A Novel One-Pot Oxidative Deformylation of *N*-Formyldihydroquinolines Employing Ferric Chloride Hexahydrate. Synthesis of 4-Chloro-2-phenylquinolines and 4-Chloro-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)quinolines.

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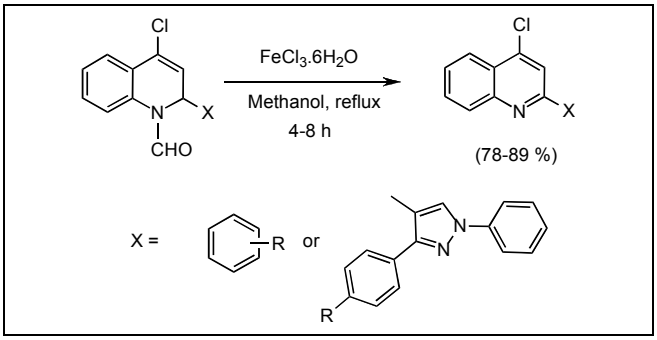

A novel versatile one-pot oxidative deformylation approach has been developed to synthesize 4-chloro-2-phenylquinolines and 4-chloro-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)quinolines from the corresponding N-formyldihydroquinolines.

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INTRODUCTION

4-Chloroquinolines are very useful intermediates in the synthesis of the highly active 4-aminoquinoline groups of potential antimalarial drugs and 4-quinolyl isothiocyanates [1-3]. However a few methods have been developed in the literature towards construction of quinoline molecules that have involved tedious procedures [4]. Nevertheless, it is still of continued interest and great significance to explore novel and efficient synthetic approaches for this class of compounds.

RESULTS AND DISCUSSION

In recent years ferric chloride hexahydrate has been increasingly utilized in a wide variety of organic reactions such as the oxidation of benzoin, Michael reaction and in deprotection chemistry [5]. Generally N-deformylation of formamides was achieved by heating in strongly acidic or basic solutions or by the other methods reported in literature [6]. To the best of our knowledge $FeCl_3.6H_2O$ had never been studied for the oxidative deformylation of *N*-formyldihydroquinolines. As a continuation of our studies on the synthesis of heterocyclic compounds with potential medicinal values from 2'-aminochalcones and 2'-hydroxychalcones [7] in this letter we wish to report a one-pot oxidative deformylation of N-formyldihydroquinolines by employing a mild and cheap reagent, $FeCl_3.6H_2O$ in methanol (Scheme 1).

The various substituted *N*-formyldihydroquinolines required for this reaction were prepared by the cyclization of 2'-aminochalcones with the Vilsmeier reagent [8]. In the present work, the initial studies were performed on the oxidative deformylation with different oxidizing agents. Among the oxidizing agents screened only $FeCl_3.6H_2O$ led to the effective oxidative deformylation while the rest failed. The results are summarized in Table 1.

Scheme 1

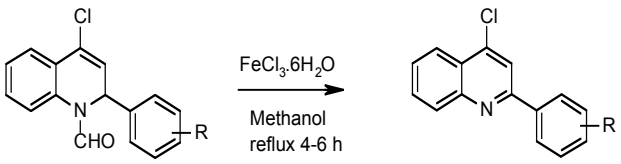


Table 1

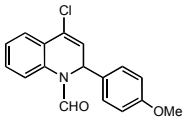
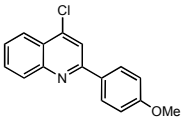
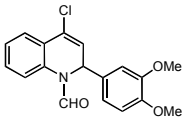
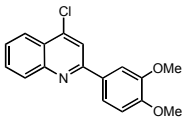
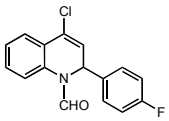
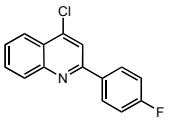
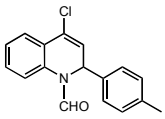
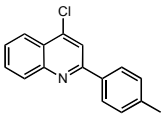
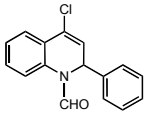
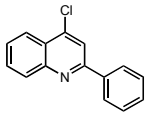
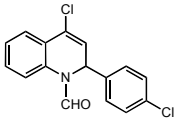
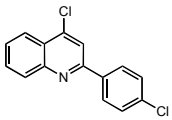
The oxidative deformylation of N-formyldihydroquinolines with different oxidizing agents.

