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One-Pot Oxidative Synthesis of Substituted Quinolines from Alcohols and Arylamines Catalyzed by $Fe(CrO_2)_2$ in Water Medium

A. R. Makhmutov[a]*

[a] *Bashkir State University, ul. Z. Validi 32, Ufa, Bashkortostan, 450076 Russia*
**e-mail: ainurmax@mail.ru*

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Abstract—One-pot tandem synthesis was developed for substituted quinolines (in up to 97% yields) involving a selective catalytic oxidation of primary amines to aldehydes and their condensation with arylamines under the action of a dispersion of $Fe(CrO_2)_2$ and water solution of H_2O_2 at room temperature. The stage of catalytic oxidation of alcohols was accelerated by photoactivation. A presumable mechanism of the photoactivated tandem synthesis of 2-methylquinoline was suggested. Catalyst $Fe(CrO_2)_2$ was prepared by photochemical synthesis.

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Development of processes based on the catalytic oxidation of alcohols into the corresponding aldehydes or ketones followed by their use in the subsequent synthesis of diverse classes of organic substances attracts especial scientific and practical interest. Application of alcohols as reagents is due to their availability and stability. These processes as a rule belong to tandem syntheses involving two or more reactions with new bonds formation proceeding in a one-pot mode under the same conditions without additional charging of some reagents or catalysts and, consequently, without isolation of intermediate products. Therewith the subsequent reaction is caused by the formation of an active intermediate in the previous stage. Tandem approach was successfully implemented in the synthesis of esters [1], amides [2], alkenes [3], heterocycles [4], substrates with an activated C–H bond [5], and acetals [6]. Catalytic systems in tandem syntheses bear two main functions. The first function consists in the oxidation of the alcohol to the corresponding oxo compound (mainly owing to the hydrogen atoms transfer to acceptor compounds). The second function consists in the catalytic synthesis of target products by the condensation of aldehydes or ketones with diverse organic substrates. The most detailed descriptions concern catalytic systems based on complex compounds of ruthenium $Ru(PPh_3)_3(CO)(H)_2$ [7] and $[Ru(p\text{-cymene})Cl_2]_2$ [8]. Crotononitrile is commonly used as hydrogen acceptor. The existence of anhydrous and anaerobic environment in the tandem syntheses involving ruthenium catalyst is essential.

The tandem syntheses are known to be utilized in the preparation of practically important nitrogen heterocycles. For example, 2,3-dialkylindoles were obtained by catalytic reaction of aniline with vicinal diols in the presence of iridium and ruthenium complexes at 170°C within 24 h [9]. A synthesis is described of substituted quinolines from alcohols and arylamines in CCl_4 [10]. The reaction proceeds in a pressure reactor at 140°C at fractional charging of the reagents in the course of 4 h. Effective catalytic activity was found in iron containing compounds.

Iron compounds are capable to act as mediators in redox processes due to the existence of variable valence: $Fe^{3+} + e^- \leftrightarrow Fe^{2+}$ [11]. As a rule compounds of Fe(III) are oxidants for organic substances [12]. Oxidative qualities of Fe^{3+} ions are fairly well activated both thermally and under UV irradiation. For instance, the photooxidation of primary aliphatic alcohols activated by $FeCl_3$ is described. The reaction comes to an end complete reduction of Fe^{3+} ions. The composition of photooxidation products obtained from alcohols depends on the conditions of the process (pH of the medium, presence of water in the system, etc.).

Scheme 1.

$$4FeCl_3 + 4K_2Cr_2O_7 + 7EtOH \xrightarrow[20°C,\ 1\ h]{\lambda < 400\ nm} 4Fe(CrO_2)_2 + 8KCl + 4HCl + 5H_2O + 7AcOH$$

The aerobic photocatalytic oxidation of water-alcohol mixtures in the presence of a system containing $FeCl_3$ and $NaNO_2$ leads to the selective formation of aldehydes [13].

