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Synthesis of substituted quinolines by iron-catalyzed oxidative coupling reactions

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ABSTRACT

A simple and efficient method has been developed for the synthesis of quinoline derivatives from *N*-alkyl anilines and alkynes or alkenes by iron-catalyzed oxidative coupling reactions. A variety of substituted quinolines are prepared in good to excellent yields.

Quinolines and their derivatives occur in numerous natural products, and display a wide variety of biological activities.[1] The quinoline skeleton is a valuable synthetic intermediate of many synthetic compounds with pharmacological properties. In addition, these compounds are well-known ligands for the preparation of OLED phosphorescent complexes.[2] In view of these points, a great deal of effort has been done to develop new and efficient synthetic methods for quinoline derivatives in both synthetic organic and medicinal chemistry. Up to now, many methods have been developed for the synthesis of these compounds, such as Skraup, Doebner-von Miller, Friedländer, Combes methods, and so on.[3] Among these methods, The most simple and straightforward method is the Friedländer synthesis based on acid- or base-catalyzed Aldol condensation of unstable 2-aminobenzaldehyde or ketone with a carbonyl compound containing a reactive methylene group.[3g–l] However, this method is not satisfactory with regard to relatively low yield, low regioselectivity, and drastic reaction conditions due to the occurrence of several side reactions. Recently, transition metal-catalyzed coupling reactions have emerged as a powerful tool for the synthesis of heterocyclic compounds. These reactions provide an effective route to the synthesis of quinoline derivatives.[4] Uneyama et al. reported that Rh(I) complexes could catalyze the coupling cyclization of *N*-aryl trifluoroacetylimidoyl chloride with alkynes to give 2-trifluoromethylated quinolines in good yields.[4c] Fujiwara found an efficient synthesis of quinolin-2(1*H*)-ones by using Pd(II) via the activation of aromatic C–H bonds for addition to C–C multiple bonds.[4d] Takai and Kuninobu developed an efficient synthesis of 2,4-disubstituted quinoline derivatives from *N*-aryl-2-propynylamines with Au(I) and Cu(I) used as catalysts.[4e] Also, an efficient synthesis of quinoline derivatives through a three-component reaction of aldehydes, amines, and alkynes has been reported using $AuCl_3$/CuBr as catalyst.[4f] Recently, Tu and co-workers reported $FeCl_3$-catalyzed three-component coupling of aldehydes, amines, and alkynes to give quinoline derivatives for the first time.[4g] Although these methods provide efficient access to quinoline derivatives, the development of more facile and economic synthetic approaches is still desirable.

Recently, our group reported the iron-catalyzed direct cross-dehydrogenative coupling reactions of glycine derivatives and alkynes or ketones.[5] Following the work, we have developed an efficient process wherein oxidative coupling is carried out between *N*-alkyl anilines and alkynes or alkenes; the iron salts in a tandem process subsequently catalyze in situ cyclization and dehydrogenation to form interesting quinoline derivatives. Three processes are involved as shown in Figure 1: (i) the formation of an iminium ion intermediate, (ii) the oxidative coupling reaction and cyclization in the presence of an alkyne or alkene as nucleophile and (iii) the final oxidative aromatization step of the hydroquinoline intermediate to form the quinoline unit.

To initiate our study, the reaction of *N*-alkyl aniline **1a** (1.0 equiv) with phenylacetylene (**2a**, 1.2 equiv) catalyzed by various iron salts (10 mol %) with *di-tert*-butyl peroxide (2.0 equiv) as the oxidant in 1,2-dichloroethane (DCE) at 80 °C was carried out in a Schlenk reaction tube. Friedel–Crafts reaction and the followed oxidation to provide final product **3a** are assumed to occur after the coupling reaction. As seen from Table 1, $FeCl_3$ (entry 1, Table 1) was found to be the best catalyst using *di-tert*-butylperoxide as the

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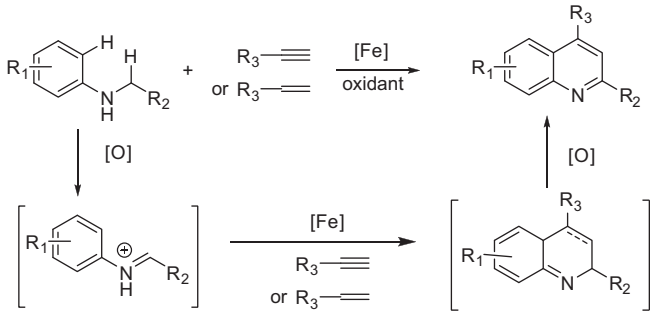
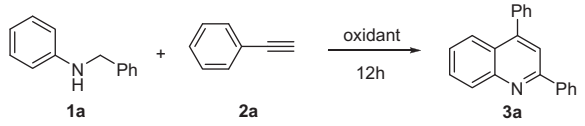


Figure 1. Synthesis of quinolines in a one-pot reaction.

