Quinoline Synthesis by the Reaction of Anilines with 1,2-diols Catalyzed by Iron Compounds

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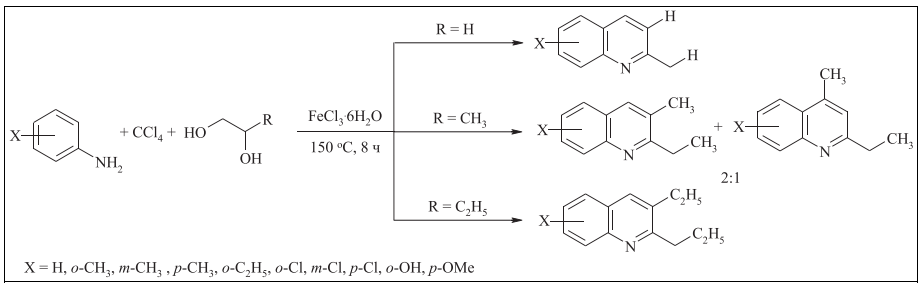

The synthesis of quinoline derivatives by cyclocondensation of anilines with 1,2-ethanediol, 1,2-propanediol, and 1,2-butanediol in the presence of iron-containing catalysts was performed for the first time.

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INTRODUCTION

Quinoline and its derivatives constitute an important class of nitrogen-containing heterocycles. They are widely used for production of extractants, sorbents, cyanine dyes, and corrosion inhibitors. Quinoline is the key structural element for many drugs having broad spectrum of action.

Most of the known Skraup, Dobner–Miller, Comber, and Conrad–Limpach methods to synthesize quinolines are based on the acid-catalyzed condensation of anilines with glycerin and carbonyl compounds. The principal drawback is the low environmental friendliness, because of the need to use stoichiometric amounts of acid catalysts because of their binding to the nitrogen-containing substrates. Furthermore, the employment of high reactive acid catalysts roughly narrows the range of functionally substituted substrates involving in the quinoline synthesis. Furthermore, the employment of strong acid catalysts abruptly narrows the range of functionally substituted substrates involved in the quinoline synthesis.

Metal complex catalysis has opened a new page in the synthesis of quinolines. The catalytic approach has three absolute advantages: tolerance to most functional groups, significant expansion of the C_3–sinton assortment suitable for the use as the building blocks for the construction of the quinoline ring, and minimum flow rate of the catalyst.

This paper describes the development of a new method for the synthesis of quinoline and its derivatives by the reaction of anilines with 1,2-diols catalyzed by iron compounds.

It is known from literature that the catalytic condensation of anilines with 1,2-diols is a key method for the synthesis of fused indole-based nitrogen heterocycles.

The catalytic condensation of aniline and its derivatives with 1,2-diols is a key method for the synthesis of fused indole-based nitrogen heterocycles [1–5].

Aniline and its derivatives react with 1,2-propanediol at 260–310°C under the action of heterogeneous catalysts: Ag/SiO_2 [2], $Ag/SiO_2/ZnO$ [3], and ZrO_2/SiO_2 [4], to give 3-methyl-substituted indoles in 12–48% yields.

A similar reaction of anilines with 1,2-diols, resulting in the formation of indoles, is catalyzed by ruthenium and iridium complexes, which perform this reaction under milder conditions (170°C) [5].

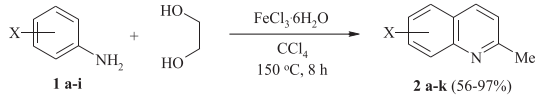
RESULTS AND DISCUSSION

We have established that the pathway of the reaction between anilines and 1,2-diols such as 1,2-ethanediol (1,2-ethylene glycol), 1,2-propanediol, and 1,2-butanediol under the action of iron-containing catalysts [$FeCl_3 \cdot 6H_2O$, $FeCl_3$, $FeCl_2 \cdot 4H_2O$, $Fe(C_2H_5)_2$, $Fe(acac)_3$, $Fe(OAc)_2$, $Fe_2(CO)_9$] mediated by CCl_4 differs from that of in the known condensation reaction, providing the formation of quinolines. The best results were obtained by using $FeCl_3 \cdot 6H_2O$ as the catalyst at 150°C for 8 h at a molar ratio of the catalyst and starting reagents [Fe]:[aniline]:[CCl_4]:[1,2-propanediol] = 1:100:200:400.

