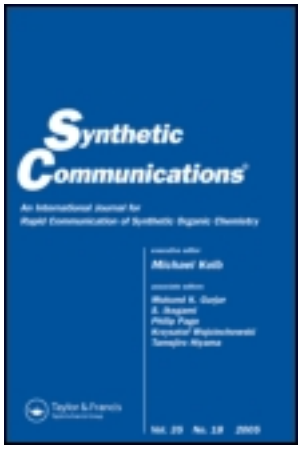

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Oxidant Effect of H_2O_2 for the Syntheses of Quinoline Derivatives via One-Pot Reaction of Aniline and Aldehyde

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OXIDANT EFFECT OF H_2O_2 FOR THE SYNTHESES OF QUINOLINE DERIVATIVES VIA ONE-POT REACTION OF ANILINE AND ALDEHYDE

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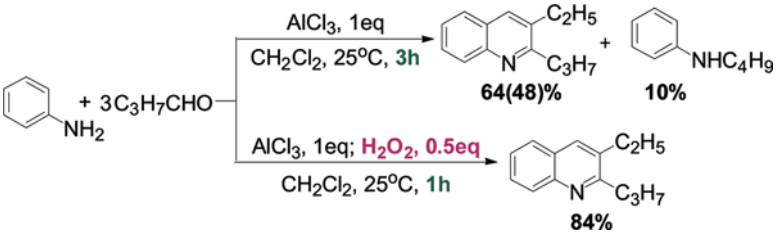
GRAPHICAL ABSTRACT



Abstract *A convenient one-pot method for the synthesis of substituted quinolines via the reaction of aniline and aldehyde in the presence of a Lewis acid ($AlCl_3$) and an oxidant (H_2O_2) has been developed. Hydrogen peroxide was found to promote the reaction by its function as a hydrogen hunter, hindering the formation of by-product N-alkylaniline. The effect of the oxidant on the yield and selectivity was studied. When the molar ratio of aniline, n-butyraldehyde, and H_2O_2 was 1:3:0.5 at 25 °C, the yield of 3-ethyl-2-propyl-quinoline was improved from 64% (reaction without H_2O_2) to 84% (with H_2O_2), and the quinoline selectivity was improved to almost 100%. Moreover, the reaction time was obviously reduced. The substituent effect was also investigated in this work.*

Keywords Aldehyde; aniline; hydrogen peroxide; oxidation; quinoline derivatives

INTRODUCTION

Quinolines and their derivatives are very important chemicals in the medical industry and have been explored for more than one hundred years. The quinoline ring system exists in various natural products, especially in alkaloids. Recently, quinolines have been applied as antioxidants in rubber synthesis and in some biological systems.[1] Furthermore, they play important roles in metal ion detection in the

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environment and lots of fine chemicals.[2] The synthesis of quinoline derivatives has always been one of the hot areas of organic chemistry research.

To date, various methods of quinoline synthesis have been explored, including Doebner–Miller,[3] Skraup,[4] and Friedländer[5] syntheses and some modifications.[6–9] These methods show great power to synthesize versatile quinolines. However, most of them suffer from harsh reaction conditions or multiple steps. Moreover, the products are always in poor yield and low selectivity because the by-product (*N*-alkylaniline) competes with quinolines, which leads to laborious product isolation and material waste.

Previous mechanism studies[9a,10] suggest the possibility of quinoline formation via a tetrahydroquinoline intermediate. After dehydration and dehydrogenation,[10b] the intermediate can be oxidized to quinoline and secondary amines. Nakajima et al. reported that the yield of substituted quinolines was promoted by using $[IrCl_2H(cod)]_2$ as a catalyst under an O_2 atmosphere.[9a] Leardini et al. reported that $FeCl_3$ could catalyze the transformation from imines to quinoline in good yield.[9c] Shindoh et al. described the formation of quinolines from imines with the assistance of an expensive oxidant, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[11] Tanaka et al. found that aerobic conditions prevent the reduction of imines effectively.[12] In the classical Skraup method, nitrobenzene was used as an oxidizing agent.[4a,10b,13]

It is known that hydrogen peroxide (H_2O_2) is used as an oxidant in the epoxidation of olefin and selective oxidations of aldehyde, ketone, and alkane.[14] Most important, it is an environmentally friendly reagent.[15] However, to the best of our knowledge, no literature was found on the syntheses of quinolines using hydrogen peroxide as an oxidant.

