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A highly efficient biomimetic aromatization of Hantzsch-1,4-dihydropyridines with *t*-butylhydroperoxide, catalysed by iron(III) phthalocyanine chloride

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ABSTRACT

Rapid aromatization of Hantzsch-1,4-DHPs with *t*-butylhydroperoxide catalysed by iron(III) phthalocyanine chloride is described. The reaction proceeds smoothly at room temperature within 1–35 min and the products of high purity were isolated in excellent yields. To explain the reactivity of this catalytical system plausible mechanism have been proposed to involve formation of high-valent oxoferryl species as in cytochrome P450 itself.

1. Introduction

The first generation of 1,4-dihydropyridines (1,4-DHPs) synthesised more than 30 years ago possess valuable pharmacological activity as calcium antagonists and found application in drugs for the treatment of hypertension and atherosclerosis.[1] On the molecular level 1,4-DHP compounds cause vasorelaxation by blocking voltage-operated calcium channel in smooth muscle cells and also by increasing NO release from intact endothelium.[2] One of the representative, amlodipine (Fig. 1) is one of the best selling drug in pharmaceutical industry. Although there is still attempts to improve pharmacological characteristics of 1,4-DHPs such as better bioavailability, activity, and solubility,[3] much attention have been devoted to improve their recently discovered pharmacological activities such as antitumor,[4] bronchodilating,[5] antidiabetic,[6] antiviral[7] and antianginal.[8] Moreover, 1,4-DHP motif present in coenzymes NADH (Fig. 1) and NADPH mediates hydrogen transfer reactions in biological systems.[9] The oxidation (aromatization) of 1,4-DHPs into corresponding pyridines is the first step of the metabolism of these drugs and is catalysed by the cytochrome P450 (CYP) 3A4 isoform.[10,11] The active site of all cytochrome family contain iron ion surrounded with heme ligand (Fig. 1) which interconverts between several oxidation states (+2, +3, +4 and +6).

Thus, cytochrome is capable of performing many oxidation and reduction reactions in biological systems. In order to understand these biological processes, as well as to develop a practical synthetic methods for the preparation of polysubstituted pyridines, the aromatization of 1,4-DHP derivatives has received considerable attention from synthetic chemists and plethora of reagents have been used for that purpose such as nitric acid,[10,12]

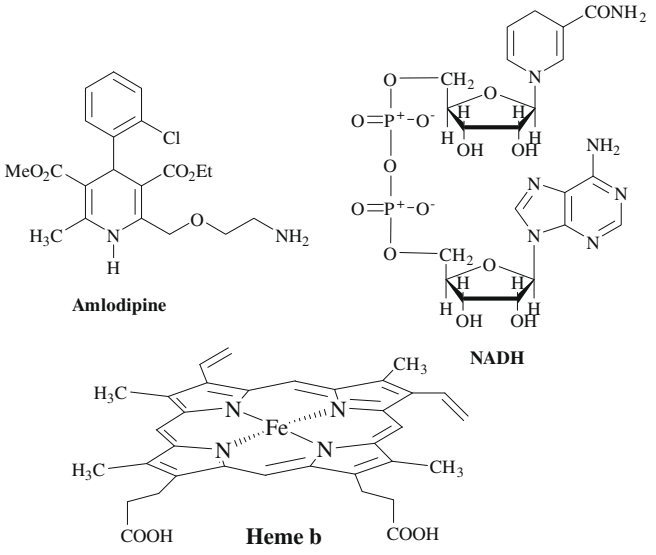

Figure 1. Chemical structures of amlodipine, NADH and Heme b.

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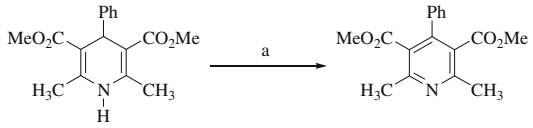
nitrous acid,[13] metallic nitrates,[14] chromium(VI) oxidants,[15] CrO_2,[16] $KMnO_4$,[17] $BaMnO_4$,[18] MnO_2,[19] $Mn(OAc)_3$,[20] $FeCl_3{\cdot}6H_2O$,[21] $K_3[Fe(CN)_6]$,[22] Hg(II) and Tl(III) salts,[23] $SnCl_4$,[24] $Pb(OAc)_4$,[25] $SbCl_5$,[26] I_2,[27] SeO_2,[28] H_2O_2 in ionic liquid[29] amongst many others.[30] The catalytical oxidations of 1,4-DHPs have recently been developed such as $RuCl_3/O_2$,[31] activated charcoal/O_2,[32] $Co(OAc)_2/H_2O_2$,[33] I_2/urea hydrogen peroxide adduct[34] and others.[35] Most of the methods including oxidation with stoichiometric oxidants as well as catalytical versions use toxic solvents, suffer from low selectivity, harsh reaction condition, and cumbersome work-up and thus development of mild, more selective and practical method is still demanded. Moreover, methods published as the biomimetic version of 1,4-DHPs aromatization were performed with Mn catalysts[35f,35g,35i,36] and Ph_2S_2[37] but catalysts containing iron ion as in Heme b (Fig. 1) have not been tested so far. Metalloporphyrins in oxidation of substrates with various single-oxygen atom donors have had a major role for understanding of biological related reaction of cytochrome P-450, where oxo-metalloporphyrins are accepted as reactive intermediate. There is stark contrast between state of art porphyrin and phthalocyanine oxidation chemistry. Although phthalocyanine complexes with a similar planar structure to the porphyrins have been actively investigated as oxidation catalysts their catalytic chemistry is practically not developed in terms of mechanisms and active species involved in these catalytic oxidations. Therefore, we concentrated our efforts on the development of catalytic methods for aromatization of 1,4-DHP compounds employing phthalocyanine catalysts as well as to investigate the mechanism and active species involved in these oxidations.