#	Oxidizing agent	Equi-	time	Yield (%)
1	$Mn(OAc)_3$	2.5	10 h	-
2	CAN	2.5	10 h	-
3	$Mn(OAc)_3$-$Cu(OAc)_2$	2:1	10 h	-
4	$Cu(OAc)_2$-$K_2S_2O_8$	1:1	10 h	-
5	$FeCl_3.6H_2O$	2.5	4 h	88
6	NBS	1.0	10 h	-
7	I_2	1.1	10 h	-
8	$Co(NO_3)_2$-$K_2S_2O_8$	1:1	10 h	-
9	PCC	2.2	10 h	-
10	TBADC	2.2	10 h	-

To extend the scope of this reaction, a wide range of substituted and structurally diverse *N*-formyldihydroquinolines were subjected to this reaction. The reaction proceeded in a similar fashion. Substituted quinolines were obtained in good yields. The results are summarized in Table 2.

Table 2

The oxidative deformylation of *N*-formyldihydroquinolines by $FeCl_3.6H_2O$

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]
1			4	88
2			4	85
3			5	80
4			6	82
5			4	84
6			5	76

[a]all products were characterized by ^{1}H NMR and mass spectra and by elemental analysis. [b] Yield of isolated products.

Pyarazole nucleosides have shown potent and selective antiviral antitumor activity [9]. Thus to synthesize pyrazole nucleoside having quinoline unit we have extended this oxidative deformylation approach to synthesize 4-chloro-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-quinolines under similar conditions (Scheme 2) and the results are summarized in Table 3.

Scheme 2

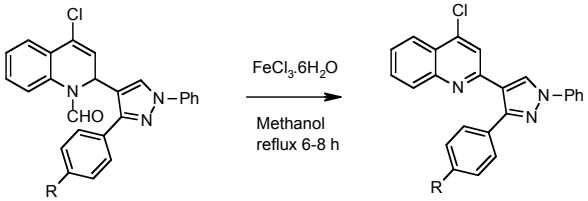
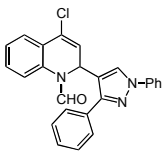
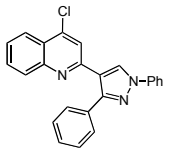
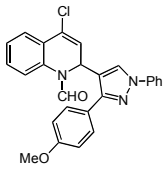
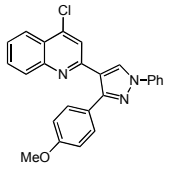
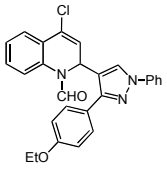
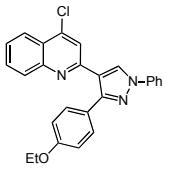
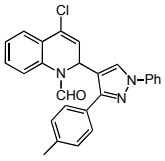
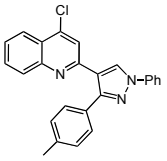


Table 3

The oxidative deformylation of pyrazolylquinoline-1(2*H*)-carbaldehydes by $FeCl_3.6H_2O$

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]
1			6 h	84
2			6 h	89
3			8 h	85
4			7 h	78

[a]all products were characterized by ^{1}H NMR and mass spectra and by elemental analysis. [b]Yield of isolated products.

We believe that this procedure will provide a better scope and more practical alternative to the existing procedures for the synthesis of 4-chloro-2-phenylquinolines and 4-chloro-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)quinolines from the corresponding N-formyldihydroquinolines.

