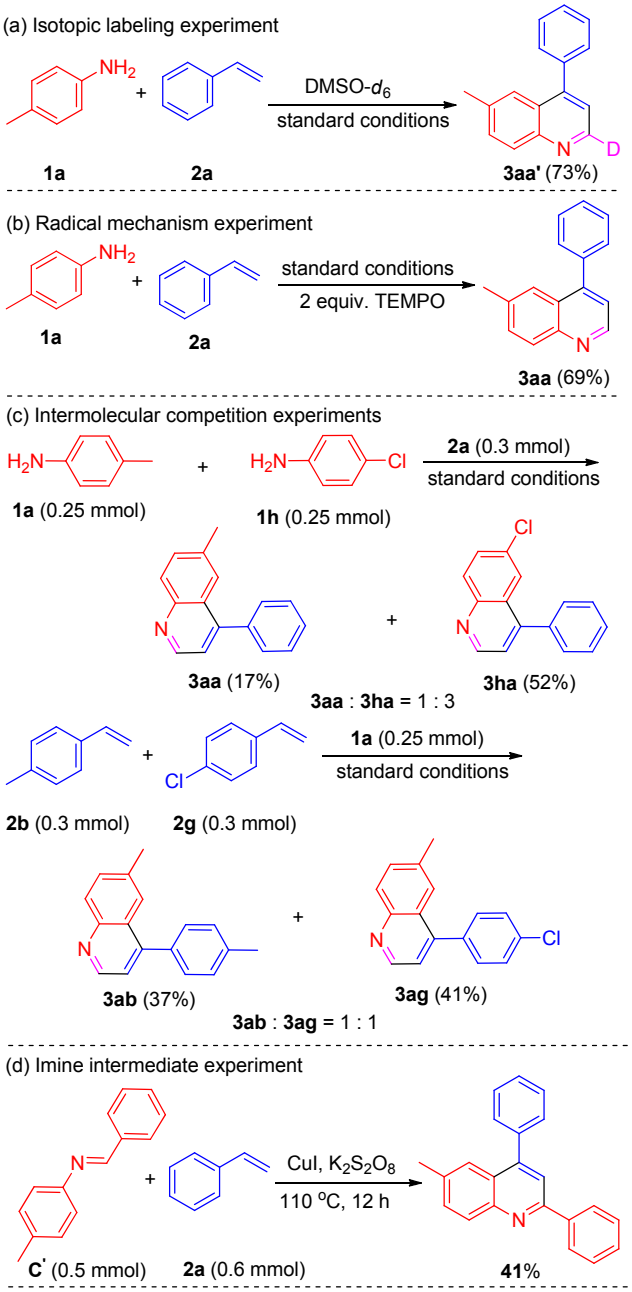
Acetophenone, the possible oxidation product of styrene, was not detected in the reaction system.

However, 6-methyl-2,4-diphenylquinoline could be obtained in 41% yield by using *N*-(4-methylphenyl)-1-phenyl imine as the reaction substrate under the standard conditions (Scheme 3d). The experiments proved that imine may be an intermediate in this reaction. Moreover, when CuI was removed under standard conditions, the reaction did not occur, which indicated that the catalyst played a vital role in the cyclization process.

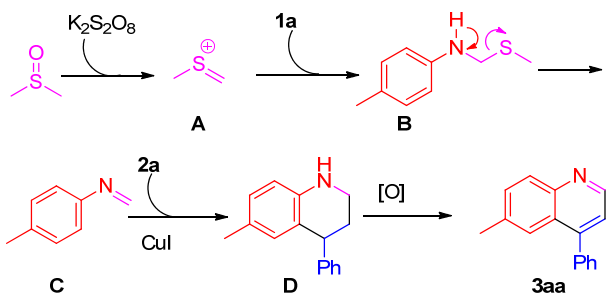
On the basis of the experimental results described above and several previous literatures,[20] a plausible reaction mechanism was proposed (Scheme 4). Firstly, DMSO is activated to give sulfenium ion (**A**) in the presence of $K_2S_2O_8$.[17] Then, **A** reacts with *p*-toluidine (**1a**) to produce intermediate **B**, which then generates imine intermediate **C**. Next, Lewis acid CuI catalyzed Povarov reaction, an inverse-electron-demand Aza-Diels-Alder reaction (IEDDA reaction) between **C** and olefins **2a** occurred, which results in the formation of 1,2,3,4-tetrahydroquinoline (**D**).[21] Finally, quinoline **3aa** was afforded by further oxidation and aromatization.