Here we report on the results of investigation of one-pot tandem (oxidative) synthesis involving selective catalytic oxidation of primary aliphatic and aromatic alcohols into aldehydes and their subsequent utilization in the synthesis of substituted quinoline bases via condensation with arylamines under the action of a dispersion of iron chromite $Fe(CrO_2)_2$ and oxidant, 5% water solution of H_2O_2. The studied tandem synthesis is performed at a one-pot charge and atmospheric pressure in water environment. The acceleration of the tandem synthesis by photoactiva-tion was tested. The heterogenic catalyst – iron chromite $Fe(CrO_2)_2$, synthesized by photochemical process is not previously described in the literature.

The reason of catalyst choice for the tandem synthesis. Photochemical synthesis of catalyst $Fe(CrO_2)_2$. The iron chromite $Fe(CrO_2)_2$ was chosen as heterogenic catalyst for the tandem synthesis of substituted quinolones by alcohols oxidation and condensation of the oxidation products with arylamines. The singularity of the selected catalyst consists in the capability to reveal the catalytic activity both in the process of primary alcohols oxidation with H_2O_2 water solution to form the corresponding aldehydes and in the condensation of aldehydes with arylamines. This feature of the catalyst makes it possible to combine the oxidation and the condensation in a joint tandem synthesis.

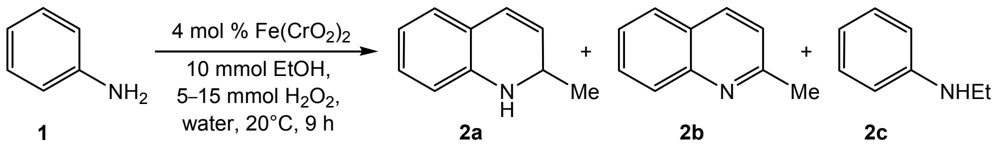
Quite a number of studies treat the issue of oxidation of organic substances including alcohols with H_2O_2 solution in the presence of iron compounds [14, 15]. This process has an overall name of Fenton's reaction. As a rule the oxidation process is aimed on the total destruction of organic substances. Yet Fenton's reaction is utilized as well in the synthetic practice [16]. Therefore, to prevent a deep oxidation of alcohols to carboxylic acids and CO_2, we used a dilute water solution of H_2O_2 of 5 wt % concentration and a less active insoluble form of iron(II), $Fe(CrO_2)_2$, as catalyst. Consequently, the stage of alcohols oxidation in the tandem synthesis may be regarded as a particular case of Fenton's reaction.

The catalytic activity of iron compounds in the synthesis of quinolone bases by aldehydes condensation with aniline is described in [17]. An essential advantage of the catalytic condensation catalyzed with $Fe(CrO_2)_2$ consists in the possibility of performing heterogeneous catalysis for after completion of the tandem process the catalyst is easily separated from the reaction products by simple precipitation or filtration. The catalytic activity of the heterogenic $Fe(CrO_2)_2$ with respect to the yield of the target reaction products and the conversion of initial arylamines is not worse than the known homogeneous catalyst $FeCl_3{\cdot}6H_2O$ [18].

The formation of the heterogenic catalyst $Fe(CrO_2)_2$ in a photochemical reaction between $FeCl_3{\cdot}6H_2O$ and $K_2Cr_2O_7$ in water-ethanol solution (Scheme 1) occurs under irradiation with a Hg-lamp for 60 min at 20°C in a quantitative yield. The obtained catalyst is dispersed black-brown powder.

Model tandem synthesis and effect of H_2O_2 content on the yield of reaction products. Reaction products of the model tandem reaction (Scheme 2) of ethanol with aniline **1** are 2-methyl-1,2-dihydroquinoline **2a** being a stable intermediate of the target 2-methylquinoline **2b** and *N*-ethylaniline **2c** – a by-product of the reaction. This tandem synthesis was developed proceeding from previously studied two stage catalytic synthesis of 2,3-dialkylquinolines by the condensation of products of alcohols photooxidation with aniline catalyzed by $FeCl_3{\cdot}6H_2O$ [19].

Scheme 2.