EXPERIMENTAL

General procedure for the oxidative deformylation of N-formyldihydroquinolines. *N*-Formyldihydroquinoline (1 mmol) was taken in a 100 mL RB flask containing 15 mL methanol to this $FeCl_3.6H_2O$ (2.5 mmol) was added and the reaction mixture was refluxed on an oil-bath for adequate time at 100°C until the disappearance of the starting material in TLC. Then ice-cold water was added to the reaction mixture and extracted with ethyl acetate (4x20ml) and the extract was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave the crude product, which was further purified by column chromatography on silica gel ethyl acetate-hexane (1:9) as eluent to afford pure product.

Spectral data.

4-Chloro-2-(4-methoxyphenyl)quinoline (Entry 1, Table 2). White solid. Mp : 77-78°C, FT-IR (KBr) ν_{max} cm^{-1} : 1594, 1508, 1415, 1218. ^{1}H NMR (500 MHz, $CDCl_3$) δ : 3.86(s, 3 H, OCH_3), 7.01(d, *J* = 8.55 Hz, 2 H), 7.54-7.57(m, 1 H), 7.71-7.74(m, 1 H), 7.89(s, 1 H, H-3), 8.09(m, 3 H), 8.2(d, J = 7.45 Hz, 1 H, H-5). ^{13}C

NMR (125 MHz, $CDCl_3$) δ : 55.46, 114.37, 118.67, 124.00, 125.08, 126.89, 128.95, 129.91, 130.56, 131.17, 143.02, 149.16, 156.87, 161.24. MS *m/z* : 269 (M^+). Anal. calcd for $C_{16}H_{12}NOCl$: C, 71.25; H, 4.48; N, 5.19. Found : C, 71.08; H, 4.19; N, 5.06.

4-Chloro-2-(3,4-dimethoxyphenyl)quinoline (Entry 2, Table 2). White solid. Mp : 116-117 °C. FT-IR (KBr) ν_{max} cm^{-1} : 1593, 1515, 1400, 1216. ^1H NMR (500 MHz, $CDCl_3$) δ : 3.94(s, 3 H, OCH_3), 4.03(s, 3 H, OCH_3), 6.95(d, *J* = 8.4 Hz, 1 H), 7.55-7.83(m, 4 H), 7.91(s, 1 H, H-3), 8.13(d, *J* = 8.45 Hz, 1 H, H-8), 8.17(d, *J* = 8.4 Hz, 1 H, H-5). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 56.09, 56.13, 110.30, 111.08, 118.73, 120.36, 124.01, 125.15, 126.98, 129.89, 130.59, 131.43, 143.02, 149.07, 149.51, 150.82, 156.80.MS *m/z* : 299 (M^+). Anal. calcd for $C_{17}H_{14}NO_2$ Cl : C, 68.12; H, 4.71; N, 4.67. Found C, 67.88; H, 4.69; N, 4.49.

4-Chloro-2-(4-fluorophenyl)quinoline (Entry 3, Table 2). White solid. Mp : 87-89 °C. FT-IR (KBr) ν_{max} cm^{-1} : 1592, 1522, 1420, 1229. ^1H NMR (500 MHz, $CDCl_3$) δ : 7.18-7.21(m, 2 H), 7.59-7.78(m, 2 H), 7.90(s, 1 H, H-3), 8.11-8.15(m, 3 H), 8.19(d, *J* = 8.0 Hz, 1 H, H-5) ^{13}C NMR (125 MHz, $CDCl_3$) δ : 115.90, 116.07, 118.80, 124.05, 125.28, 127.38, 129.45, 129.52, 130.04, 134.80, 143.37, 149.07, 156.18. MS *m/z* : 257 (M^+). Anal. calcd for $C_{15}H_9NClF$: C, 69.91; H, 3.52; N, 5.44. Found : C, 69.67; H, 3.69; N, 5.38.