3 Conclusions

In summary, to avoid the use of precious metals and complex ligands, a copper-catalyzed cascade reaction to synthesize quinoline derivatives via oxidation and intermolecular Povarov reaction using styrene as substrates



Scheme 3 Control experiments



Scheme 4 A plausible mechanism

and DMSO as carbon source was developed. A wide range of styrenes and anilines were significantly employed in this oxidation and cyclization process to afford 4-aryl-quinolines. This is a novel, simple, and effective method for the synthesis of functionalized quinolines, and has the characteristics of simple operation, easy availability of raw materials, cheap catalyst, high yield, and wide substrate range. Application of this method toward the synthesis of other biological heterocycles through atom-/step-economical and environmentally process is being pursued in our laboratories.

4 Experimental section

4.1 General information

All starting materials and reagents were commercially available and used directly without further purification. All known products gave satisfactory analytical data by NMR spectra, which corresponding to the reported literature values. Unknown compounds were confirmed by HRMS additionally. NMR spectra were determined at room temperature on Bruker Avance-400 or Bruker Avance-500 at 400 MHz or 500 MHz with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given relative to TMS. High resolution mass spectra (HRMS) were measured on Agilent 6200 LC/MS TOF using APCI in positive mode. Melting points were determined using X-4 micro melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed using commercially available 100～400 mesh silica gel plates (GF254).

4.2 Experimental method

p-Toluidine **1** (0.5 mmol), styrene **2** (0.6 mmol), $K_2S_2O_8$ (1.5 equiv.), CuI (10 mol%) and DMSO (2.5 mL) were added to a 20 mL tube equipped with magnetic stirrer bar. The mixture was stirred at 110 ℃ (oil bath temperature) for 12 h under open air. After the reaction was finished, the mixture was cooled to room temperature and extracted with EtOAc (10 mL×3). The combined organic fraction was washed with brine (10 mL) and dried over anhydrous $MgSO_4$, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (V∶V=10∶1) as an eluent to afford the corresponding products.

6-Methyl-4-phenylquinoline (**3aa**):[18] Orange oil, 79 mg, 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, J=4.0 Hz, 1H), 8.0 (d, J=8.0 Hz, 1H), 7.59 (s, 1H), 7.51～7.46 (m, 2H), 7.46～7.42 (m, 4H), 7.22 (d, J=4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.1, 146.9, 146.3, 137.3, 135.7, 130.7, 128.6, 128.6, 127.6, 127.4, 125.8, 123.6, 120.5, 20.9

4-Phenylquinoline (**3ba**):[18] Yellow oil, 70 mg, 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.12 (d, J=2.4 Hz, 1H), 8.25 (d, J=2.0 Hz, 1H), 8.08 (d, J=8.4 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.69～7.64 (m, 3H), 7.54～7.44 (m, 3H), 7.40～7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.9, 146.3, 136.9, 132.9, 132.3, 128.4, 128.2, 127.1, 127.0, 126.4, 126.0.

6-Methoxy-4-phenylquinoline (**3ca**):[18] Orange oil, 76 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (d, J=4.4 Hz, 1H), 8.09 (d, J=9.2 Hz, 1H), 7.54～7.49 (m, 5H), 7.41～7.38 (m, 1H), 7.29 (d, J=4.4 Hz, 1H), 7.20 (d, J=2.8 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 147.4, 147.1, 144.6, 138.2, 131.1, 129.2, 128.6, 128.3, 127.6, 121.7, 121.6, 103.6, 55.3.