Effect of alcohol nature, H_2O_2 amount, and photoactivation on conversion of compound **1** and yield of products of tandem synthesis

Run no.	Alcohol	Conversion of **1**, %	Reaction products (content in the mixture, %)		
15 mmol of oxidant (H_2O_2)					
1	EtOH	62	**2a** (–)	**2b** (98)	**2c** (2)
2	PrOH	60	**3a** (–)	**3b** (96)	**3c** (4)
3	BuOH	57	**4a** (–)	**4b** (95)	**4c** (5)
4	AmOH	52	**5a** (–)	**5b** (92)	**5c** (8)
10 mmol of oxidant (H_2O_2)					
5	EtOH	44	**2a** (50)	**2b** (38)	**2c** (12)
6	PrOH	41	**3a** (54)	**3b** (34)	**3c** (12)
7	BuOH	38	**4a** (56)	**4b** (31)	**4c** (13)
8	AmOH	33	**5a** (61)	**5b** (24)	**5c** (15)
5 mmol of oxidant (H_2O_2)					
9	EtOH	29	**2a** (62)	**2b** (22)	**2c** (16)
10	PrOH	25	**3a** (63)	**3b** (20)	**3c** (17)
11	BuOH	22	**4a** (62)	**4b** (20)	**4c** (18)
12	AmOH	20	**5a** (63)	**5b** (19)	**5c** (18)
Photoactivation					
13	EtOH	98	**2a** (–)	**2b** (97)	**2c** (3)
14	PrOH	92	**3a** (–)	**3b** (95)	**3c** (5)
15	BuOH	89	**4a** (–)	**4b** (95)	**4c** (5)
16	AmOH	87	**5a** (–)	**5b** (91)	**5c** (9)
17	EtOH + BnOH	>99	**2a** (–)	**2b** (24) **6b** (66)	**2c** (8) **6c** (2)

A maximum conversion of compound **1** (up to 62%) into quinoline **2b** was observed in the presence of 15 mmol of H_2O_2 (see the table, run no. *1*). However, with decreasing the H_2O_2 content to 10 mmol the conversion dropped to 44% (run no. *5*) and in the reaction products except the compound **2b** (38% of the total amount of the mixture) compounds **2a** (50%) and **2c** (12%) contain. Molar ratio of compounds **2a**–**2b**–**2c** is 4 : 3 : 1. Intermediate compound **2a** can easily be oxidized into **2b** by adding more oxidant, H_2O_2 solution (5 mmol). With further decrease in H_2O_2 amount to 5 mmol the conversion of compound **1** is only 29% (run no.*9*). The molar ratio of products slightly changes towards compound **2c** formation.