4-Chloro-2-(4-methylphenyl)quinoline (Entry 4, Table 2). White solid. Mp : 94-95 °C. FT-IR (KBr) ν_{max} cm^{-1} : 1589, 1519, 1430, 1209. ^1H NMR (500 MHz, $CDCl_3$) δ : 2.43(s, 3 H, CH_3), 7.32(d, *J* = 8.0 Hz, 2 H), 7.74-7.77(m, 2 H), 7.94(s, 1 H, H-3), 8.03(d, *J* = 8.6 Hz, 2 H), 8.15(d, *J* = 8.6 Hz, 1 H, H-8), 8.19(d, *J* = 7.45 Hz, 1 H, H-5). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 21.51, 119.02, 119.08, 123.84, 125.30, 127.42, 127.51, 129.61, 129.84, 130.57, 135.86, 140.08, 143.10, 157.33. MS *m/z* : 253 (M^+). Anal. calcd for $C_{16}H_{12}NCl$: C, 75.74; H, 4.77; N, 5.44. Found : C, 75.64; H, 4.56; N, 5.40.

4-Chloro-2-phenylquinoline (Entry 5, Table 2). White solid. Mp : 82-83 °C. FT-IR (KBr) ν_{max} cm^{-1} : 1582, 1521, 1428, 1200. ^1H NMR (500 MHz, $CDCl_3$) δ : 7.30-7.78(m, 5 H), 7.93(s, 1 H, H-3), 8.03(d, *J* = 8.6 Hz, 2 H), 8.16(d, *J* = 8.6 Hz, 1 H, H-8), 8.20(d, *J* = 7.45 Hz, 1 H, H-5). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 119.02, 119.08, 123.84, 125.30, 127.42, 127.51, 129.61, 129.84, 130.57, 135.86, 140.08, 143.10, 157.33. MS *m/z* : 239 (M^+). Anal. calcd for $C_{15}H_{10}NCl$: C, 75.31; H, 4.18; N, 5.85. Found: C, 75.34; H, 4.26; N, 5.50.

4-Chloro-2-(4-chlorophenyl)quinoline (Entry 6, Table 2). White solid. Mp : 102-104°C. FT-IR (KBr) ν_{max} cm^{-1} : 1590, 1525, 1421, 1219. ^1H NMR (500 MHz, $CDCl_3$) δ : 7.20-7.23(m, 2 H), 7.60-7.80(m, 2 H), 7.93(s, 1 H, H-3), 8.14-8.17(m, 3 H), 8.20(d, *J* = 8.0 Hz, 1 H, H-5) ^{13}C NMR (125 MHz, $CDCl_3$) δ : 115.93, 116.17, 117.90, 123.55, 125.48, 127.39, 129.45, 129.60, 130.14, 134.85, 143.42, 149.17, 156.18. MS *m/z* : 273 (M^+). Anal. calcd for $C_{15}H_9NCl_2$: C, 65.93; H, 3.29; N, 5.12. Found : C, 65.67; H, 3.19; N, 5.38.

4-Chloro-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)quinoline (Entry 1, Table 3). White solid. Mp : 122-123 °C. FT-IR (KBr) ν_{max} cm^{-1} : 1596, 1545, 1419, 1223.^1H NMR (500 MHz, $CDCl_3$) δ : 7.31(t, *J* = 7.45 Hz, 1 H, H-7), 7.40(s, 1 H, H-3), 7.42-7.86(m, 11 H), 8.08(d, *J* = 8.0 Hz, 1 H, H-8), 8.16(d, *J* = 8.0 Hz, 1 H, H-5). 8.54(s, 1 H, pyrazole-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 118.35, 118.99, 119.35, 120.65, 122.26, 123.82, 124.13, 127.13, 128.66, 128.74, 129.07, 129.60, 130.67, 132.83, 139.76, 142.40, 143.05, 149.64, 150.34, 156.16. MS *m/z* : 381 (M^+). Anal. calcd for $C_{24}H_{16}N_3Cl$: C, 75.49; H, 4.22; N, 11.00. Found : C, 75.19; H, 4.39; N, 10.85.