6-Tertbutyl-4-phenylquinoline (**3da**):[18] Yellow oil, 79 mg, 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, J=4.4 Hz, 1H), 8.05 (d, J=8.8 Hz, 1H), 7.81～7.75 (m, 2H), 7.48～7.42 (m, 5H), 7.24 (d, J=4.4 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4, 148.2, 147.4, 137.1, 128.5, 128.2, 127.5, 127.4, 127.3, 125.2, 120.4, 119.7, 34.0, 30.1.

4,6-Diphenylquinoline (**3ea**):[18] Yellow oil, 85 mg, 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.92 (s, 1H), 8.40 (d, J=8.5 Hz, 1H), 8.08 (d, J=7.5 Hz, 1H), 7.99 (d, J=7.5 Hz, 1H), 7.53～7.45 (m, 6H), 7.42～7.35 (m, 4H), 7.32～7.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.3, 147.6, 145.5, 139.3, 139.0, 136.6, 128.9, 128.6, 128.1, 128.0, 127.9, 127.9, 126.9, 126.6, 126.1, 122.7, 120.9.

6-Isopropyl-4-phenylquinoline (**3fa**):[18] Yellow oil, 76 mg, 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.81 (d, J=4.5 Hz, 1H), 8.08 (d, J=8.5 Hz, 1H), 7.65 (d, J=2.0 Hz, 1H), 7.60～7.57 (m, 1H), 7.49～7.42 (m, 5H), 7.24 (d, J=4.5 Hz, 1H), 2.96～2.92 (m, 1H), 1.19 (d, J=4.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.8, 147.5, 146.5, 146.2, 137.1, 128.6, 128.4, 128.1, 127.6, 127.5, 125.7, 124.5, 121.1, 120.4, 33.4, 22.9.

6-Fluoro-4-phenylquinoline (**3ga**):[18] Yellow oil, 89 mg, 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.83 (d, J=4.0 Hz, 1H), 8.13～8.10 (m, 1H), 7.46～7.40 (m, 7H), 7.29 (d, J=4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.8 (d, J=247.5 Hz), 148.1, 147.4, 143.9, 136.3, 130.7, 128.3, 127.9 (d, J=8.75 Hz), 127.8, 121.0, 119.2 (d, J=26.25 Hz), 119.0, 108.4 (d, J=22.5 Hz).

6-Chloro-4-phenylquinoline (**3ha**): White solid, 97 mg, 82% yield. m.p. 71～73 ℃ (Lit.[18] 72～73 ℃); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.94 (d, J=4.0 Hz, 1H), 8.13 (d, J=9.0 Hz, 1H), 7.89 (d, J=2.0 Hz, 1H), 7.69～7.60 (m, 1H), 7.58～7.52 (m, 3H), 7.50～7.48 (m, 2H), 7.37 (d, J=4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.1, 146.8, 146.1, 136.3, 131.6, 130.5, 129.3, 128.4, 127.8, 127.7, 126.5, 123.7, 121.0.

6-Bromo-4-phenylquinoline (**3ia**): White solid, 111 mg, 79% yield. m.p. 98～100 ℃ (Lit.[15] 97～98 ℃); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.88 (s, 1H), 7.99 (d, J=7.5 Hz, 2H), 7.73 (d, J=7.5 Hz, 1H), 7.50～7.45 (m, 3H), 7.42 (d, J=7.5 Hz, 2H), 7.30 (d, J=3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.2, 146.8, 146.3, 136.2, 131.9, 131.1, 130.6, 128.4, 127.8, 127.8, 127.0, 126.0, 121.1, 120.7, 119.9.

6-Iodine-4-phenylquinoline (**3ja**): Yellow solid, 115 mg, 77% yield. m.p. 77～78 ℃ (Lit.[6c] 97～99 ℃); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.90 (d, J=4.0 Hz, 1H), 8.21 (d, J=1.5 Hz, 1H), 7.29～7.86 (m, 2H), 7.50～7.46 (m, 3H), 7.41 (d, J=7.5 Hz, 2H), 7.30 (d, J=4.5 MHz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.1, 147.2, 146.0, 137.5, 136.1,

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133.7, 130.1, 128.5, 127.9, 128.0, 127.5, 121.1, 92.0.