The condensation of aniline and its derivatives **1** with 1,2-ethanediol in CCl_4 in the presence of $FeCl_3 6H_2O$ affords 2-methylquinolines **2a–k** in 56–97% yields (Scheme 1).

The condensation of anilines **1** with 1,2-propanediol in the presence of $FeCl_3 6H_2O$ in a CCl_4 medium gives a difficult-to-separate mixture of 2,3-substituted **3a–k** and

Scheme 1



1 a-i **2 a-k** (56-97%)

2,4-substituted **4a–i** quinolines in a 75–94% total yield and with predominance of the former isomer (Scheme 2).

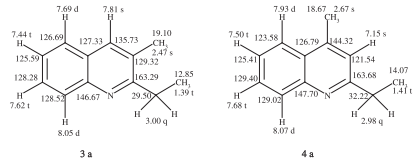
Compounds **3a** and **4a** were characterized as a mixture by ^{1}H and ^{13}C NMR spectral data. According to the integrated intensities of the methyl proton signals at $\delta_{Ia}(CH_3) = 2.47$ ppm and $\delta_{Ib}(CH_3) = 2.67$ ppm, compound **3a** predominates in the mixture (**3a**:**4a** = 2:1) (Fig. 1).

The assignment of proton and carbon signals was based on the data of 2D NMR experiments: correlation spectroscopy, heteronuclear single quantum coherence, and heteronuclear multiple bond correlation (HMBC). The position of the methyl group at C^4 is unambiguously determined by the presence of HMBC cross peaks between the methyl group proton signals and the quaternary carbon atom signals at $\delta C^{4a} = 126.79$ ppm and by the low-field signal at $\delta C^4 = 144.32$ ppm and high-field signal of the methine carbon atom $\delta C^3 = 121.54$ ppm.

The ^{1}H and ^{13}C NMR spectra of 2,3- and 2,4-alkyl quinoline derivatives (**3a–e**, **3g–k**, **4c**, and **4f**) were identical to the reported spectra [6–12]. The singlet in the 7.59–7.77 ppm range in the ^{1}H NMR spectrum of compound **3a** belongs to the hydrogen atom at C^4 that corresponds to the 2,3-disubstituted quinoline structure, while the singlet in the range of 7.11–7.19 ppm characteristic of the proton at C^3 attests to the presence of 2,4-disubstituted quinoline isomers in the mixture. The formation of a mixture of 2-alkyl-substituted quinolines (**3a** and **4a**) follows from the gas chromatography/mass spectrometry (GC–MS) data and the ^{13}C NMR spectrum that exhibits two signals in the range of 163–164 ppm typical of C^2 carbon atoms.

The condensation of 1,2-butanediol with aniline **1a–i** in the presence of $FeCl_3 \cdot 6H_2O$ fairly proceeds actively to give the corresponding quinolines (Scheme 3).

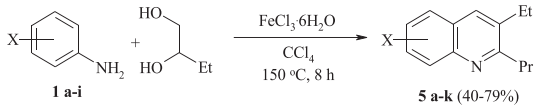
The composition and the yield of quinolines are substantially affected by the substituent position in the aniline molecule. Anilines with *ortho*-substitution and with one vacant position for heterocyclic ring closure form 2,3,8-substituted quinolines; *para*- substituted anilines cyclize at both *ortho*-positions to yield 2,3,6-substituted quinolines; and *meta*-substituted anilines are converted to mixtures of 2,3,5-isomer and 2,3,7-isomer.



3 a 4 a

Figure 1. Assignment of the ^{1}H and ^{13}C NMR signals of compounds **3a** and **4a**.

Scheme 3



1 a-i **5 a-k** (40-79%)

It can be seen from experimental data that the closer the substituent to the carbon atom bearing the amino group, the more pronounced its unfavorable influence on the conversion of the aniline derivative.

