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Synthesis of Quinolines by Iron-Catalyzed Reaction of Anilines with Propane-1,3-diol

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Abstract—Quinoline and its derivatives were synthesized by cyclocondensation of anilines with propane-1,3-diol in 57–96% yield in the presence of iron-containing catalysts in carbon tetrachloride.

Keywords: *N*-heterocyclization, aniline, propane-1,3-diol, carbon tetrachloride, quinolines

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Quinoline and its derivatives are the most important class of fused azaheterocycles widely used for the synthesis of highly effective anti-malarial, anti-tuberculosis, anti-rheumatic, anesthetic, and anti-bacterial drugs, as well as corrosion inhibitors, cyanine dyes, extractants, and sorbents. Known methods of the quinolines synthesis are based on cyclocondensation of anilines with oxygen-containing compounds like glycerol, α,β-unsaturated aldehydes, β-diketones, and β-ketoesters under the action of mineral acids [1–4].

Catalysis has opened new opportunities for the preparation of quinolines in the absence of acids and expanded significantly the range of C_3-substrates used to construct the quinoline ring applying aniline and its derivatives.

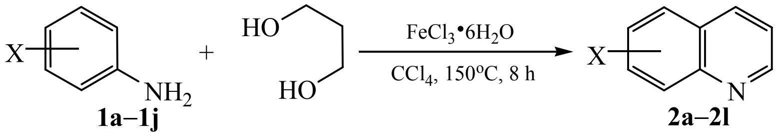
Ruthenium compounds and complexes activated with organophosphorus ligands are effective metal complex catalysts for the synthesis of quinolines via cyclocondensation of anilines with propane-1,3-diol [5, 6]. Best results have been obtained when using $RuCl_3\cdot nH_2O$–PBu_3 and $RuCl_3\cdot nH_2O$–PEt_3 catalyst systems while refluxing the reaction mixture in diglyme for 5 h. It is interesting to note that under these conditions the use of a hydrogen acceptor is not required; the aromatization proceeds due to dehydrogenation under the action of ruthenium catalyst. In spite of high yields of quinolines, the main disadvantage of this method is the use of expensive ruthenium catalysts.

In this work we developed a procedure for the synthesis of quinolines based on the reaction of anilines $XC_6H_4NH_2$ (X = H, *o*-CH_3, *m*-CH_3, *p*-CH_3, *o*-C_2H_5, *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3, *o*-OH) with 1,3-propanediol under the action of iron catalysts $FeCl_3\cdot 6H_2O$, $FeCl_3$, $FeCl_2\cdot 4H_2O$, $Fe(C_5H_5)_2$, $Fe(acac)_3$, $Fe(OAc)_2$, $Fe_2(CO)_9$, the best of which was $FeCl_3\cdot 6H_2O$.

The reaction of aniline **1a** with propane-1,3-diol afforded quinoline **2a**. The reaction took place at 150°C in CCl_4 for 8 h at a molar ratio of $FeCl_3\cdot 6H_2O$: aniline : CCl_4 : 1,3-propanediol = 1 : 100 : 200 : 400. Substituted anilines **1b**–**1j** also reacted with 1,3-propanediol to afford the corresponding quinoline derivatives **2b**–**2l** in 57–96% yields. The yield of the target compounds did not exceed 40–63% when using other iron catalysts (Scheme 1).

According to the experimental data, the reactions did not occur in the absence of CCl_4. To clarify the

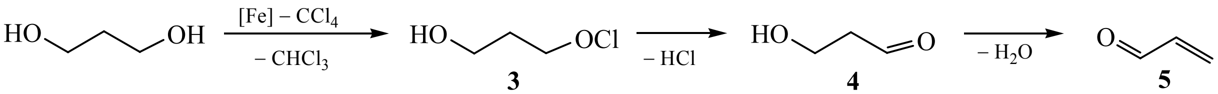
Scheme 1.