Table 1
Optimization of reaction conditions[a]



1a **2a** **3a**

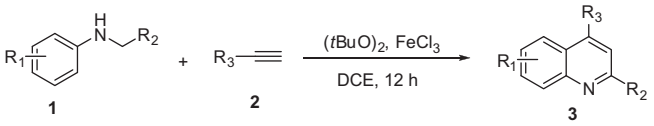
Entry	Cat.	Solvent	T (°C)	Oxidant	Yield[b] (%)
1	$FeCl_3$	DCE	80	$(tBuO)_2$	81
2	$FeCl_2{\cdot}4H_2O$	DCE	80	$(tBuO)_2$	28
3	$FeCl_3{\cdot}6H_2O$	DCE	80	$(tBuO)_2$	69
4	$Fe(ClO_4)_3$	DCE	80	$(tBuO)_2$	72
5	—	DCE	80	$(tBuO)_2$	N.R.[c]
6	$Fe(DMF)_6(ClO_4)_3$	DCE	80	$(tBuO)_2$	21
7	$FeCl_3$	DCE	80	TBHP	50
8	$FeCl_3$	DCE	80	H_2O_2	8
9	CF_3SO_3H	DCE	80	$(tBuO)_2$	40
10	$FeCl_3$	$CHCl_3$	60	$(tBuO)_2$	46
11	$FeCl_3$	CH_2Cl_2	40	$(tBuO)_2$	31
12	$FeCl_3$	CH_3CN	80	$(tBuO)_2$	56
13	$FeCl_3$	Toluene	80	$(tBuO)_2$	45
14	$FeCl_3$	THF	60	$(tBuO)_2$	43
15	$FeCl_3$	MeOH	60	$(tBuO)_2$	12
16	$FeCl_3$	acetone	50	$(tBuO)_2$	23

[a] Reaction conditions: **1a**:**2a**:oxidant:cat. = 1:1.2:2:0.1, 12 h.
[b] Isolated yield.
[c] N.R.: no quinoline product detected.

oxidant. As seen from entries 2-4, $FeCl_2{\cdot}4H_2O$, $FeCl_3{\cdot}6H_2O$, and $Fe(ClO_4)_3$ are less effective as catalysts. Clearly a catalyst is necessary as seen from entry 5. Iron complex $Fe(DMF)_6(ClO_4)_3$ was disappointing as a catalyst (entry 6). The effect of varying the oxidant was examined. Both TBHP and H_2O_2 were found to lead to lower or no yields (entries 7, 8). Brønsted acid CF_3SO_3H was relatively ineffective as the catalyst (entry 9). Different solvents were also screened and 1,2-dichloroethane was found to be the best for this reaction (entries 10–16).

The scope of this synthesis method for quinoline derivatives using oxidative coupling reactions was explored and the results are summarized in Table 2. Various *N*-alkyl anilines and a range of substituted acetylenes examined under the standard reaction condition provided moderate to excellent yields. **1a** readily reacted with various substituted alkynes, including electron-donating or electron-withdrawing substituents on the aryl ring of the alkynes, which proceeded well (entries 2–6). Notably, a bulky substituent at the *para*-position **2e** does not affect the reaction process at all in terms of steric effect (entry 5). However, the catalytic process was unsatisfactory with simple aliphatic substrates **2g**, and no quinoline product was detected (entry 7). But 73% yield was obtained, when electron-deficient aliphatic alkyne **2h** was used (entry 8). We also found that substituents on *N*-alkyl aniline

Table 2
Synthesis of quinolines from alkynes[a]