The aniline conversion and the quinoline yield are markedly affected by the substituent nature in the aniline molecule. The electron-withdrawing chlorine, which decreases the amino group basicity, considerably reduces the reactivity of aniline [13] and its derivatives.

As follows, from experimental data, the reaction does not proceed without CCl_4. To elucidate the role of CCl_4, the reaction mixture was analyzed by GLC and GC–MS and was found to contain chloroform and only traces of CCl_4.

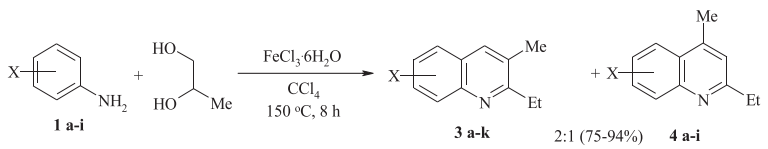
In addition, according to mercurimetric titration data, the reaction mixture contained HCl and chloride ions, their concentrations varying in the following way depending on the experiment duration: after 2 h, $[Cl^-] = 85.9$ mg/mL, [HCl] = 98.3 mg/mL; after 4 h, $[Cl^-] = 171.8$ mg/mL, [HCl] = 176.6 mg/mL; and after 8 h, $[Cl^-] = 266.9$ mg/mL, [HCl] = 274.4 mg/mL.

In view of the composition of by-products and published data [14] on the possibility of catalytic oxidation of alcohols by CCl_4 to aldehydes via hypochlorite, the following mechanism can be proposed for the quinoline formation with participation of 1,2-propanediol and 1,2-butanediol (Scheme 4).

At the initial step, diol **A** is oxidized by CCl_4 at the primary alcohol group to give aldehydoalcohol **B**, which can in turn be dehydrated to give unsaturated aldehyde **C**.

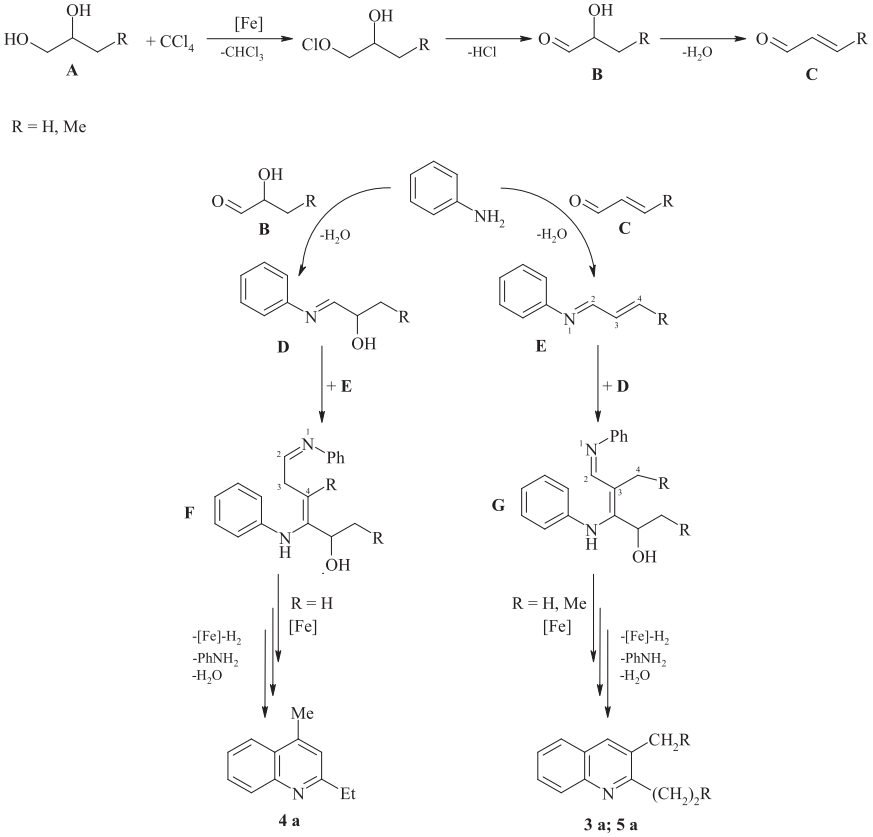
Then aldehydes **B** and **C** react with aniline to give Schiff bases **D** and **E**. The next step is codimerization of