2. Results and discussion

Herein, we would like to report a first biomimetic aromatization of 1,4-DHPs employing *t*-butylhydroperoxide as stoichiometric oxidant catalysed by iron(III) phthalocyanine chloride as effective catalyst.[38] We began our studies with several iron(II, III) and copper(II) phthalocyanine complexes **1**–**5** (Fig. 2). From our previous experience in aromatization of 1,4-DHPs[25,26,34] we have chosen 1,4-DHP **6** as model compound. The reaction was initially tested in acetic acid as solvent due to the best solubility of catalysts (Scheme 1). The obtained results which are outlined in Table 1 show superiority of iron(III) phthalocyanine chloride (**1**, Entry 1) toward all tested catalysts. Moreover, iron catalysts (Entries 1–4) in general possess higher catalytical activity than corresponding copper(II) phthalocyanines **4** and **5** (Entries 5 and 6). The complete consumption of starting 1,4-DHP **6** with anhydrous $FeCl_3$ as catalyst (Entry 4) has been observed after 4 days at room temperature indicating increased reactivity of complexed iron(III) with phthalocyanine ligands.



6 7

Scheme 1. Reagents: (a) *t*-BuOOH (2 equiv), catalyst **1** - **5**, AcOH, rt.

This is also the case with $K_3[Fe(CN)_6]$,[22] as stoichiometric oxidant which shows higher reactivity than noncomplexed iron(III) salts. An interesting result has been obtained with Fe(II) phthalocyanine (**2**, Entry 2) which is almost four times less active than the corresponding iron(III) complex **1**.

Probably, the main reason for that difference in reactivity is the presence of chloride ion which mimics aminoacid ligand present in cytochrome active site.

The electron-withdrawing chlorine atoms in Fe(II) 1,2,3,4,8,9,10,11,15,16,17,18,22,23,24,25-hexadecachloro-29*H*,31*H*-phthalocyanine (**3**) drastically decrease speed of aromatization suggesting that e-reach phthalocyanine ligand as in complex **1** plays crucial role of its reactivity. From the solvent screening (Table 2) acetic acid emerged as the most convenient (Entry 3) due to the fact that the product was isolated in almost quantitative yield in shortest reaction time.

The other tested solvents required prolonged stirring to reach satisfactory conversion (Entry 1) or reaction was not selective (Entry 5). Beside *t*-butylhydroperoxide as stoichiometric oxidant used in preliminary studies, sodium perborate and percarbonate were also tested (Table 3). However, the reactions were sluggish and the products were isolated in only 50 and 30%, respectively. The reaction with urea–hydrogen peroxide adduct did not give a trace of the product (Entry 4) due to rapid decomposition of the hydrogen peroxide in acetic acid.

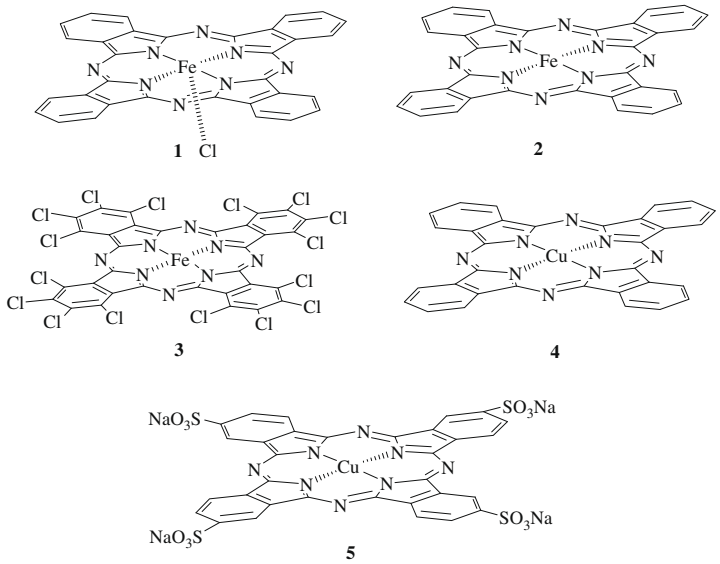


Figure 2. Phthalocyanine complexes.

Table 1
Aromatization of **6** with phthalocyanine catalysts

Entry	Catalyst[a]	Time[b]
1	Fe(III) phthalocyanine chloride (**1**)	20 min
2	Fe(II) phthalocyanine (**2**)	75 min
3	Fe(II) 1,2,3,4,8,9,10,11,15,16,17,18,22,23,24,25-hexadecachloro-29*H*,31*H*-phthalocyanine (**3**)	12 h
4	$FeCl_3$	4 days
5	Cu(II) phthalocyanine (**4**)	15 days
6	Cu(II) phthalocyanine-tetrasulfonic acid, tetrasodium salt (**5**)	15 days

[a] 2 mol%.
[b] Complete conversion of starting material.

Table 2
Aromatization of **6** in different solvents

Entry	Solvent	Time (h)	Yield (%)
1	$CHCl_3$	1	93
2	CH_2Cl_2	24	50
3	CH_3COOH	0.3	99
4	CH_3CN	43	—[a]
5	DMF	24	—[b]
6	Acetone	43	—[a]
7	Toluene	24	60

[a] Low chemoselectivity.
[b] Low conversion (<10%).

Table 3
Aromatization of **6** with different oxidants

Entry	Oxidant	Time (h)	Yield (%)
1	*t*-BuOOH	0.3	99
2	$NaBO_3{\cdot}4H_2O$	120[a]	50
3	$Na_2CO_3{\cdot}1.5H_2O_2$	120[a]	30
4	$CO(NH_2)_2{\cdot}H_2O_2$	24	0

[a] Low chemoselectivity.