Therefore, in the course of our study on the oxidative reagent effect on the formation of quinoline derivatives, the widely available hydrogen peroxide was selected to introduce as an oxidant into the reaction mixture to trap hydrogens from dihydroquinoline in order to prevent the reduction of imines. We expected to enhance quinoline yield and selectivity under mild conditions instead of the previous harsh conditions. $AlCl_3$ was selected as catalyst, which is usually used as a traditional Lewis acid to mediate or catalyze organic transformations.[16] Our target is to improve quinoline yield and selectivity.

EXPERIMENTAL

Unless noted otherwise, all starting materials were obtained from commercial supplies and used without further purification. All reactions were performed under anhydrous conditions and a dry nitrogen atmosphere. The crude products were purified by column chromatography over silica gel (300–400 mesh) using Et_2O/hexane/petroleum ether (1:10:20) as eluent. The yield was analyzed on a Shimadzu gas chromatograph (GC-14B, Shimadzu) equipped with a fused silica capillary column (CBP1-M25-025, Shimadzu) and a chromatopacy integrator (C-R8A, Shimadzu). The detection temperature was set from 60 °C to 270 °C through temperature programming. Dodecane was used as an internal standard. Proton (300 MHz) and carbon (75 MHz) NMR spectroscopy were performed in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard at 25 °C on a JNM-LA300 FT-NMR (Jeol Ltd.) spectrometer.

Representative Experimental Procedure

CH_2Cl_2 (20 mL) was added to a dried Schlenk tube with Teflon-coated magnetic stir bar under an N_2 atmosphere. While stirring, aluminium trichloride ($AlCl_3$, 0.1333 g, 1 mmol), aniline (0.09 mL, 1 mmol), *n*-butyraldehyde (0.26 mL, 3 mmol), and H_2O_2 (0.10 mL, 30% in H_2O, 1 mmol) were added sequentially to the solution at room temperature. Dodecane was added as an internal standard. The resulting mixture was stirred at room temperature and monitored by gas chromatographic (GC) analysis until the reaction finished. Then it was quenched with 3 M ammonia solution (in H_2O), and the mixture was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with H_2O, $NaHCO_3$ (20%, aq.), H_2O, and brine in sequential order, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica-gel chromatography using (Et_2O–hexane–petroleum ether = 1:10:30) as eluent to give pure product 3-ethyl-2-propylquinoline. The products were characterized by gas chromatography (GC), GC–mass spectrometry (MS), and NMR.

3-Ethyl-2-propylquinoline (3a)

^{1}H NMR ($CDCl_3$, Me_4Si): δ 1.07(t, J = 7.5 Hz, 3H), 1.33(t, J = 7.5Hz, 3H), 1.77–1.87 (m, 2H), 2.83 (q, J = 7.4 Hz, 2H), 2.96 (t, J = 7.8 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.85 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 14.3, 14.4, 22.8, 25.1, 37.7, 125.5, 126.9, 127.3, 128.3, 128.4, 133.9, 135.3, 146.3, 162.0.

N-Butylaniline (4a)

^{1}H NMR ($CDCl_3$, Me_4Si): δ 0.95 (t, J = 7.4 Hz, 3H), 1.36–1.48 (m, 2H), 1.55–1.64 (m, 2H), 3.10 (t, J = 7.1 Hz, 2H), 3.32 (s, 1H), 6.58–6.70 (m, 3H), 7.13–7.23 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 13.8, 20.2, 31.7, 43.6, 112.7, 117.1, 129.2, 148.5.