Scheme 2



1 a-i **3 a-k** 2:1 (75-94%) **4 a-i**

Scheme 4. The proposed mechanism of the reaction synthesis of quinolines by the condensation of anilines with 1,2-propanediol and 1,2-butanediol catalyzed by $FeCl_3 \cdot 6H_2O$.



compounds **D** and **E**, resulting in two isomeric intermediates **F** and **G**. Heterocyclization, dehydrogenation, dehydration, and deamination of **F** and **G** under the action of iron-containing catalysts afford the final products: 2,3-substituted and 2,4-substituted quinolines, **4a** and **3a** in the case of 1,2-propanediol; and **5a** in the case of 1,2-butanediol.

According to the Fischer titration of water, the reaction gives three water molecules that supports the proposed mechanism. In the reaction of aniline with 1,2-propanediol, the content of water in the reaction mixture was 11.87%, while in the case of 1,2-butanediol, it was 12.17%, which is close to the theoretical values (10 and 11%).

As regards, the mechanism of reaction between aniline or its derivatives **1** and 1,2-ethanediol in the presence of $FeCl_3 6H_2O$ in CCl_4 to give 2-methylquinolines **2a–k** (Table 1), we suggest that the reaction includes oxidation of one hydroxy group of ethylene glycol to give glycolaldehyde **B**, which reacts with aniline **1a** to give Schiff base. The latter dimerizes and, upon water and aniline elimination, is converted to 2-methylquinoline **2a**, the structure of which was proven based on ^1H and ^{13}C NMR data (Scheme 5).

CONCLUSION

Thus, we have developed a catalytic method for the synthesis of monosubstituted, disubstituted, and trisubstituted quinolines through the condensation reaction of anilines with 1,2-ethanediol, 1,2-propanediol, and 1,2-butanediol mediated by CCl_4 under the action of iron-containing catalysts in $40-94\%$ yield. This reaction may serve as the basis for designing new convenient and efficient procedures to obtain quinolines used in different pharmaceutical industries especially in pharmaceutical compound production.

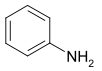
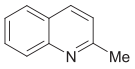
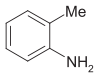
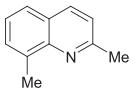
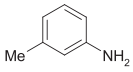
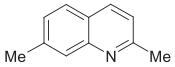
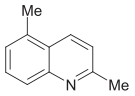
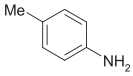
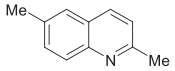
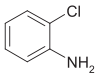
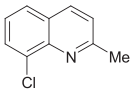
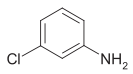
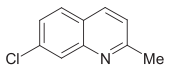
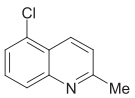
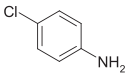
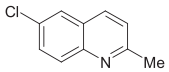
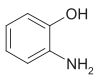
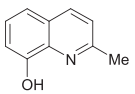
Thus, we have synthesized monosubstituted, disubstituted, and tri-substituted quinolines via the interaction between anilines and 1,2-dioles in CCl4 in the presence of $FeCl_3{\circ}6H_2O$ as the catalyst in 40-94% yield (Table 2).

EXPERIMENTAL

^1H, ^{13}C NMR spectra were measured on a Bruker Avance-400 spectrometer (400.13 and 100.62 MHz, respectively) in $CDCl_3$; the chemical shifts are referred to tetramethylslane. Mass spectra were run on a Shimadzu GCMS-QP2010Plus GC–MS spectrometer (an SPB-5 capillary column, 30 m × 0.25 mm, helium as a

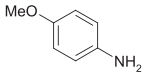
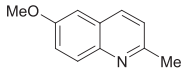
Table 1

Synthesis of 2-methylquinolines **2a–k** by the condensation of anilines **1a–i** with 1,2-ethanediol catalyzed by $FeCl_3 \cdot 6H_2O$.