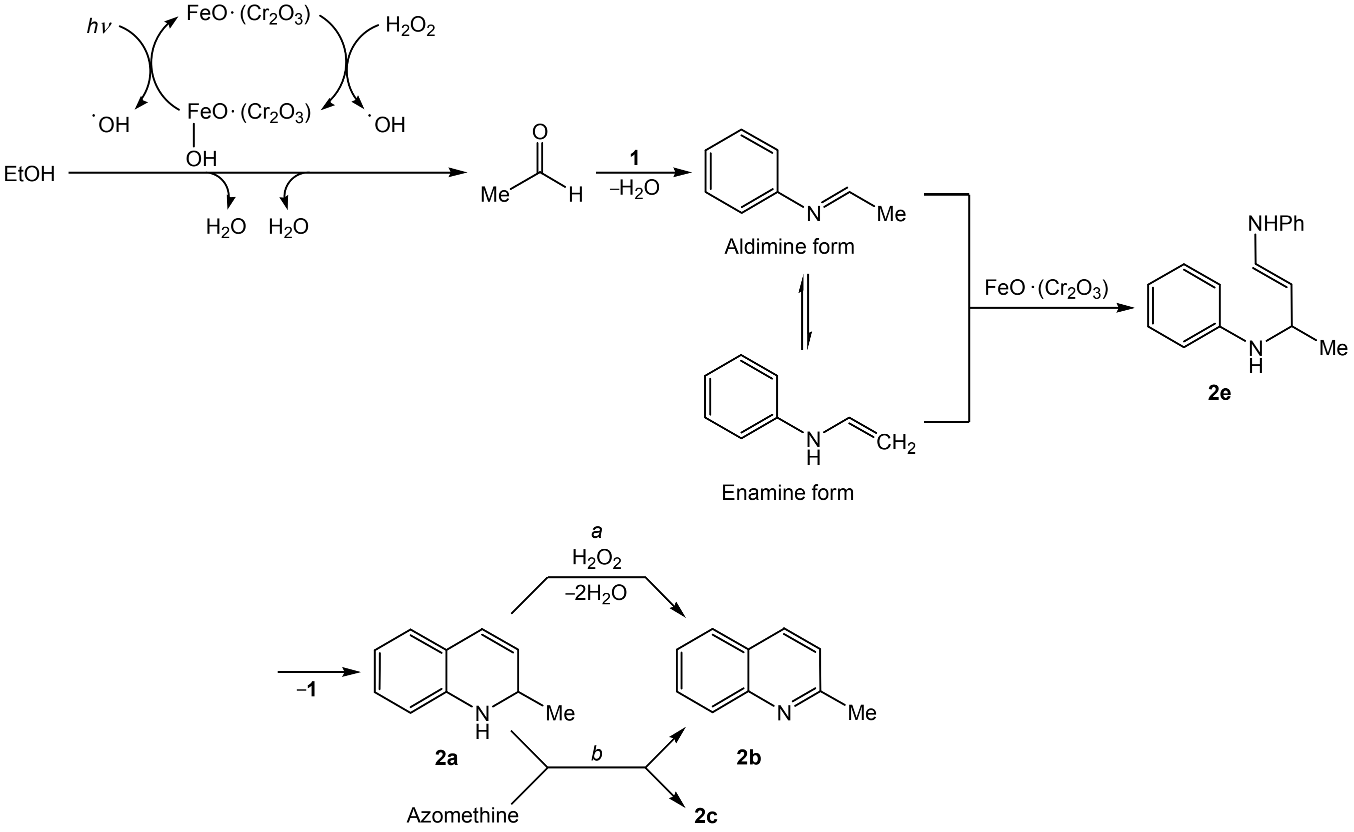
The oxidation of EtOH to acetaldehyde by H_2O_2 in the presence of catalyst $Fe(CrO_2)_2$ proceeds within 9 h at 20°C and is the slow stage of the tandem synthesis. The attempt to accelerate the oxidation stage by thermal method results in the formation of a mixture of EtOH oxidation products containing acetaldehyde, acetic acid, acetal, ethyl acetate, and CO_2. Hence at elevated temperature the selectivity of aldehyde formation decreases and further leads to nonselective occurrence of the condensation stage.

Photoactivation method to increase the efficiency of 2-methylquinoline tandem synthesis. To accelerate the process and to increase the efficiency of the stage of selective EtOH oxidation to acetaldehyde a photoactivation is applied. UV irradiation is known to improve the productivity of photo-Fenton reaction due to the emergence of a generation stage of a hydroxyl radical: $Fe(OH)^{2+} + h\nu \rightarrow Fe^{2+} + {}^{\bullet}OH$ [20, 21]. As was formerly established [12], photo generated radicals ${}^{\bullet}OH$ can easily and selectively oxidize water-alcohol mixtures to aldehydes in the system $FeCl_3{\cdot}6H_2O$–ROH. This method of radicals ${}^{\bullet}OH$ photogeneration is successfully applied to the tandem synthesis reducing the oxidation time of EtOH to 2 h and increasing the efficiency of the tandem process as a whole due to the improvement of the selectivity of EtOH oxidation to acetaldehyde. The probable mechanism of photoactivation of EtOH oxidation to acetaldehyde and its further condensation with compound **1** catalyzed by $Fe(CrO_2)_2$ in a water solution of H_2O_2 is presented in Scheme 3.