3-Ethyl-6-methyl-2-propylquinoline (3b)

^{1}H NMR ($CDCl_3$, Me_4Si): δ 1.07(t, J = 7.4 Hz, 3H), 1.33 (t, J = 7.6 Hz, 3H), 1.78–1.85 (m, 2H), 2.50 (s, 3H), 2.82 (q, J = 7.6 Hz, 2H), 2.94 (t, J = 7.9 Hz, 2H), 7.44 (d, J = 8.3 Hz, 1H), 7.48 (s, 1H), 7.76 (s, 1H), 7.90 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 14.5, 14.6, 21.6, 23.0, 25.3, 37.8, 125.9, 127.3, 128.2, 130.6, 133.4, 135.3, 135.4, 145.1, 161.1.

6-Chloro-3-ethyl-2-propylquinoline (3c)

^{1}H NMR ($CDCl_3$, Me_4Si): δ 1.06 (t, J = 7.4 Hz, 3H), 1.33 (t, J = 7.6 Hz, 3H), 1.80–1.86 (m, 2H), 2.82 (q, J = 7.5 Hz, 2H), 2.94 (t, J = 7.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.70 (s, 1H), 7.76 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 14.3, 14.4, 22.8, 25.2, 37.8, 125.7 128.0, 129.2, 130.2, 131.2, 132.9, 136.5, 144.8, 162.4.

6-Bromo-3-ethyl-2-propylquinoline (3d)

^{1}H NMR ($CDCl_3$, Me_4Si): δ 1.06 (t, $J = 7.4$ Hz, 3H), 1.33 (t, $J = 7.4$ Hz, 3H), 1.80–1.86 (m, 2H), 2.82 (q, $J = 7.5$ Hz, 2H), 2.92 (t, $J = 7.8$ Hz, 2H), 7.64–7.67 (m, 1H), 7.74 (s, 1H), 7.85–7.87 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 14.3, 14.4, 22.7, 25.2, 37.8, 119.3, 128.6, 129.0, 130.4, 131.7, 132.8, 136.5, 145.0, 162.6.

3-Ethyl-6-methoxy-2-propylquinoline (3e)

^{1}H NMR($CDCl_3$, Me_4Si): δ 1.06 (t, $J = 7.2$ Hz, 3H), 1.33 (t, $J = 7.4$ Hz, 3H), 1.79–1.84 (m, 2H), 2.81 (q, $J = 7.5$ Hz, 2H), 2.91 (t, $J = 8.0$ Hz, 2H), 3.91 (s, 3H), 7.01 (s, 1H), 7.25–7.28 (m, 1H), 7.76 (s, 1H), 7.90 (d, $J = 9.2$ Hz, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ14.4, 14.6, 23.0, 25.3, 37.7, 55.5, 104.7, 120.8, 128.2, 130.0, 133.0, 135.7, 142.6, 157.2, 159.5.

2-Heptyl-3-hexylquinoline (3g)

^{1}H NMR ($CDCl_3$, Me_4Si): δ 0.89–0.91 (m, 6H), 1.30–1.50 (m, 14H), 1.65–1.70(m, 2H), 1.76–1.82 (m, 2H), 2.77 (t, $J = 7.9$ Hz, 2H), 2.97 (t, $J = 8.3$ Hz, 2H), 7.42 (t, $J = 7.2$ Hz, 1H), 7.59 (t, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 8.3$ Hz, 1H), 7.82 (s, 1H), 8.02 (d, $J = 8.3$ Hz, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 14.2, 22.7, 22.8, 29.3, 29.4, 29.9, 30.0, 30.6, 31.8, 31.9, 32.5, 36.0, 125.6, 126.9, 127.3, 128.3, 128.6, 134.2, 134.9, 146.6, 162.4.