Entry	Anilines	**1**	2-Methylquinolines	**2**[ref]	Yields (%)
1		**1a**		**2a**[6]	97
2		**1b**		**2b**[7]	68
3		**1c**		**2c**[8]	67
				**2d**[a]	
4		**1d**		**2e**[9]	81
5		**1e**		**2f**	72
6		**1f**		**2g**[8][a]	56
				**2h**[8][a]	
7		**1g**		**2i**[10]	80
8		**1h**		**2j**[10]	88

(*Continued*)

Table 1
(*Continued*)

Entry	Anilines	**1**	2-Methylquinolines	**2**[ref]	Yields (%)
9		**1i**		**2k**[8]	81

[a]The isomer ratio **2 c:2 d** = 3:1, **2 g:2 h** = 6:1.

Scheme 5. The proposed mechanism of the reaction of 2-methylquinolines by the condensation of anilines with 1,2-ethanediol catalyzed by $FeCl_3 \cdot 6H_2O$.

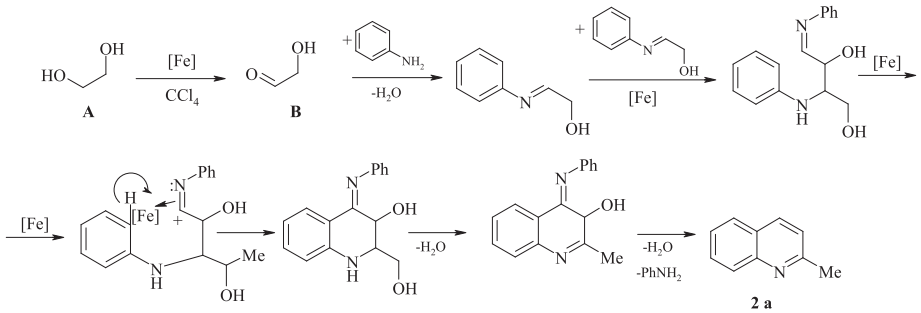
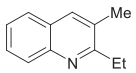
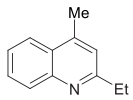
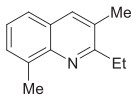
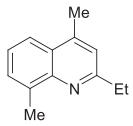
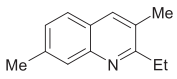
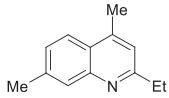
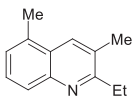


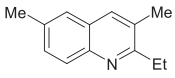
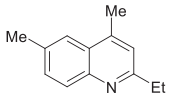
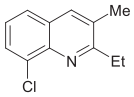
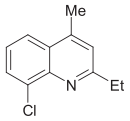
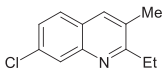
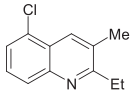
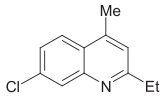
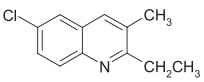
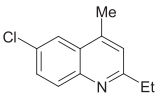
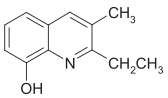
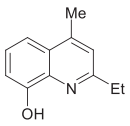
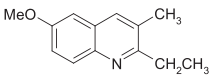
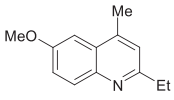
Table 2

Synthesis of 2,3-substituted **3a–k** and 2,4-substituted **4a–i** quinolines by the condensation of anilines **1a-i** with 1,2-propanediol catalyzed by $FeCl_3 \cdot 6H_2O$.

Entry	Anilines **1**	2-substituted quinolines	**3**[ref]	4-substituted quinolines	**4**	Yields (%)
1	**1a**		**3a**[6]		**4a**	94
2	**1b**		**3b**[8]		**4b**	90
3	**1c**		**3c**[8]		**4c**[a]	85
			**3d**[8]			

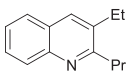
(Continued)

Table 2
(*Continued*)

Entry	Anilines **1**	2-substituted quinolines	**3**[ref]	4-substituted quinolines	**4**	Yields (%)
4	**1d**		**3e**[8]		**4d**	76
5	**1e**		**3f**		**4e**	87
6	**1f**	 	**3g**[8] **3h**[8]		**4f**[a]	83
7	**1g**		**3i** [8]		**4g**	80
8	**1h**		**3j**[11]		**4h**	86
9	**1i**		**3k**[8]		**4i**	75