On the surface of the catalyst $Fe(CrO_2)_2$ (or FeO × Cr_2O_3) as a result of reaction of H_2O_2 with FeO a hydroxyl radical ${}^{\bullet}OH$ and an oxidized form of the catalyst Fe(OH)O are formed. Consuming quanta of Hg-lamp light the oxidized form of Fe(OH)O decomposes with ${}^{\bullet}OH$ liberation, and the catalyst recovers its initial form. Thus a cyclic photoredox process arises generating hydroxyl radicals. In one photoactivated catalytic cycle two hydroxyl radicals ${}^{\bullet}OH$ are formed.

In the water medium EtOH molecules are selectively oxidized with hydroxyl radicals giving acetaldehyde [13]. Aniline reacts with acetaldehyde forming Schiff bases existing in two isomeric structures: aldimine and enamine. The reaction of these azomethine forms under the action of the catalyst $Fe(CrO_2)_2$ results in 1,2-dihydroquinoline **2a** through an intermediate **2e** which has been studied in detail by

Scheme 3.



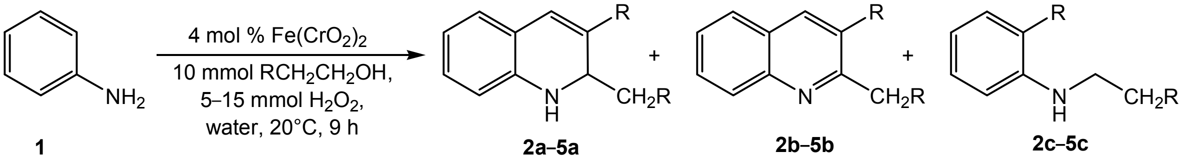
chemiluminescence method [22, 23]. The final target product **2b** is formed by oxidation of **2a** with H_2O_2 along path *a* (Scheme 3).

Yet at a deficit of H_2O_2 azomethine molecules (Schiff bases) may serve as oxidant, then the reaction proceeds along path *b* leading to the formation of side by-product **2c**. More thorough study of the mechanism of photoactivated catalytic tandem process will be performed in future.

The influence of alcohol and arylamine nature on the tandem synthesis. The influence of primary aliphatic alcohol nature (length of hydrocarbon chain) on the conversion of compound **1** and the yield of reaction product were explored (see the table, Scheme 4).

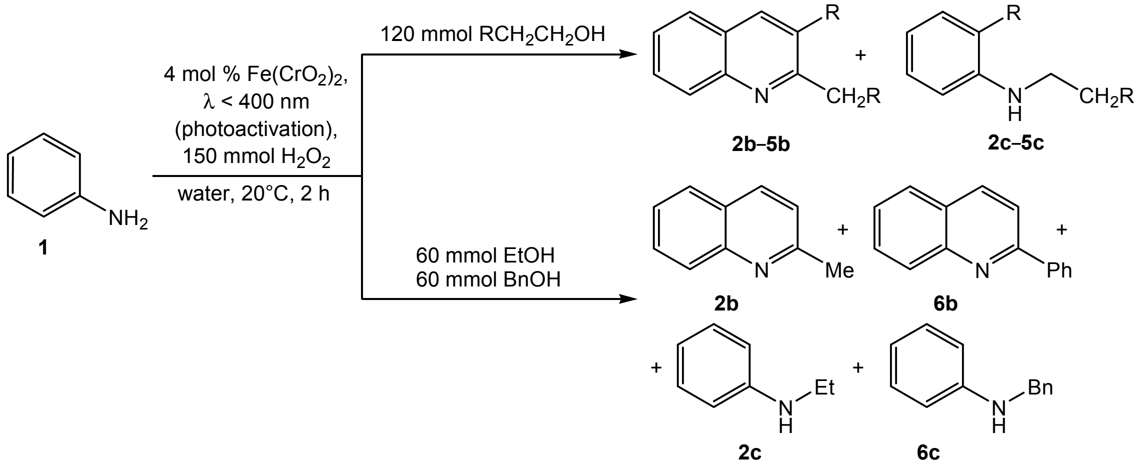
With growing length of the hydrocarbon chain of the alcohol the conversion of compound **1** decreases. In the presence of excess oxidant (15 mmol H_2O_2) selective conversion occurres of compound **1** in substituted quinolines **2b–5b** (see the table, runs nos. *1–4*). Yet, as in the case of the model system, the decrease in the amount of the oxidant affected the composition of reaction products. In the presence of 10 mmol of H_2O_2 in the reaction products content of hydroquinolines **2a–5a** and *N*-alkylaniline **2c–5c** increases (runs nos. *5–8*). It is clear that with the lengthening of the alkyl chain in the alcohol, the

Scheme 4.