N-Benzylideneaniline (i)

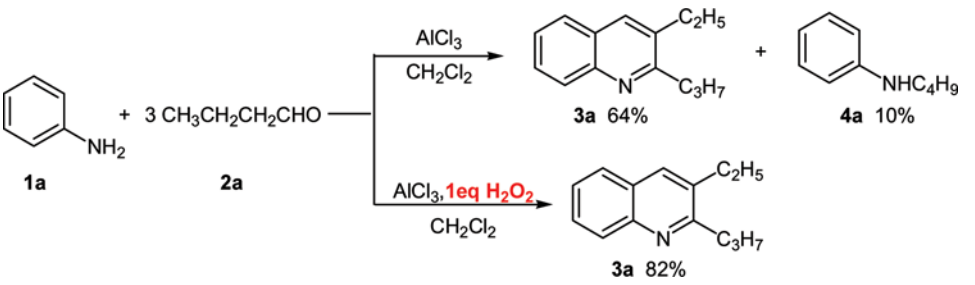
^{1}H NMR ($CDCl_3$, Me_4Si): δ 7.18–7.20 (m, 3H), 7.34–7.35 (m, 2H), 7.41–7.42 (m, 3H), 7.86–7.87 (m, 2H), 8.39 (s, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 121.1, 126.1, 128.9, 129.0, 129.3, 131.5, 136.4, 152.3, 160.5.

3-Ethyl-6-nitryl -2-propylquinoline (3f)

^{1}H NMR ($CDCl_3$, Me_4Si): δ 1.09 (t, $J = 7.4$ Hz, 3H), 1.38 (t, $J = 7.5$ Hz, 3H), 1.82–1.94 (m, 2H), 2.89 (q, $J = 7.6$ Hz, 2H), 3.00 (t, $J = 7.9$ Hz, 2H), 8.02 (s, 1H), 8.11 (d, $J = 9.3$ Hz, 1H), 8.37 (d, $J = 12.4$ Hz, 1H), 8.71 (s, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 13.8, 14.1, 22.1, 24.9, 37.3, 121.8, 123.8, 126.0, 130.1, 135.0, 137.7, 144.9, 148.5, 166.4.

RESULTS AND DISCUSSION

The reaction scheme, and the results are shown in Scheme 1. First, the reaction of aniline **1a** and *n*-butyraldehyde **2a** was run with $AlCl_3$ in CH_2Cl_2 at 25 °C for 6 h without H_2O_2. The desired product, 3-ethyl-2-propylquinoline, was obtained in 64% GC yield (isolated yield was 48%) with 10% of the by-product, **4a** (*N*-butylaniline). In contrast, when H_2O_2 (0.10 mL, 30% in H_2O, 1 mmol) was added into the reaction mixture, the reaction gave 3-ethyl-2-propylquinoline in 82% GC yield and 70% isolated yield without the detectable formation of **4a** (*N*-butylaniline) (Scheme 1).



Scheme 1. Model reaction of aniline and *n*-butyraldehyde. (Figure is provided in color online.)

The effect of the H_2O_2 amount is shown in Table 1. The yield of 3-ethyl-2-propylquinoline was sharply increased from 64% to 84% with the addition of 0.5 equiv H_2O_2. The yield was 82% with the addition of 1 equiv. and 1.5 equiv. of H_2O_2. These results indicate that the oxidative effect is notable and that 0.5 equiv. H_2O_2 is sufficient for the reaction.

Table 2 presents the effect of reaction temperature. The reactions occurred rapidly at different temperatures with high oxidant efficiency. The yield of 3-ethyl-2-propylquinoline **3a** was increased by at least 14% under different temperatures, and a temperature of 25 °C was the most effective. At 0 °C or 15 °C, the product yield was increased because of the presence of H_2O_2, but not as high as at 25 °C. High temperature (35 °C) did not improve the quinoline yield noticeably. This may be attributed to the decomposition of H_2O_2 at higher temperatures. Thus, a temperature of 25 °C was finally selected. The reaction time was also reduced when H_2O_2 was used as an oxidant. Moreover, to our surprise, the yield of the by-product (*N*-butylaniline) was greatly decreased.