Table 4
Optimization of the amount of oxidant

Entry	*t*-BuOOH (equiv)	Time (min)	Yield (%)
1	1	180	97
2	2	20	99
3	3	20	99
4	5	15	99

The optimization of the amount of the oxidant (Table 4) did not give significant difference in selectivity and the yield of the product was almost quantitative.

However, the reaction with 2 equiv of *t*-butylhydroperoxide appeared to be optimal due to the fact that the reaction is much faster compared to stoichiometric amount and similar to incremental amount of the oxidant. The last parameter tested for the optimization of the reaction was the amount of the catalyst. The results presented in Table 5 show shortening of the reaction time as the amount of catalyst increased. Although 0.1 mol% and 1 mol% of the catalyst gave complete conversion of the starting 1,4-DHP **6**, the reaction with 2 mol% was significantly faster. The 5 and 10 mol% of the catalyst gave almost instant reaction but slightly less selective than 2 mol%.

With optimized condition in hand, we have decided to explore the scope and limitation of this new catalytic method. The series of substituted 1,4-DHPs was subjected to reaction and the obtained

Table 5
Optimization of the amount of the catalyst **1**

Entry	**5** (mol%)	Time (min)	Yield (%)
1	0.1	7440	96
2	1	1218	97
3	2	20	99
4	5	2	99
5	10	1	98

results are shown in Table 6. The obtained results indicate high efficacy of the new catalytical system. The reactions proceeded at room temperature and were completed within 1–35 min. To our knowledge this is one of the fastest oxidation system used so far for the aromatization of 1,4-DHPs at room temperature. The characteristics of the reaction are high selectivity and tolerance to many functional groups present on 1,4-DHP ring. The yields of the products were high-to-excellent and were ranged between 88 and 99%. Although, the reaction was very fast, a still slight difference in reactivity between aryl substituted 1,4-DHPs having electron donating and withdrawing substituents was observed. When methyl ester group (Entry 8) in molecule was replaced with more hydrophobic ethyl, isopropyl and *t*-butyl groups (Entries 27–29), a drastical shortening of reaction time was observed. This fact increases the value of our method due to the fact that most of the published methods were tested on 1,4-DHPs having ethyl ester groups rather than less reactive dimethyl ester groups as in our work. Moreover, the 1,4-DHP **36** having *n*-propyl groups on positions 2 and 6 instead of the methyl groups was slower oxidized suggesting that lipophilicity on that positions decrease the reaction speed.

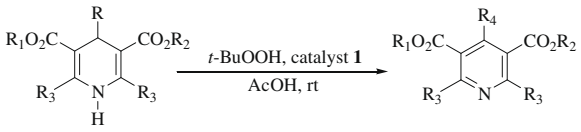
Based on this observations as well as similarity to cytochrome promoted aromatization of 1,4-DHP drugs, we have concluded that from the obtained results speed of metabolism for newly synthesised generation of 1,4-DHPs could be predicted, Figure 3. This aspect is very important during the drug design.

The 1,4-DHPs having alkyl substituents on position 4 (Entries 1–7) were almost instantly oxidized with expected results, extrusion of alkyl radicals affording unsubstituted pyridine derivative **37**. This phenomena is typical for the aromatization with metallic salts[15,20,21,24–26] as well as for cytochrome P450.[39] This findings demonstrate that our catalytical system behaves as cytochrome. Unexpectedly, 4-*n*-propyl derivatives **38**–**40** afforded nondealkylated products (Entries 5–7) in high yields. However, pyridine derivative **38** was isolated as a mixture with a small amount (4%) of **37** as product of dealkylation. The dealkylation of 4-benzyl-1,4-DHP **10** afforded benzaldehyde as side-product which was isolated during the chromatographic purification of crude product **37**. In our recent paper, employing I_2/urea hydrogen peroxide adduct[34] as oxidant, we have described formation of benzyl iodide as dealkylation side product which suggests that conditions employing catalytical system *t*-BuOOH/iron(III) phthalocyanine chloride might cause overoxidation of benzylalcohol to benzaldehyde. To prove this hypothesis, we performed the oxidation of benzylalcohol in conditions employed for the aromatization of 1,4-DHPs, Scheme 2. To our surprise, the reaction was selective using stoichiometric amount of oxidant and was completed within one hour. The product was isolated in 90% yield.

The further examination of this catalytical system for the selective oxidation of alcohols to aldehydes and ketones is beyond the scope of this article and the obtained results will be published in due course.

Plausible mechanism of the Fe(III) phthalocyanine chloride-catalysed aromatization of 1,4-DHPs with *t*-BuOOH is outlined in Scheme 3 using the reaction with model 1,4-DHP **6** as a representative. As already mentioned, less catalytical activity of anhydrous

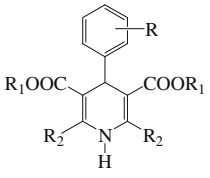
Table 6
Aromatization of substituted 1,4-DHPs with *t*-BuOOH (2 equiv) catalysed by iron(III) phthalocyanine chloride **1** (2 mol%) in acetic acid at rt