6-Nitro-4-phenylquinoline (**3ka**): Yellow solid, 65 mg, 52% yield. m.p. 82～85 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.98 (d, J=4.0 Hz, 1H), 8.13～8.10 (m, 1H), 7.45～7.40 (m, 7H), 7.29 (d, J=4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.1, 149.9, 149.6, 144.8, 135.4, 130.7, 128.7, 128.5, 128.2, 124.9, 122.1, 121.9, 121.9; HRMS (ESI) m/z calcd for $C_{15}H_{11}N_2O_2$ $[M+H]^+$ 251.0815, found 251.0812.

4-Phenylquinolin-6-carboxylic acid methyl ester (**3la**):[16]: Yellow liquid, 101 mg, 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.98 (d, J=4.5 Hz, 1H), 8.63 (d, J=1.5 Hz, 1H), 8.27～8.25 (m, 1H), 8.19 (d, J=10.5 Hz, 1H), 7.53～7.44 (m, 5H), 7.38 (d, J=4.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.6, 150.5, 149.6, 148.9, 136.1, 129.2, 128.7, 128.6, 128.2, 128.0, 129.9, 127.4, 125.1, 121.1, 51.4.

7-Methyl-4-phenylquinoline (**3na**):[18] Yellow liquid, 51 mg, 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.06 (d, J=4.0 Hz, H), 8.19 (d, J=2.0 Hz, H), 7.85 (s, H), 7.70 (d, J=8.4 Hz, H), 7.65～7.62 (m, 2H), 7.47～7.42 (m, 2H), 7.38～7.33 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.1, 147.0, 144.9, 136.8, 136.2, 131.2, 128.5, 127.6, 127.6, 127.5, 125.8, 123.7, 120.4, 20.9.

6,7-Dimethyl-4-quinoline (**3oa**): Yellow solid, 73 mg, 54% yield. m.p. 123～125 ℃ (Lit.[18] 122～123 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (d, J=4.4 Hz, 1H), 7.96 (s, 1H), 7.69 (s, 1H), 7.48～7.43 (m, 5H), 7.23 (s, 1H), 2.43 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.8, 146.5, 145.1, 139.5, 136.8, 136,2, 128.3, 127.5, 127.4, 126.8, 124.2, 123.9, 119.5, 19.2, 19.2.

6-Methyl-4-p-tolylquinoline (**3ab**):[12b] Yellow oil, 88 mg, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 8.11 (d, J=8.4 Hz, 1H), 7.66 (s, 1H), 7.54～7.51 (m, 1H), 7.54～7.51 (m, 5H), 2.41 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 148.0, 147.0, 145.1, 137.5, 135.9, 133.9, 131.1, 128.4, 128.3, 127.6, 123.7, 120.3, 20.8, 20.3.

4-(4-Ethylphenyl)-6-methylquinoline (**3ac**):[12b] Yellow liquid, 91 mg, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (s, 1H), 8.05～8.02 (m, 1H), 7.64 (s, 1H), 7.49 (d, J=7.6 Hz, 1H), 7.35～7.23 (m, 5H), 2.72～2.66 (m, 2H), 2.39 (s, 3H), 1.27～1.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.7, 147.3, 143.7, 135.8, 134.2, 130.9, 128.5, 127.9, 127.1, 125.8, 123.7, 122.6, 120.4, 27.6, 20.8, 14.5.

4-(4-Methoxyphenyl)-6-methylquinoline (**3ad**):[12b] Yellow liquid, 89 mg, 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (d, J=4.5 Hz, 1H), 7.99 (d, J=8.5 Hz, 1H), 7.63 (s, 1H), 7.48～7.46 (m, 1H), 7.37～7.36 (m, 2H), 7.20～7.18 (m, 1H), 7.00～6.97 (m, 2H), 3.83 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ: 158.7, 147.8, 146.6, 146.0, 135.3, 131.4, 130.4, 129.6, 129.3, 128.2, 125.8, 123.5, 120.1, 54.3, 20.7.