The influence of the amounts of $AlCl_3$ on quinoline yield is summarized in Table 3. It didnot show big difference in quinoline yield when 0.2 equiv. of $AlCl_3$ was used instead of 1 equiv. Treatment of 1 equiv. aniline and 3 equiv. aldehyde with 0.1 equiv of $AlCl_3$ afforded quinoline in 72% GC yield and N-butylaniline in 27% GC yield, which indicated that $AlCl_3$ should be catalytic to the overall transformation. In contrast, when 1 equiv. of $FeCl_3$ was used instead of $AlCl_3$, quinoline was obtained only in 8% GC yield under the same conditions, and when 1 equiv. $ZnCl_2$ was used, almost no quinoline was formed. This difference, compared to

Table 1. Influence of different amounts of H_2O_2 on quinoline yield[a]

Entry	Equivalent of H_2O_2[b]	Yield (%)
1	0.25	47[c]
2	0.5	84
3	1.0	82
4	1.5	82

[a]The ratio of aniline–butyraldehyde–$AlCl_3$ was 1:3:1 in CH_2Cl_2 at 25 °C.
[b]The equiv of H_2O_2 was based on aniline.
[c]The yield of the by-product (N-butylaniline) was 7%.

Table 2. Yield of quinoline **3a** at different temperatures[a]

		H_2O_2 absent[b]			H_2O_2 present[b]		
Entry	Temperature (°C)	**3a**	**4a**	Complete reaction time (h)	**3a**	**4a**	Complete reaction time (h)
1	0	17	11	6	65	Trace	1
2	15	40	20	6	68	Trace	3
3	25	64 (48)	10	3	84	Trace	1
4	35	69	15	3	83	Trace	1

[a]The ratio of aniline–butyraldehyde–$AlCl_3$–H_2O_2 was 1:3:1:0.5 in CH_2Cl_2.
[b]GC yields; isolated yields are in parentheses.

the literature results,[3c,5d] may be ascribed to the poor solubility of $FeCl_3$ and $ZnCl_2$ in dichloromethane.

The scope of substrates was explored under optimized reaction conditions. The substrates include *p*-tolylamine **1b**, *p*-chloroaniline **1c**, *p*-bromaniline **1d**, *p*-methoxyaniline **1e**, *p*-nitroaniline **1f**, caprylic aldehyde **2b**, and benzaldehyde **2c**. For **1a–1e, 2a**, and **2b** (Table 4, entries 1–9), H_2O_2 showed a positive effect on yield and selectivity, and the quinoline yields were obviously increased with the use of H_2O_2. However, for **1c** and **1d**, although the quinoline yields were increased with 0.5 equiv H_2O_2, a small amount of *N*-butylaniline still occurred (Table 4, entries 3 and 5). Further, 1 equiv H_2O_2 was used in the cases of **1c** and **1d**, resulting in a slight increase in quinoline yields and undetectable amount of the by-product (N-butylaniline). It indicated that H_2O_2 plays an important role in preventing the reduction of imine. Murahashi et al. reported the tungstate-catalyzed oxidation of tetrahydroquinolines with H_2O_2 to synthesize cyclic hydroxamic acid, affording small amounts of quinolines as by-product, which shows the capability of H_2O_2 to dehydrogenize tetrahydroquinoline to quinoline.[17] The reaction was also carried out under air ambience, and parallelling the condition of H_2O_2, the yield of 3-ethyl-2-propylquinoline was increased from 64% to 70% (Table 4, entry 13), indicating that the oxidation could take place in the presence of air even if it is not good as H_2O_2. This result was consistent with data in the literature.[12]