6, **8** - **36** **7**, **37** - **62**

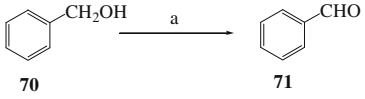
Entry	1,4-DHP	R	R_1;R_2;R_3	Product	R_4	Time (min)	Yield[a] (%)
1	**8**	H	Me; Me; Me	**37**	H	2	94
2	**9**	*i*-Pr	Me; Me; Me	**37**	H	3	94
3	**10**	CH_2Ph	Me; Me; Me	**37**[b]	H	3	90
4	**11**	Et	Me; Me; Me	**37**	H	3	92
5	**12**	*n*-Pr	Me; Me; Me	**38**	*n*-Pr	3	91[c]
6	**13**	*n*-Pr	Et; Et; Me	**39**	*n*-Pr	3	94
7	**14**	*n*-Pr	*i*-Pr; *i*-Pr; Me	**40**	*n*-Pr	3	92
8	**6**	Ph	Me; Me; Me	**7**	Ph	20	99
9	**15**	*o*-ClC_6H_4	Me; Me; Me	**41**	*o*-ClC_6H_4	5	96
10	**16**	*m*-ClC_6H_4	Me; Me; Me	**42**	*m*-ClC_6H_4	30	96
11	**17**	*p*-ClC_6H_4	Me; Me; Me	**43**	*p*-ClC_6H_4	20	99
12	**18**	*o*-$NO_2C_6H_4$	Me; Me; Me	**44**	*o*-$NO_2C_6H_4$	5	96
13	**19**	*m*-$NO_2C_6H_4$	Me; Me; Me	**45**	*m*-$NO_2C_6H_4$	35	93
14	**20**	*p*-$NO_2C_6H_4$	Me; Me; Me	**46**	*p*-$NO_2C_6H_4$	20	96
15	**21**	*m*-$NO_2C_6H_4$	Me; Et; Me	**47**	*m*-$NO_2C_6H_4$	4	90
16	**22**	*o*-$CH_3C_6H_4$	Me; Me; Me	**48**	*o*-$CH_3C_6H_4$	5	89
17	**23**	*m*-$CH_3C_6H_4$	Me; Me; Me	**49**	*m*-$CH_3C_6H_4$	5	93
18	**24**	*p*-$CH_3C_6H_4$	Me; Me; Me	**50**	*p*-$CH_3C_6H_4$	7	92
19	**25**	2,4-$(CH_3)_2C_6H_4$	Me; Me; Me	**51**	2,4-$(CH_3)_2C_6H_4$	9	91
20	**26**	*o*-$CH_3OC_6H_4$	Me; Me; Me	**52**	*o*-$CH_3OC_6H_4$	17	89
21	**27**	*m*-$CH_3OC_6H_4$	Me; Me; Me	**53**	*m*-$CH_3OC_6H_4$	10	94
22	**28**	*p*-$CH_3OC_6H_4$	Me; Me; Me	**54**	*p*-$CH_3OC_6H_4$	7	97
23	**29**	2-Thienyl	Me; Me; Me	**55**	2-Thienyl	3[d]	89
24	**30**	2-(5-Br-thienyl)	Me; Me; Me	**56**	2-(5-Br-thienyl)	22[d]	88
25	**31**	2-Furyl	Me; Me; Me	**57**	2-Furyl	8[d]	92
26	**32**	*p*-Ph-C_6H_4	Me; Me; Me	**58**	*p*-Ph-C_6H_4	30	93
27	**33**	Ph	Et; Et; Me	**59**	Ph	3	95
28	**34**	Ph	*i*-Pr; *i*-Pr; Me	**60**	Ph	1	99
29	**35**	Ph	*t*-Bu; *t*-Bu; Me	**61**	Ph	1	97
30	**36**	Ph	Et; Et; *n*-Pr	**62**	Ph	30	91

[a] Isolated yields. All products were identified by comparison with authentic samples (mp, IR, ^1H and ^{13}C NMR).
[b] Benzaldehyde was isolated as a side-product.
[c] According to HPLC analysis the crude product contains 4% of dealkylated product **37**.
[d] 3 equiv of *t*-BuOOH was used.



R = Electronic nature of substituents slightly influence aromatization speed
R_1 = More lipophyllic substituents accelerate the reaction
R_2 = More lipophylllic substituents decelerate reaction

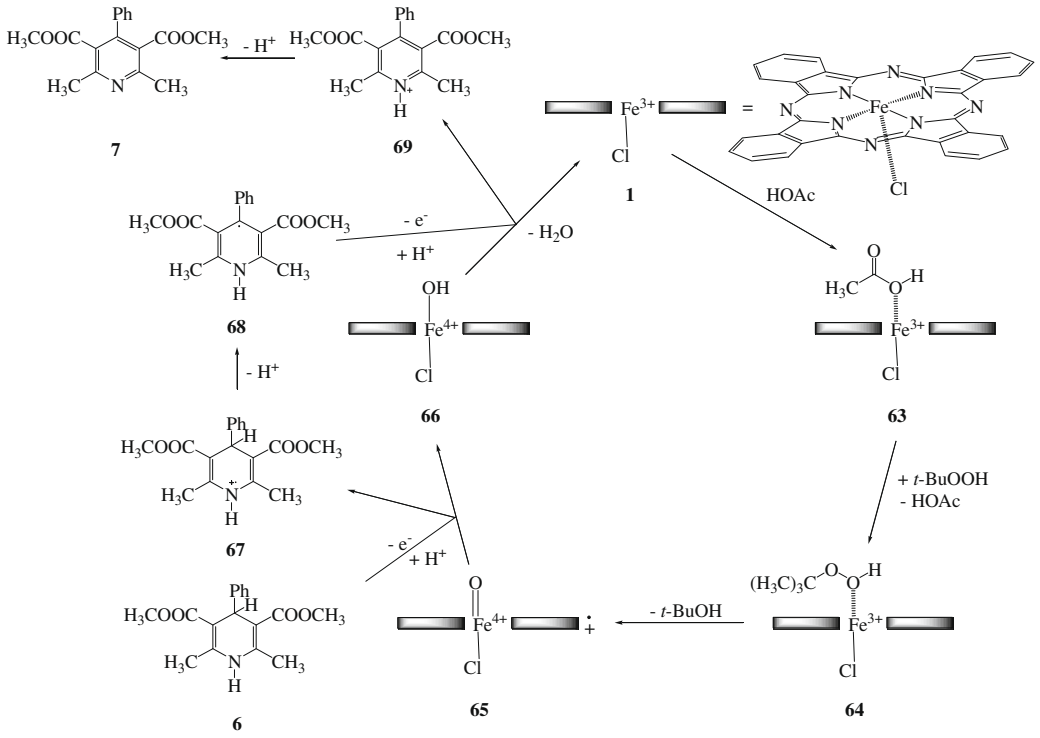
Figure 3. The influence of substituents on aromatization speed.