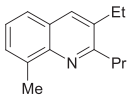
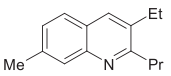
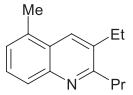
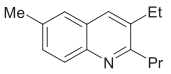
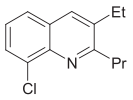
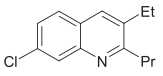
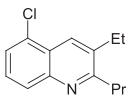
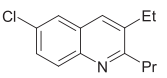
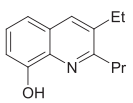
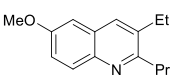
[a]The isomer ratio **3c:3d:4c** и **3g:3 h:4f** = 3:1:2.

Table 3
Synthesis of quinolines **5a–k** by the condensation of anilines **1a–i** with 1,2-butanediol catalyzed by $FeCl_3 \cdot 6H_2O$.

Entry	Anilines **1**	2-substituted quinolines	**5**[ref]	Yields (%)
1	**1a**		**5a**[6]	73

(Continued)

Table 3
(*Continued*)

Entry	Anilines **1**	2-substituted quinolines	**5**[ref]	Yields (%)
2	**1b**		**5b**[8]	42
			**5c**[8]	
3	**1c**			59
			**5d**[8]	
4	**1d**		**5e**[8]	71
5	**1e**		**5f**[8]	40
			**5g**[8]	
6	**1f**			58
			**5h**[8]	
7	**1g**		**5i**[8]	46
8	**1h**		**5j**[12]	78
9	**1i**		**5k**[8]	79

[a]The isomer ratio **5 c:5 d** and **5 g:5 h** = 3:1.

carrier gas, temperature programming from 40 to 300°C at 8°C/min, evaporation temperature 280°C, temperature of the ion source 200°C, and ionization energy 70 eV). Chromatographic analysis was carried out on a Shimadzu GC-9A, GC-2014 instrument [2 m × 3 mm column, silicone SE-30 (5%) on Chromaton N-AW-hexamethyldisiloxane as the stationary phase, temperature programming from 50 to 270°C at 8°C/min, helium as the carrier gas (47 mL/min)].

Commercially, available substituted anilines, 1,2-ethanediol, 1,2-propanediol, 1,2-butanediol (Acros), carbon tetrachloride (reagent grade, component-reactive), were used as the starting agents with distillation before use.

Iron containing catalysts $FeCl_3$•$6H_2O$ (Sigma-Aldrich), $FeCl_3$, $FeCl_2$•$4H_2O$, $Fe(C_5H_5)_2$, $Fe(acac)_3$, $Fe(OAc)_2$, and $Fe_2(CO)_9$ (Acros) were recrystallized and dried in a vacuum desiccator before use.

The synthesis of quinolines 2-5. The reactions were carried out in a glass ampoule (V = 10 mL), placed in a stainless steel microautoclaves (V = 17 mL) under constant stirring and controlled heating.

The ampoule was charged with $FeCl_3 \cdot 6H_2O$ ($FeCl_3$, $FeCl_2 \cdot 4H_2O$, $Fe(C_5H_5)_2$, $Fe(acac)_3$, $Fe(OAc)_2$, $Fe_2(CO)_9$) (0.02 mmol), aniline (2 mmol), 1,2-diol (8 mmol), and carbon tetrachloride (4 mmol) in an argon flow. The sealed ampoule was placed in an autoclave. The autoclave was air-tightly closed and heated at 150°C for 8 h under continuous stirring. After completion of the reaction, the autoclave was cooled to room temperature, the ampoule was opened, and the reaction mixture was treated with diluted (10%) hydrochloric acid. The water layer was separated, neutralized with 10% solution of sodium hydroxide, and extracted with dichloromethane. The organic layer was filtered, and the solvent was distilled off. The residue was distilled in a vacuum or recrystallized from hexane (Table 3).

Detailed NMR spectra are given in the Supplementary Data file.

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