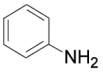
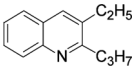
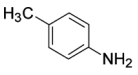
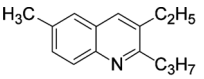
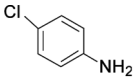
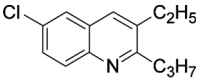
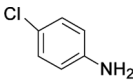
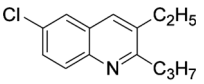
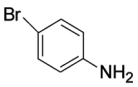
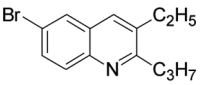
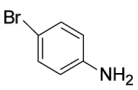
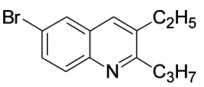
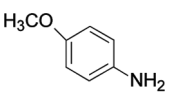
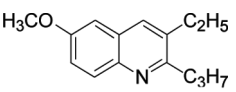
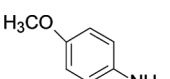
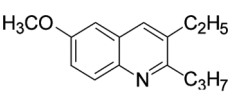
In contrast, H_2O_2 showed negative influence on the quinoline yield of **1f**. In fact, a greater yield of **1f** was obtained when H_2O_2 was absence (Table 4, entries 11 and 12). This result may be due to the presence of the nitro group (NO_2) of **1f**.[4a,10b,13] Furthermore, the α-carbon hydrogen of the aldehyde is necessary for

Table 3. Influence of different amounts of $AlCl_3$ on quinoline yield[a]

Entry	Amount of $AlCl_3$ (eq)	Conditions	Quinoline yield (%)[b]	N-Butylaniline yield (%)[b]
1	1	25 °C, 3 h	64 (48)	10
2	0.2	25 °C, 1 h	65	35
3	0.1	25 °C, 7 h	72	27

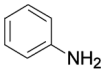
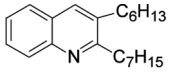
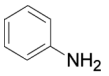
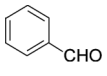
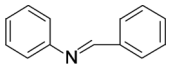
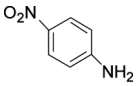
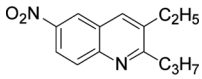
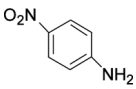
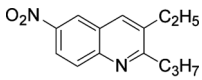
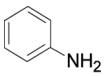
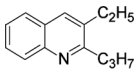
[a]The ratio of aniline–butyraldehyde was 1:3 in CH_2Cl_2.
[b]GC yields; isolated yields are in parentheses.

Table 4. Reaction of anilines, aldehyde, and H_2O_2[a]

Entry	Aniline	Aldehyde	Amount of H_2O_2	Product	Yield (%)[b]	
					H_2O_2 absent	H_2O_2 present
1	 **1a**	*n*-C_3H_7CHO **2a**	0.5	 **3a**	64 (48)	84
2	 **1b**	*n*-C_3H_7CHO	0.5	 **3b**	37	65 (53)
3	 **1c**	*n*-C_3H_7CHO	0.5	 **3c**	85	90
4	 **1c**	*n*-C_3H_7CHO	1.0	 **3c**	87 (85)	93 (90)
5	 **1d**	*n*-C_3H_7CHO	0.5	 **3d**	53 (50)	64
6	 **1d**	*n*-C_3H_7CHO	1.0	 **3d**	53 (50)	67 (60)
7	 **1e**	*n*-C_3H_7CHO	0.5	 **3e**	30	36
8	 **1e**	*n*-C_3H_7CHO	1.0	 **3e**	29	63 (56)

(*Continued*)