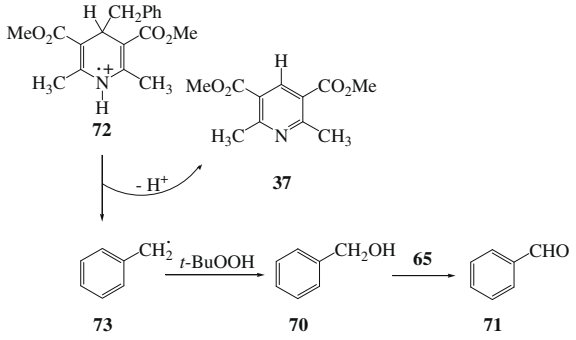
70 **71**

Scheme 2. Reagents: (a) *t*-BuOOH, catalyst **1**, AcOH, rt.

$FeCl_3$ compared to iron(III) phthalocyanine chloride (**1**) suggests formation of active species of higher oxidation states of iron, formed by the action of *t*-butylhydroperoxide. This is the main reason why cytochrome P450 is capable of reacting with chemically nonreactive compounds such as alkanes (for example, oxidation of cholesterol).[40] Therefore, the mechanism of iron(III) phthalocyanine chloride catalysed aromatization of 1,4-DHPs is probably very similar to cytochrome promoted oxidations in biological systems. As proposed in Scheme 3 the catalytical cycle begins with dissolution of the catalyst **1** in acetic acid. Good solubility of the catalyst is a result of coordination of one molecule of the solvent on free coordination place of iron to form complex **63**. In the next step the replacement of the solvent with *t*-BuOOH takes place affording **64** which upon oxidative cleavage followed by elimination of *t*-butanol give oxoferryl radical cation **65**. This type of the reactive intermediates is proposed and evidenced in cytochrome promoted oxidations,[41] although there are still controversies of its existance.[42] Due to the fact that oxoferryl radical cation in cytochrome promoted reaction is equally formed by the action of any oxygen donor (molecular oxygen or peroxides), we have proposed its formation in our reaction. The next step of the cytochrome-promoted hydroxylations of alkanes is oxygen insertion to form corresponding alcohols. According to some authors this process takes place in two steps via alkyl radical.[43] Thus, the formation of radical cation **67** with subsequent protonation of the catalyst to form hydroxyferryl complex **66** is the first step in aromatization of 1,4-DHP **6**. By this process the iron(IV) does not change its oxidation state but free oxygen radical is paired and stabilized. The radical cation **67**



Scheme 3. Plausible mechanism for the iron(III) phthalocyanine chloride (**1**) catalysed aromatization of 1,4-DHPs.



Scheme 4. Plausible mechanism for the oxidative rearrangement of radical cation 72 affording product of dealkylation 37 and benzaldehyde (71).

rearranges to more stable benzylic radical with elimination of proton similarly to mechanism of $Mn(OAc)_3$ promoted aromatization of 1,4-DHPs.[20] The second electron transfer leads to formation of protonated pyridine **69** which after deprotonation gives the product of aromatization **7**. The catalyst **1** is regenerated by reductive elimination of water molecule and thus closing the catalytic cycle.

The mechanism for the oxidative dealkylation of 4-benzyl-1,4-DHP **10** is outlined in Scheme 4.

The radical cation **72** obtained by one electron transfer to oxoferryl specie **65**, rearranges followed by deprotonation to form dealkylation product **37** and benzyl radical **73** which is instantly quenched by the oxidant to furnish benzylalcohol **70**. The latter is further oxidized probably by oxoferryl radical cation **65** (Scheme 3) to give benzaldehyde **71** as final product.

We believe that this catalytic system better describes cytochrome P450 than any of published in the literature due to the fact that iron(III) phthalocyanine chloride is a few times more active catalyst and contain iron ion surrounded with phthalocyanine ligand of planar structure as heme ligand.

3. Conclusions

In summary, this paper describes a new biomimetic aromatization of substituted 1,4-DHPs employing 2 mol% of iron(III) phthalocyanine chloride as catalyst and *t*-butylhydroperoxide as stoichiometric oxidant. This catalytic system is superior over literature employed methods concerning reaction speed and catalyst activity. The reaction is carried out at room temperature in acetic acid as solvent and the products, substitute pyridines, were isolated in high purity and excellent yield. The obtained results showed that the model is behaved as enzyme cytochrome P450.

4. Experimental

4.1. General

IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 600 for $CDCl_3$ solutions, shifts are given in ppm downfield from TMS as an internal standard. HPLC analyses for determination of the amount of dealkylation product **37** were performed with a Thermo Separation Products (San Jose, USA) instrument equipped with vacuum degasser SCM 1000, quaternary gradient pump P 4000, autosampler AS 3000, scanning UV/vis detector UV 3000 HR and ChromQuest 251 software. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel 60_{254}. Melting points were determined using a Büchi B540 instrument. The 1,4-DHPs were prepared by modified Hantzsch procedures[38,44,45] and fully characterized (mp, IR, ^{1}H, ^{13}C NMR spectra and elemental analysis) in our recent paper.[34] The literature known aromatization products were characterized by a comparison with authentic samples (melting point) and their NMR (^{1}H, ^{13}C) and IR spectra.[15e,15l,15n,25,27a,29,34]

4.2. General procedure for the aromatization of 1,4-DHPs

To a solution of corresponding 1,4-DHP (1.0 mmol) in AcOH (10 mL), Fe(III) phthalocyanine chloride **1** (12 mg, 2.0 mol%,

0.02 mmol) was added at once and after that to the resulting solution *t*-butylhydroperoxide (0.36 mL, 5.5 M in decane, 2.0 mmol) was added dropwise. Reaction mixture was stirred at rt during the time indicated in Table 6. After that to the reaction mixture water (20 mL) and dichloromethane (10 mL) were added. The pH was adjusted to seven with solid $NaHCO_3$, organic extract was separated and water layer was additionally extracted with dichloromethane (2× 10 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1) to yield the product of purity >98%. The identities of products were confirmed by mp, IR, ^1H, and ^{13}C NMR spectral data.