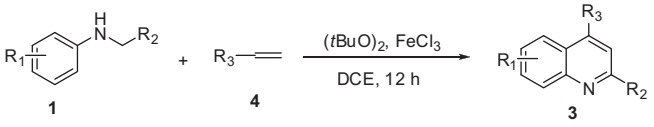


1 **2** **3**

Entry	R_1, R_2	R_3	Product	Yield[b] (%)
1	Ph, Ph (**1a**)	Ph (**2a**)	**3a**	81
2	Ph, Ph (**1a**)	*p*-FPh (**2b**)	**3b**	72
3	Ph, Ph (**1a**)	*p*-MePh (**2c**)	**3c**	78
4	Ph, Ph (**1a**)	*p*-OMePh (**2d**)	**3d**	83
5	Ph, Ph (**1a**)	*p*-*t*-BuPh (**2e**)	**3e**	86
6	Ph, Ph (**1a**)	*o*-MePh (**2f**)	**3f**	74
7	Ph, Ph (**1a**)	Cyclopropyl (**2g**)		N.R.[c]
8	Ph, Ph (**1a**)	COOMe (**2h**)	**3g**	73
9	*o*-ClPh, Ph (**1b**)	Ph (**2a**)	**3h**	86
10	*m*-ClPh, Ph (**1c**)	Ph (**2a**)	**3i**, **3j**	32, 51
11	*p*-ClPh, Ph (**1d**)	Ph (**2a**)	**3k**	76
12	Ph, *p*-MePh (**1e**)	Ph (**2a**)	**3l**	72
13	Ph, *p*-MePh (**1e**)	*p*-FPh (**2b**)	**3m**	67
14	Ph, *p*-MePh (**1e**)	*p*-MePh (**2c**)	**3n**	69
15	Ph, *p*-ClPh (**1f**)	*p*-MePh (**2c**)	**3o**	74
16	Ph, Me (**1g**)	Ph (**2a**)		N.R.[c]
17	Ph, PhCO (**1h**)	Ph (**2a**)	**3p**	75

[a] Reaction conditions: **1**:**2**:oxidant:cat. = 1:1.2:2:0.1, 12 h.
[b] Isolated yield.
[c] N.R.: no quinoline product detected.

Table 3
Synthesis of quinolines from alkenes[a]



1 **4** **3**

Entry	R_1, R_2	R_3	Product	Yield[b] (%)
1	Ph, Ph (**1a**)	Ph (**4a**)	**3a**	64
2	Ph, Ph (**1a**)	*p*-ClPh (**4b**)	**3q**	68
3	Ph, Ph (**1a**)	*p*-OMePh (**4c**)	**3d**	71
4	Ph, Ph (**1a**)	*o*-MePh (**4d**)	**3f**	65
5	*p*-ClPh, Ph (**1d**)	Ph (**4a**)	**3k**	75
6	Ph, *p*-MePh (**1e**)	Ph (**4a**)	**3l**	69
7	Ph, *p*-ClPh (**1f**)	Ph (**4a**)	**3r**	78
8	Ph, PhCO (**1h**)	Ph (**4a**)	**3p**	73

[a] Reaction conditions: **1**:**4**:oxidant:cat. = 1:1.2:2:0.1, 12 h.
[b] Isolated yield.

(**1b**–**1f**) have no significant effect on the reaction (entries 9-15). When *meta*-substitution on aniline part **1c** was employed, the products of C–H bond activated at *ortho*- and *para*-positions of Cl were obtained in 32 and 51% yields, respectively (entry 10). Unfortunately, no reaction was detected when *N*-alkyl aniline **1g** reacted with **2a** under the standard reaction condition (entry 16). The phenyl group on *N*-alkyl aniline was then changed to electron withdrawing group such as ketone **1h**, providing the corresponding quinolines in good yields (entry 17).

We continued to explore the scope of the oxidative coupling reactions by changing alkynes to alkenes, quinoline derivatives being prepared in good yield under the optimized condition (Table 3). Quinoline derivative **3a** was prepared in 64% yield, when **1a** reacted with styrene **4a** (entry 1). The scope of substituted styrenes was studied first. Both electron withdrawing (entry 2) and electron donating groups (entry 3) were compatible, providing the corresponding quinolines **3q** and **3d** in good yields (68 and 71%). *Ortho* substituent was also tolerated to give 65% yield (entry

4). The substitution at the *N*-alkyl aniline was then explored (entries 5–8), similar to the reaction with alkynes, providing the corresponding quinolines in good yields.

In summary, we have developed a simple and efficient method for the synthesis of quinoline derivatives from *N*-alkyl anilines and alkynes or alkenes by iron-catalyzed oxidative coupling reactions. This approach allows the direct reaction of simple *N*-alkyl anilines with a variety of alkynes or alkenes to give quinoline derivatives in good to excellent yield. Moreover, the iron catalyst is cheap, readily available, and environmentally friendly.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.090.

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