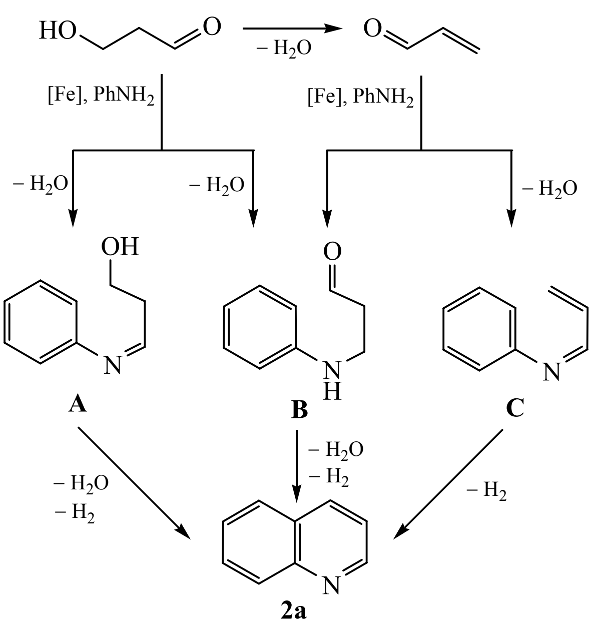
1a–**1j** **2a**–**2l**

X = H, *o*-CH_3, *m*-CH_3, *p*-CH_3, *o*-C_2H_5, *o*-Cl, *m*-Cl, p-Cl, *p*-OCH_3, *o*-OH.

Scheme 2.



Scheme 3.



role of CCl_4 in this reaction, we analyzed the reaction mixture, which contained chloroform and propionaldehyde (by GC and GC-MS data). Iodometric titration allows to confirm the presence of hypochlorite (0.6 mg/mL). According to mercurometric titration data, concentration of HCl was 79 mg/mL. Taking into account the known literature data [7–9], it was possible to assume that the process began with the oxidation of 1,3-propanediol by CCl_4 with sequential formation of 3-hydroxypropyl-1-hypochlorite **3** and 3-hydroxypropanal **4**, which at dehydration gave acrolein **5** (Scheme 2).

In the next step 3-hydroxypropanal **4** and acrolein **5** react with aniline **1a** to give the corresponding intermediates **A**, **B**, and **C** that undergo heterocyclization, dehydration, and dehydrogenation to afford quinoline **2a** (Scheme 3).

In summary, this study provided a convenient approach to the synthesis of quinolines based on the reaction of aniline and its derivatives with 1,3-propanediol under the action of $FeCl_3{\cdot}6H_2O$ in the presence of CCl_4. The latter promotes the oxidation of 1,3-diol converting it into a carbonyl compound.

EXPERIMENTAL

^1H and ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded on a Bruker Avance-400 spectrometer (400.13 and 100.62 MHz, respectively), internal reference TMC. Mass spectra were obtained on a

Synthesis of quinolines by reacting of anilines with 1,3-diols under catalysis with $FeCl_3{\cdot}6H_2O$[a]

Aniline **1**	Quinoline **2**	Yield, %
H (**1a**)	Quinoline (**2a**)	96
o-CH_3 (**1b**)	8-Methylquinoline (**2b**)	92
m-CH_3 (**1c**)	7-Methyl- (**2c**) and 5-methylquinoline (**2d**)	71
p-CH_3 (**1d**)	6-Methylquinoline (**2e**)	96
o-C_2H_5 (**1e**)	8-Ethylquinoline (**2f**)	88
o-Cl (**1f**)	8-Chloroquinoline (**2g**)	57
m-Cl (**1g**)	7-Chloro- (**2h**) and 5-chloroquinoline (**2i**)	66
p-Cl (**1h**)	6-Chloroquinoline (**2j**)	86
p-OCH_3 (**1i**)	6-Methoxyquinoline (**2k**)	69
o-OH (**1j**)	8-Hydroxyquinoline (**2l**)	79

[a] Reaction conditions: 150°C, 8 h, $FeCl_3{\cdot}6H_2O$: aniline : CCl_4 : 1,3-diol = 1 : 100 : 200 : 400.

Shimadzu GCMS-QP2010Plus instrument (capillary column SPB-5, 30 m × 0.25 mm, carrier gas helium, temperature programming from 40 to 300°C at a rate of 8 deg/min, evaporation temperature 280°C, the ion source temperature 200°C, ionization energy 70 eV).

The solvents and reagents of analytically pure grade were used for the synthesis.

General procedure for the preparation of quinolines 2a–2l. An ampule was charged with 0.02 mmol of $FeCl_3 \cdot 6H_2O$, 2 mmol of aniline, 4 mmol of carbon tetrachloride, and 8 mmol 1,3-propanediol under argon. The sealed ampule was placed into a pressure reactor, which was hermetically closed and heated at 150°C for 8 h with continuous stirring. After the reaction completion, the reactor was cooled to room temperature, the ampule was opened, the reaction mixture was poured in hydrochloric acid. The aqueous layer was separated, neutralized with 10% sodium hydroxide solution, and extracted with methylene chloride. The organic layer was filtered, the solvent was distilled off, and the residue was distilled in a vacuum. Physicochemical characteristics and spectral data of the obtained compounds **2a**–**2l** corresponded to the literature data [10–19].

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