Acknowledgments

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References and notes

1. (a) Grün, A.; Fleckenstein, A. *Arzneim. Forsch. (Drug Res.)* **1972**, *22*, 334; (b) Godfraind, T. *Phil. Trans. R. Soc. B* **2005**, *360*, 2259.
2. Berkels, B.; Roesen, R.; Dhein, S.; Fricke, U.; Klaus, W. *Cardiovasc. Drug Rev.* **1999**, *17*, 179.
3. (a) Miri, R.; Javidnia, K.; Sarkarzadeh, H.; Hemmateenejad, B. *Bioorg. Med. Chem.* **2006**, *14*, 4842; (b) Son, H. Z.; Wang, T.; Zhang, K. J.; Hu, Z. D.; Fan, B. T. *Bioorg. Med. Chem.* **2006**, *14*, 4834.
4. Tsuruo, T.; Iida, H.; Nojiri, M.; Tsukagoshi, S.; Sakurai, Y. *Cancer Res.* **1983**, *43*, 2905.
5. Chapman, R. W.; Danko, G.; Siegels, M. I. *Pharmacology* **1984**, *29*, 282.
6. Malaise, W. J.; Mathias, P. C. F. *Diabetologia* **1985**, *28*, 153.
7. Krauze, A.; Germane, S.; Eberlins, O.; Sturms, I.; Klusa, V.; Duburs, G. *Eur. J. Med. Chem.* **1999**, *34*, 301.
8. Peri, R.; Padmanabhan, S.; Singh, S.; Rutledge, A.; Triggle, D. J. *J. Med. Chem.* **2000**, *43*, 2906.
9. The Merck Index, 13th ed., Merck Research Laboratories, New Jersey, 2001, 6370.
10. Böcker, R. H.; Guengerich, F. P. *J. Med. Chem.* **1986**, *28*, 1596.
11. Kudo, S.; Okumura, H.; Miyamoto, G.; Ishizaki, T. *Drug Metab. Dispos.* **1999**, *27*, 303.
12. (a) Mohr, E.; Schneider, W. *J. Prakt. Chem.* **1904**, *69*, 245; (b) Kröhnke, F.; Ahrenhok, G. M.; Gross, K. F. *J. Prakt. Chem.* **1960**, *11*, 256; (c) Furdík, M.; Gvozdjanová, A. *Acta Fac. Rerum Nat. Univ. Comenianae Chim.* **1964**, 581; (d) Kuno, A.; Sugiyama, Y.; Katsuta, K.; Kamitani, T.; Takasugi, H. *Chem. Pharm. Bull.* **1992**, *40*, 14523; (e) Shibanuma, T.; Iwanami, M.; Fujimoto, M.; Takenaka, T.; Murakami, M. *Chem. Pharm. Bull.* **1980**, *28*, 2600; (f) Weidolf, L.; Hoffman, K. J.; Carlsson, S.; Borg, K. O. *Acta Pharm. Sue.* **1984**, *21*, 209; (g) Vigante, B. A.; Ozols, Y. Y.; Dubur, G. Y.; Belash, E. M.; Beilis, Y. I. *Khim. Geterotsikl. Soed.* **1984**, 170.
13. (a) Geita, L. S.; Vanag, G. Y. *Zh. Obschch. Khim.* **1957**, *27*, 1058; (b) Kuthan, J.; Bartoníčkova, R. *Z. Chem.* **1964**, *4*, 271; (c) Vanag, G. Y.; Stankevich, E. I. *Zh. Obshch. Khim.* **1960**, *30*, 3257; (d) Görlitzer, K.; Buß, D. *Arch. Pharm. (Weinheim)* **1981**, *314*, 949; (e) Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Memarian, H. R.; Mohammadpoor-Baltork, I. *Synth. Commun.* **2000**, *30*, 2945; (f) Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R. *Synth. Commun.* **2000**, *30*, 3919; (g) Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R. *Synth. Commun.* **2000**, *30*, 551; (h) Niknam, K.; Zolfigol, M. A.; Razavian, S. M.; Mohammadpoor-Baltork, I. *Heterocycles* **2005**, *65*, 657; (i) Zolfigol, M. A.; Shirini, F.; Choghamarani, A. G.; Mohammadpoor-Baltork, I. *Phosphorus Sulfur Silicon* **2003**, *178*, 1709; (j) Zolfigol, M. A.; Choghamarani, A. G.; Dialameh, S.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R. *J. Chem. Res.* **2003**, 18; (k) Hashemi, M. M.; Ghafuri, H.; Karimi-Jaberi, Z. *Monatsch. Chem.* **2006**, *134*, 197; (l) Zolfigol, M. A.; Bagherzadeh, M.; Niknam, K.; Shirini, F.; Mohammadpoor-Baltork, I.; Choghamarani, A. G.; Baghbanzadeh, M. *J. Iran Chem. Soc.* **2006**, *3*, 73; (m) Niknam, K.; Zolfigol, M. A.; Razavian, S. M.; Mohammadpoor-Baltork, I. *J. Heterocycl. Chem.* **2006**, *43*, 199; (n) Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. *J. Org. Chem.* **1997**, *62*, 3582; (o) Zhu, X. Q.; Zhao, B. J.; Cheng, J. P. *J. Org. Chem.* **2000**, *65*, 8158; (p) Zolfigol, M. A.; Zebarjadian, M. H.; Sadegh, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R.; Shamsipur, M. *Synth. Commun.* **2001**, *31*, 929.
14. (a) Mashraqui, S. H.; Karnik, M. A. *Synthesis* **1998**, 713; (b) Pfister, J. R. *Synthesis* **1990**, 689; (c) Sabitha, G.; Kiran Kumar Reddy, G. S.; Reddy, Ch. S.; Fatima, N.; Yadav, J. S. *Synthesis* **2003**, 1267; (d) Balogh, M.; Hermecz, I.; Mészáros, Z.; Laszlo, P. *Helv. Chim. Acta* **1984**, *67*, 2270.