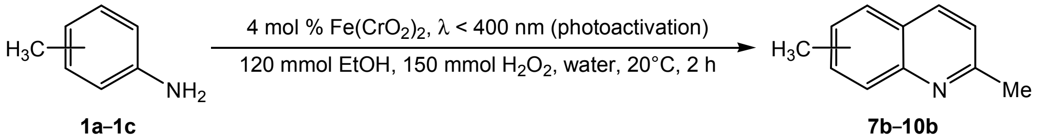


R = H (**2**), Me (**3**), Et (**4**), Pr (**5**).

Scheme 5.



Scheme 6.



Initial compound	Reaction product	Yield, %
1a	**7b**	94
1b	**8b** + **9b**	51 + 45
1c	**10b**	92

1, *o*-CH$_3$ (**a**), *m*-CH$_3$ (**b**), *p*-CH$_3$ (**c**); 2,8-dimethylquinoline (**7**), 2,7-dimethylquinoline (**8**), 2,5-dimethylquinoline (**9**), 2,6-dimethylquinoline (**10**).

content of hydroquinolines increases. In the presence of a minimum oxidant quantity (5 mmol) the conversion of compound **1** considerably decreases and the content of *N*-alkylanilines **2c–5c** increases with the growing length of the hydrocarbon chain of the alcohol (runs nos. *9–12*).

Under photoactivetion conditions of the tandem synthesis the conversion of compound **1** and yields of target products **2b–5b** are maximum and do not depend on the nature of the studied alcohol series (Scheme 5, see the table, runs nos. *13–16*). The products of the tandem synthesis with aliphatic alcohols under photoactivation conditions are only 2,3-substituted quinolines **2b–5b** and *N*-alkylanilines **2c–5c**, no hydroquinolines **2a–5a** are found since they are completely oxidized with H_2O_2.

In the reaction involving an equimolar mixture of EtOH and benzyl alcohol BnOH 2-phenylquinolines **6b** and **2b** and small quantities of by-products **2c** and *N*-benzylaniline **6c** form (Scheme 5). As seen from experimental data (run no. *17*), compound **6b** prevails among the synthesis products. Consequently, more favorable process of the photoactivated tandem synthesis with a mixture of aliphatic and aromatic alcohol is the formation of aryl-substituted quinolines.

The effect of the arylamine nature on the photoactivated tandem synthesis with EtOH is studied on the example of *o*-, *m*- and *p*-toluidines (Scheme 6). The presence of a methyl group and its position in the benzene ring does not affect arylamines conversion which reaches 98%. The yield of target dimethylquinolines attains 96%.

Therefore in this publication results of the investigation of catalytic tandem synthesis involving a selective catalytic oxidation of primary alcohols to the corresponding aldehydes and their condensation with arylamines under the action of heterogenic catalyst $Fe(CrO_2)_2$ and oxidant, 5% water solution of H_2O_2 are presented. Target reaction products are alkyl- and aryl-substituted quinolines. The catalyst $Fe(CrO_2)_2$ was obtained by photochemical synthesis formerly undescribed in the literature. The yield of target products of the tandem synthesis essentially depends on the conditions of the process. The oxidant concentration and photoactivation produce the strongest effect on the yield of the target products. The photoactivation accelerates the tandem synthesis of substituted quinolines and results in increasing their yield. A probable mechanism of photoactivated tandem synthesis of 2-methylquinoline is suggested.