4-(4-(Tertbutyl)phenyl)-6-methylquinoline (**3ae**):[12b] Yellow liquid, 100 mg, 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.79 (d, J=3.5 Hz, 1H), 8.07 (d, J=8.5 Hz, 1H), 7.69 (s, 1H), 7.52～7.48 (m, 3H), 7.39 (d, J=8.5 Hz, 2H), 7.26 (d, J=4.5 Hz, 1H), 2.42 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.5, 147.6, 178.3, 145.7, 135.6, 134.1, 130.7, 128.2, 128.1, 125.8, 124.5, 123.7, 120.4, 120.4, 33.7, 30.3, 20.8.

4-(4-Fluorophenyl)-6-methylquinoline (**3af**): Yellow solid, 91 mg, 77% yield. m.p. 89～90 ℃ (Lit.[12b] 90～92 ℃). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.86 (d, J=4.5 Hz, 1H), 8.10 (d, J=3.5 Hz, 1H), 7.61～7.57 (m, 2H), 7.49～7.47 (m, 2H), 7.29～7.22 (m, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.0 (d, $J_{C\text{-}F}$=246.3 Hz), 149.0, 147.2, 147.0, 136.9, 134.2 (d, $J_{C\text{-}F}$=3.8 Hz), 131.9, 131.3 (d, $J_{C\text{-}F}$=8.75 Hz), 129.6, 126.8, 124.4, 121.6, 115.8 (d, $J_{C\text{-}F}$=21.25 Hz), 22.0.

4-(4-Chlorophenyl)-6-methylquinoline (**3ag**): Yellow solid, 94 mg, 75% yield. m.p. 123～125 ℃ (Lit.[12b] 121～123 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87 (d, J=4.4 Hz, 1H), 8.11 (d, J=8.4 Hz, 1H), 7.59 (d, J=10.8 Hz, 2H), 7.52 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 7.28 (d, J=4.4 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.1, 147.3, 147.2, 137.5, 137.3, 132.2, 131.5, 129.7, 126.8, 124.6, 123.2, 121.6, 105.4, 22.3.

4-(4-Bromophenyl)-6-methylquinoline (**3ah**): Yellow solid, 109 mg, 74% yield. m.p. 127～129 ℃ (Lit.[12b] 123～126 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (s, 1H), 8.08 (d, J=8.4 Hz, 1H), 7.68 (d, J=8.0 Hz, 2H), 7.58 (d, J=10.4 Hz, 2H), 7.38 (d, J=8.4 Hz, 2H), 7.27(s, 1H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.1, 147.3, 147.2, 137.5, 137.3, 132.4, 132.2, 131.5, 129.7, 126.8, 124.6, 123.2, 121.6, 105.4, 22.3.

4-(2-methylphenyl)-6-methylquinoline (**3ai**): White solid, 43 mg, 37% yield. m.p. 84～85 ℃ (Lit.[17b] 86～87 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, J=4.0 Hz, 1H), 8.04 (d, J=8.8 Hz, 1H), 7.50～7.48 (m, 1H), 7.31～7.23 (m, 3H), 7.18～7.12 (m, 3H), 2.35 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.4, 147.3, 145.2, 136.4, 135.8, 134.9, 130.8, 129.1, 128.4, 127.8, 127.3, 126.2, 124.6, 123.5, 120.4, 20.6, 18.8.

4-(3-methylphenyl)-6-methylquinoline (**3aj**)[17b]: Yellow oil, 60 mg, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.79 (s, 1H), 8.03 (d, J=8.4 Hz, 1H), 7.60 (s, 1H), 7.49 (d, J=8.4 Hz, 1H), 7.36～7.32 (m, 2H), 7.25～7.20 (m, 3H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.5, 145.7, 137.3, 137.0, 135.7, 130.8, 129.1, 128.1, 127.4, 125.6, 123.7, 120.3, 103.9, 20.8, 20.5.

Supporting Information ^{1}H NMR, ^{13}C NMR and MS spectra for obtained compounds. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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