15. (a) Khadilkar, B.; Jaisinghani, H.; Khare, A. *Ind. J. Chem.* **1998**, *37B*, 817; (b) Meyer, H.; Wehinger, E.; Bossert, F.; Scherling, D. *Arzneim. Forsch. (Drug Res.)* **1983**, *33*, 106; (c) Sugiyama, N.; Kubota, K.; Inouye, G. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 637; (d) Griensteius, E. E.; Stankevich, E. I.; Ya Dubur, G. *Khim. Geterotsikl. Soed.* **1967**, 1118; (e) Ko, K. Y.; Park, J. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 200; (f) Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R.; Sobhani, S. *Synth. Commun.* **2000**, *30*, 1661; (g) Vanden Eynde, J. J.; Mayence, A.; Maquestiau, A. *Tetrahedron* **1992**, *48*, 463; (h) Hashemi, M. M.; Balalaie, S. *J. Sci. I. R. Iran* **1997**, *8*, 161; (i) Wang, B.; Hu, Y.; Hu, H. *Synth. Commun.* **1999**, *29*, 4193; (j) Zolfigol, M. A.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Choghamarani, A. G.; Taqian-Nasab, A. *Asian J. Chem.* **2001**, *13*, 887; (k) Mohammadpoor-Baltork, I.; Sadeghi, M. M. M.; Memarian, H. R.; Rairow, R. *J. Chem. Res.* **2000**, 40; (l) Memarian, H. R.; Mohammadpoor-Baltork, I.; Javahery, M. *J. Chin. Chem. Soc.* **2006**, *53*, 511; (m) Heravi, M. M.; Derikvand, F.; Oskooie, H. A.; Shoar, R. H. *Synth. Commun.* **2006**, *36*, 77; (n) Zolfigol, M. A.; Salehi, P.; Ghorbani-Choghamarani, A.; Safaiee, M.; Shahamirian, M. *Synth. Commun.* **2007**, *37*, 1817.
16. Ko, K. J.; Kim, J. Y. *Tetrahedron Lett.* **1999**, *40*, 3207.
17. (a) Vanden Eynde, J. J.; D'Ozario, R.; Van Haverbeke, Y. *Tetrahedron* **1994**, *50*, 2479; (b) Choudary, B. M.; Valli, V. L. K.; Durga Prasad, A. *Synth. Commun.* **1991**, *21*, 2007; (c) Kamal, A.; Ahmad, M.; Mohd, N.; Hamid, A. M. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 610; (d) Karami, B.; Montazerozohori, M.; Habibi, M. H.; Zolfigol, M. A. *Heterocycl. Commun.* **2006**, *11*, 513.
18. Memarian, H. R.; Sadeghi, M. M.; Momeni, A. R. *Synth. Commun.* **2001**, *31*, 2241.
19. (a) Vanden Eynde, J. J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 6511; (b) Katsuyama, I.; Ogawa, S.; Nakamura, H.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Heterocycles* **1998**, *48*, 779; (c) Kuno, A.; Sakai, H.; Ohkubo, M.; Takasugi, H. *Chem. Pharm. Bull.* **1993**, *41*, 156; (d) Kuno, A.; Sakai, H.; Ohkubo, M.; Takasugi, H. *Chem. Pharm. Bull.* **1993**, *41*, 163; (e) Bagley, M. C.; Lubinu, M. C. *Synthesis* **2006**, 1283; (f) Alvarez, C.; Delgado, F.; García, O.; Medina, S.; Márquez, C. *Synth. Commun.* **1991**, *21*, 619; (g) Delgado, F.; Alvarez, C.; García, O.; Penieres, G.; Márquez, C. *Synth. Commun.* **1991**, *21*, 2137; (h) Heravi, M. M.; Moosavi, F. S. Sh.; Beheshtiha, Y. Sh.; Ghassemzadeh, M. *Heterocycl. Commun.* **2004**, *10*, 415.
20. Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 21.
21. (a) Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Li, W. *Synth. Commun.* **2001**, *31*, 2625; (b) Lu, J.; Bai, Y.-J.; Yang, B.-Q.; Ma, H.-R. *Chin. J. Org. Chem.* **2000**, *20*, 514.
22. Powell, M. F.; Wu, J. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 3850.
23. (a) Kametani, T.; Ogasawara, K.; Kozuka, A. *J. Pharm. Soc. Jpn.* **1966**, *86*, 815; (b) Hashemi, M. M.; Zakeri, M. S.; Arianfar, S. *Iran J. Chem. Chem. Eng.* **2003**, *22*, 9; (c) Momeni, A. R.; Massah, A. R.; Naghash, H. J.; Aliyan, H.; Solati, S.; Sameh, T. *J. Chem. Res.* **2005**, *4*, 227.
24. Jain, S. M.; Kant, R.; Dhar, K. L.; Singh, S.; Singh, G. B. *Ind. J. Chem.* **1990**, *29B*, 277.
25. Litvić, M.; Cepanec, I.; Filipan, M.; Kos, K.; Bartolinčić, A.; Druškovič, V.; Tibi, M. M.; Vinković, V. *Heterocycles* **2005**, *65*, 23.
26. Filipan-Litvić, M.; Litvić, M.; Cepanec, I.; Vinković, V. *Arkivoc* **2008**, *xi*, 96.
27. (a) Zeynizadeh, B.; Dilmaghani, K. A.; Roozijoy, A. *J. Chin. Chem. Soc.* **2005**, *52*, 1001; (b) Yadav, J. S.; Reddy, B. S.; Sabitha, G.; Reddy, G. S. K. K. *Synthesis* **2000**, 1532.