4-Chloro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]quinoline (Entry 2, Table 3). White solid. Mp: 136-137 °C. FT-IR (KBr) ν_{max} cm^{-1}: 1599, 1532, 1426, 1219. ^1H NMR (500 MHz, $CDCl_3$) δ : 3.85(s, 3 H, OCH_3), 6.94(d, *J* = 8.4 Hz, 2 H), 7.30(t, *J* = 7.40 Hz, 1 H, H-7), 7.43(s, 1 H, H-3), 7.46-7.76(m, 6 H), 7.83(d, J = 8.05 Hz, 2 H), 8.08(d, *J* = 8.4 Hz, 1 H, H-8), 8.16(d, *J* = 8.05 Hz, 1 H, H-5). 8.55(s, 1 H, pyrazole-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 55.40, 114.08, 119.28, 121.20, 121.24, 121.97, 124.12, 125.14, 125.25, 126.92, 127.08, 128.87, 129.52, 129.57, 130.32, 130.64, 139.79, 142.39, 149.16, 151.34, 152.67. MS *m/z* : 411 (M^+). Anal. calcd for $C_{25}H_{18}N_3OCl$: C, 72.90; H, 4.40; N, 10.20 Found: C, 72.63; H, 4.28; N, 10.15.

4-Chloro-2-[3-(4-ethoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-quinoline (Entry 3, Table 3). White solid. Mp: 140-142 °C. FT-IR (KBr) ν_{max} cm^{-1}: 1588, 1539, 1428, 1210. ^1H NMR (500 MHz, $CDCl_3$) δ : 1.42(t, *J* = 6.85 Hz, 3 H), 4.06(q, *J* = 6.85, 13.75 Hz, 2 H), 6.93(d, *J* = 8.5 Hz, 2 H), 7.30(t, *J* = 7.45 Hz, 1 H, H-7), 7.43(s, 1 H, H-3), 7.46-7.76(m, 6 H), 7.83(d, J = 8.0 Hz, 2 H), 8.08(d, *J* = 8.0 Hz, 1 H, H-8), 8.16(d, *J* = 8.05 Hz, 1 H, H-5). 8.55(s, 1 H, pyrazole-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 14.92, 63.60, 114.65, 119.28, 121.21, 121.25, 121.96, 124.11, 125.07, 125.14, 126.91, 127.06, 128.86, 129.52, 129.56, 130.28, 130.63, 139.79, 142.37, 149.16, 151.40, 152.89. MS *m/z* : 425 (M^+). Anal. calcd for $C_{26}H_{20}N_3OCl$: C, 73.32; H, 4.73; N, 9.87. Found : C, 73.20; H, 4.35; N, 9.64.

4-Chloro-2-[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-quinoline (Entry 4, Table 3). White solid. Mp: 112-113 °C. FT-IR (KBr) ν_{max} cm^{-1}: 1581, 1404, 1187, 1050. ^1H NMR (500 MHz, $CDCl_3$) δ : 2.44(s, 3 H, CH_3), 7.22-7.33(m, 3 H), 7.39(s, 1 H, H-3), 7.43-7.77(m, 6 H), 7.84(d, *J* = 7.45 Hz, 2 H), 8.0(d, *J* = 8.0 Hz, 1 H, H-8), 8.16(d, *J* = 8.05 Hz, 1 H, H-5), 8.56(s, 1 H, pyrazole CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 21.51, 119.32, 121.24, 121.29, 122.14, 124.11, 125.15, 126.36, 127.06, 128.87, 129.33, 129.54, 129.81, 130.61, 138.57, 139.81, 142.34, 148.56, 149.17, 151.57, 152.68. MS *m/z* : 395.8 (M^+). Anal. calcd for $C_{25}H_{18}N_3Cl$: C, 75.85; H, 4.58; N, 10.61. Found: C, 75.58; H, 4.29; N, 10.58.

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