EXPERIMENTAL

Identification of products was performed using GCMS-QP2010S Ultra Shimadzu (column Restek Rtx-5MS, 30 m × 0.25 mm ID, 0.25 μm df, carrier gas helium, ionizing electrons energy 70 eV). Quantitative analysis of reaction products was performed on an apparatus-programmed complex based on GC Chromatec Crystal 5000.1 and 5000.2 (columns Agilent Technologies 19091F-413 HP-FFAP, 30 m × 0.32 mm, 0.25 μm; Analytical Science 30 m × 0.32 mm ID-BPS, 0.5 μm).

^{1}H and ^{13}C NMR spectra were registered on an equipment of the Center of joint usage “Chemistry” (Federal State Institution of Science Ufa Institute of the Russian Academy of Sciences, Organic Chemistry) pulse spectrometers Bruker Avance III with operating frequencies 500.13 (^{1}H) and 125.47 (^{13}C) MHz, internal reference TMS.

Initial reagents of chemically pure grade were purchased from Joint Stocks Co “EKOS-1”,Russia (ethanol, 1-propanol, 1-butanol, amyl and benzyl alcohols, aniline, ethyl ether) and were distilled by procedures before experiments [24]. Alkylanilines *o*-, *m*- and *p*-toluidines, 99% (Acros) were used as received.

Reagents for the synthesis of catalyst: $FeCl_3 \cdot 6H_2O$ (pure grade, Joint Stocks Co “Brom”) and $K_2Cr_2O_7$ (chemically pure grade, Joint Stocks Co “Russkii Khrom”) were not subjected to an additional purification.

Water solution of H_2O_2 with a mass concentration of 5 wt % was obtained by diluting of commercial 30% hydrogen peroxide solution (special purity grade, Joint Stocks Co “Lega”).

Tandem synthesis of substituted quinolones without photiactivation. The synthesis was performed in a glass reactor of 20 mL capacity with constant stirring by magnetic stirrer. To 0.4 mmol of finely dispersed catalyst $Fe(CrO_2)_2$ was added 10 mmol of an appropriate alcohol, the reactor was shaken and left standing for 24 h to reach an equilibrium. Just before the reaction the dispersion of catalyst in the alcohol was subjected to microwave irradiation for 10 min (Ultrasound bath “Sapfir”, power 55 W), then 10 mL of 5% water solution of H_2O_2 (15 mmol of hydrogen peroxide) was added. The reaction mixture was stirred at room temperature and atmospheric pressure for 9 h. Then 5 mmol of aniline was added and the stirring was continued for 5 min. On completion of the process the reaction mixture was extracted with ethyl ether. The upper organic phase was separated and dried with anhydrous magnesium sulfate. After distilling off ethyl ether the residue was distilled in a vacuum.

Photoactivated tandem synthesis of substituted quinolines. Synthesis with the use of photoactivation was carried out in a photocatalytic installation Photo Catalytic Reactor Lelesil Innovative Systems with a quartz reactor of 500 mL capacity (Strohmeier type photoreactor with a magnetic stirrer). The reactor was charged with 4.8 mmol of catalyst $Fe(CrO_2)_2$ and 120 mmol of an appropriate alcohol, the reactor was shaken and left standing for 24 h to reach an equilibrium. Just before the reaction the dispersion of catalyst in the alcohol was subjected to microwave irradiation for 10 min (Ultrasound bath “Sapfir”, power 55 W). 102 mL of 5% aqueous solution of H_2O_2 (150 mmol of hydrogen peroxide) was added to the treated dispersion. The reactor was attached to the installation in keeping with the instructions of the producer. Light source was a Hg-lamp of moderate pressure of the power 250 W. Spectral composition of radiation by energy was as follows: 48% UV range, 43% visible range, and 9% IR range. Spectral range 222–1368 nm. The light beam went to the system through a temperature-controlled water layer (20°C). Photoactivation time 120 min. Then to the reaction mixture 50 mmol of arylamine was added, the mixture was stirred for 5 min and worked up as in the experiments without photoactivation.

Physicochemical constants and spectral characteristics of reaction products are in agreement with published data [10, 25].