28. Cai, X.-hua.; Yang, H.-jun.; Zhang, G.-lin. *Can. J. Chem.* **2005**, *83*, 273.
29. Panchgalle, S. P.; Choudhary, S. M.; Chavan, S. P.; Kalkote, U. R. *J. Chem. Res.* **2004**, 550.
30. (a) Memarian, H. R.; Mohammadpoor-Baltork, I.; Sadeghi, M. M.; Samani, Z. S. *Ind. J. Chem.* **2001**, *40B*, 727; (b) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199; (c) Varma, R. S.; Kumar, D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1755; (d) Gangadhar, N.; Kumar, Ch. H.; Krupadanam, G. L. D. *Ind. J. Chem.* **1999**, *38B*, 87; (e) Memarian, H. R.; Sadeghi, M. M.; Momeni, A. R. *Ind. J. Chem.* **1999**, *38B*, 800; (f) Memarian, H. R.; Sadeghi, M. M.; Aliyan, H. *Ind. J. Chem.* **1998**, *37B*, 219; (g) Arbuzov, A. I. *Bull. Acad. Sci. USSR, Class Sci. Chim.* **1945**, 451; (h) Davis, N. R.; Anwar, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3778; (i) Ortiz, M. E.; Núñez-Vergara, L. J.; Squella, J. A. *Pharm. Res.* **2003**, *20*, 292; (j) Ortiz, M. E.; Núñez-Vergara, L. J.; Camargo, C.; Squella, J. A. *Pharm. Res.* **2004**, *21*, 428; (k) Braude, E. A.; Hannah, J.; Linstead, R. *J. Chem. Soc.* **1960**, 3249; (l) Uldrikis, Y. R.; Kimerova, A. O.; Dubur, G. Ya. *Khim. Geterotsikl. Soed.* **1973**, 691; (m) S Chavan, S. P.; Dantale, S. W.; Kalkote, U. R.; Jyothirmai, V. S.; Kharul, R. K. *Synth. Commun.* **1998**, *28*, 2789; (n) Sadeghi, M. M. M.; Memarian, H. R.; Momeni, A. R. *J. Sci. I. R. Iran* **2001**, *12*, 141.
31. Mashraqui, S. H.; Karnik, M. A. *Tetrahedron Lett.* **1998**, *39*, 4896.
32. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis* **2004**, 1015.
33. Hashemi, M. M.; Ahmadibeni, Y.; Ghafuri, H. *Monatsh. Chem.* **2003**, *134*, 107.
34. Filipan-Litvić, M.; Litvić, M.; Vinković, V. *Tetrahedron* **2008**, *64*, 5649.
35. (a) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. *Tetrahedron Lett.* **2005**, *46*, 2775; (b) Hashemi, M. M.; Beni, Y. A. *J. Sci. I. R. Iran* **1998**, *9*, 237; (c) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955; (d) Misner, R. E. *Diss. Abstr.* **1969**, *29B*, 2817; (e) Chavan, S. P.; Kharul, R. K.; Kalkote, U. R.; Shivakumar, I. *Synth. Commun.* **2003**, *33*, 1333; (f) Nasr-Esfahani, M.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3276; (g) Moghadam, M.; Nasr-Esfahani, M.; Tangestaninejad, S.; Mirkhani, V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2026; (h) Moghadam, M.; Nasr-Esfahani, M.; Tangestaninejad, S.; Mirkhani, V.; Zolfigol, M. A. *Can. J. Chem.* **2006**, *84*, 1; (i) Karami, B.; Montazerozohori, M.; Nasr-Esfahani, M. *Heterocycles* **2005**, *65*, 2181; (j) Fang, X.; Liu, Y. C.; Li, C. *J. Org. Chem.* **2007**, *72*, 8608.
36. (a) Nasr-Esfahani, M.; Moghadam, M.; Valipour, G. *J. Iran Chem. Soc.* **2008**, *5*, 244; (b) Nasr-Esfahani, M.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Momeni, A. R. *Bioorg. Med. Chem.* **2006**, *14*, 2720.
37. Aliyan, H.; Fazaeli, R.; Momeni, A. R.; Massah, A. R.; Naghash, H. J.; Khosravi, F. *Heterocycles* **2007**, *71*, 2027.
38. Filipan-Litvić, M. *Doctoral Thesis*, University of Zagreb, 2006.
39. Kennedy, C. H.; Mason, R. P. *J. Biol. Chem.* **1990**, *265*, 11425.

40. Atkins, W. M.; Sligar, S. G. *J. Biol. Chem.* **1988**, *263*, 18842.
41. Primo, C. Di.; Hoa, G. H. B.; Douzou, P.; Sligar, S. *J. Biol. Chem.* **1990**, *265*, 5361.
42. Bassan, A.; Biomberg, M. R. A.; Siegbahn, P. E. M.; Que, L., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 11056.
43. Sbaragli, L.; Woggon, W.-D. *Synthesis* **2005**, 1538.
44. (a) Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1974**, *17*, 956; (b) Meyer, H.; Bossert, F.; Horstmann, H. *Liebigs Ann. Chem.* **1977**, 1888; (c) Phillips, A. P. *J. Am. Chem. Soc.* **1950**, *72*, 2780; (d) Litvić, M.; Cepanec, I.; Vinković, V. *Heterocycl. Commun.* **2003**, *9*, 385.
45. Litvić, M.; Filipan, M.; Pogorelić, I.; Cepanec, I. *Green Chem.* **2005**, *7*, 771.