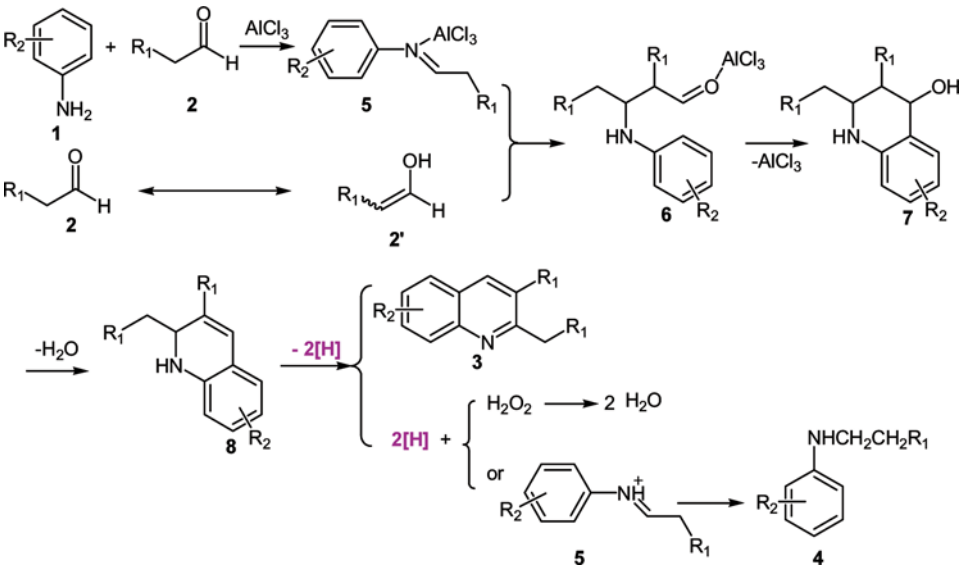
Table 4. Continued

Entry	Aniline	Aldehyde	Amount of H_2O_2	Product	Yield (%)[b]	
					H_2O_2 absent	H_2O_2 present
9	 **1a**	n-$C_7H_{15}CHO$ **2b**	0.5	 **3g**	53	73 (68)
10[c]	 **1a**	 **2c**	0.5	 **i**	100	87 (80)
11	 **1f**	n-C_3H_7CHO	0.5	 **3f**	70	55 (33)
12	 **1f**	n-C_3H_7CHO	2.0	 **3f**	29	12
13	 **1a**	n-C_3H_7CHO **2a**	0 (in air)	 **3a**	64 (48)	70[d]

[a]Aniline (1 mmol), aldehyde (3 mmol), and $AlCl_3$(1 mmol) in CH_2Cl_2, at 25 °C.
[b]GC yield; isolated yields are in parentheses.
[c]The product was isolated by recrystallization by using methanol as solvent.
[d]Accompanied by 17% of *N*-butylaniline.

the formation of the quinoline product. For example, when benzaldehyde was employed, only *N*-benzylideneaniline (Table 4, entry 10) was formed in a good yield.

Based on the results, a reaction mechanism is proposed here (Scheme 2). First, the nucleophilic addition reaction of aniline with aldehyde occurs to give imine **5** after a H_2O release. Then, the addition of another molecule of aldehyde (enol tautomer of aldehyde) to imine produces a new aldehyde **6**, which undergoes cyclization to form tetrahydroquinoline **7**. The resulting tetrahydroquinoline undergoes a dehydration process to yield dihydroquinoline **8**, followed by the dehydrogenation (oxidizing) of **8**, in which two hydrogen atoms were removed, afford quinoline **3**. Thus, a hydrogen hunter must be beneficial for the quinoline formation. If there is no additional oxidant in the reaction system, imine **5** can be easily reduced by



Scheme 2. Proposed mechanism for synthesis of quinolines promoted by H_2O_2. (Figure is provided in color online.)

dihydroquinoline to form *N*-alkylaniline **4** (Scheme 2), and quinoline yield is decreased consequently. When H_2O_2 was added in the reaction, it trapped the hydrogen from dihydroquinoline, which prevented the reduction of imine and oxidized dihydroquinoline to quinoline. As a result, the imine was not reduced by dihydroquinoline, and the quinoline yield increased distinctly without *N*-butylaniline formation. Jacob and Jones [18] the selective conversion of diallylanilines and arylimines to quinolines. In their work, in order to eliminate the reduction product, the reaction was performed in the presence of a 10-fold excess of *tert*-butylethylene to trap hydrogen produced during the reaction.

In summary, a convenient one-pot H_2O_2-promoted procedure was developed for the synthesis of 2,3-dialkylquinoline derivatives; the reaction was finished under mild conditions and without by-product formation. The good yield and selectivity of the target products make this reaction attractive, with potential for large-scale applications. Further exploration of other oxidants for quinoline synthesis is now under investigation in our laboratory.

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