REFERENCES

1. Yamamoto, N., Obora, Y., and Ishii, Y., *J. Org. Chem.*, 2011, vol. 76, p. 2937.

2. Schley, N.D., Dobereiner, G.E., and Crabtree, R.H., *Organometallics*, 2011, vol. 30, p. 4174.
3. Lee, E.Y., Kim, Y., Lee, J.S., and Park, J., *Eur. J. Org. Chem*., 2009, vol. 18, p. 2943.
4. Obora, Y. and Ishii, Y., *Synlett*., 2011, p. 30.
5. Simon, M.O., Ung, G., and Darses, S., *Adv. Synth. Catal*., 2011, vol. 353, p. 1045.
6. Gunanathan, C., Shimon, L.J.W., and Milstein, D., *J. Am. Chem. Soc*., 2009, vol. 131, p. 3146.
7. Watson, A.J.A., Maxwell, A.C., and Williams, J.M.J., *Org. Biomol. Chem*., 2012, vol. 10, p. 240.
8. Watson, A.J.A., Maxwell, A.C., and Williams, J.M.J., *Org. Lett*., 2009, vol. 11, p. 2667.
9. Tursky, M., Lorentz-Petersen, L.L.R., Olsen, L.B., and Madsen, R., *Org. Biomol. Chem*., 2010, vol. 8, p. 5576.
10. Khusnutdinov, R.I., Bayguzina, A.R., and Aminov, R.I., *Russ. Chem. Bull*., 2013, vol. 62, p. 133. doi 10.1007/s11172-013-0019-z
11. Eggins, B.R., *Chemical Sensors and Biosensors*, UK: Wiley, 2002.
12. Makhmutov, A.R. and Usmanov, S.M., *Bashkir. Khim. Zh*., 2017, vol. 24, p. 18.
13. Makhmutov, A.R. and Usmanov, S.M., *Bashkir. Khim. Zh*., 2017, vol. 24, p. 33.
14. Walling, A., *Acc. Chem. Res*., 1975, vol. 8, p. 125.
15. Tyre, B.W., Watts, R.J., and Miller, G.C., *Envir. Quality*, 1991, vol. 20, p. 832.
16. Barbusiñski, K., *Ecolog. Chem. Eng*., 2009, vol. 16, p. 347.
17. Bulgakov, R.G., Kuleshov, S.P., Vafin, R.R., and Dzhemilev, U.M., *Russ. J. Org. Chem*., 2009, vol. 45, p. 944. doi 10.1134/S1070428009060268
18. Makhmutov, A.R. and Usmanov, S.M., *Bashkir. Khim. Zh*., 2017, vol. 24, p. 45.
19. Makhmutov, A.R., *Zh. Sib. Fed. Univer*., 2017, vol. 10, p. 154.
20. Pozdnyakov, I.P., Vorobyev, D.Yu., Glebov, E.M., Plyusnin, V.F., Grivin, V.P., Ivanov, Y.V., and Bazhin, N.M., *Mendeleev Commun*., 2000, vol. 10, p. 185.
21. Pozdnyakov, I.P., Plyusnin, V.F., Glebov, E.M., Grivin, V.F., Vorobyev, D.Yu., Bazhin, N.M., and Sosedova, Yu.A., *Int. J. Photoenergy*, 2004, vol. 6, p. 89.
22. Bulgakov, R.G., Kuleshov, S.P., Makhmutov, A.R., and Dzhemilev, U.M., *Kinet. Catal*., 2010, vol. 51, p. 534. doi 10.1134/S0023158410040129
23. Bulgakov, R.G., Kuleshov, S.P., and Makhmutov, A.R., *Russ. Chem. Bull*., 2007, vol. 56, p. 443. doi 10.1007/s11172-007-0071-7
24. Weissberger, A., Proskauer, E.S., Riddick, J.A., and Toops, E.E., Jr., *Organic Solvents: Physical Properties and Methods of Purification*, New York: Wiley, 1955.
25. Makhmutov, A.R., Mustafin, A.G., and Usmanov, S.M., *Chem. Heterocycl. Compd*., 2018, vol. 54, p. 369. doi 10.1007/s10593-018-2275-1