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Biomimetic oxidative dehydrogenation of 1,4-dihydropyridines with m-chloroperoxybenzoic acid (m-CPBA) in the presence of tetraphenylporphyrinatoiron(III) chloride [Fe(TPP)Cl]

G. Karimipour*[1], T. Mousavinejad[2]

[1]*Department of Chemistry, Yasouj University, Yasouj 75918-74831, Iran; fax: (+98) 741 3342172*
[2]*Department of Coating Research Center, Industrial & Environmental Protection Division, Research Institute of Petroleum Industry (RIPI), P.O.BOX 14665-137, Tehran, Iran.*

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A simple and efficient methodology for the oxidative dehydrogenation of Hantzsch 1,4-dihydropyridines (1,4-DHPs) to their corresponding pyridine derivatives with m-chloroperoxybenzoic acid (m-CPBA) in the presence of tetraphenylporphyrinatoiron(III) chloride [Fe(TPP)Cl] was described. Product formation takes place within just a few minutes with ~100% selectivity in 95-100% yield. This method may provide valuable information for evaluating the oxidation path of 1,4-DHPs by cytochrome P-450 in the human body.

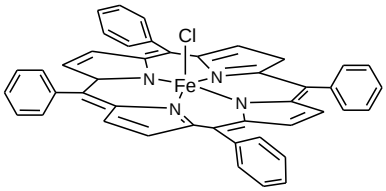
Keywords: Decarboxylation; m-Chloroperoxybenzoic Acid (m-CPBA); 1,4-Dihydropyridine (1,4-DHP) ; Tetraphenylporphyrinatoiron(III) chloride [Fe(TPP)Cl].

INTRODUCTION

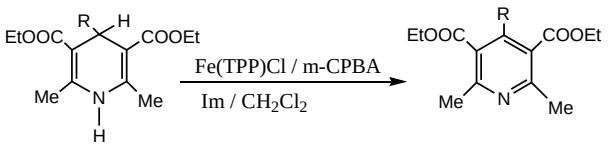
The analogies manifested between Hantzsch 1,4-dihydropyridines (1,4-DHPs) and NADH coenzymes make 1,4-DHPs an important class of drugs (amlodipine besylate and nifedipine) and define their application in organic synthesis as fine starting materials [1]. For example, various novel dihydroindolizine-based were synthesized using 2-formyl-1,4-DHP by the Michael addition/intramolecular amino-nitrile cyclization method [2].

Recently, a great number of reagents and procedures (i. e., ferric nitrate on a solid support [3] ceric ammonium nitrate [4], Claycop [5], pyridinium chlorochromate [6], nitric acid [7], nitric oxide and N-methyl-N-nitrosotoluene-P-sulfonamide [8]) has been applied for the oxidation of 1,4-DHPs. However, in most cases, researchers have to deal with problems such as harsh reaction conditions, long reaction time, tedious workup and low yields and selectivities. On the other hand, Hantzsch 1,4-DHPs are oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver [9].

So, based on the resemblance between porphyrins and P-450 enzymes, Moqhadam published some papers about the application of metalloporphyrins in catalytic dehydrogenation of 1,4-DHPs [10-13]. In this work, mimicking cytchrome P-450, we introduced tetraphenyl-porphyrinatoiron(III) chloride [Fe(TPP)Cl] as a catalyst and imidazole (Im) as a co-catalyst for oxidative dehydrogenation of 1,4-DHPs by m-chloroperoxybenzoic acid (m-CPBA) to improve the yield and selectivity (Scheme 1).



Fe(TPP)Cl



Scheme 1

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Tetraphenyl-porphyrin (H_2TPP) was prepared and metallated according to the procedure used by Adler [14]. All

* To whom all correspondence should be sent:
E-mail: ghkar@mail.yu.ac.ir

Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures [15].

All reactions were performed at room temperature in a 25 mL flask equipped with a magnetic stirring bar. To a solution of Hantzsch 1,4-dihydropyridine (0.15 mmol), Fe(TPP)Cl (0.003 mmol) and imidazole (Im) (0.045 mmol) in CH_2Cl_2 (2 mL) m-chloroperoxybenzoic acid (m-CPBA) (0.18 mmol) was added. The progress of the reactions was monitored by TLC and GC (Agilent 6890N) and HPLC (Agilent 1100). After the reaction was completed, the product was purified using a silica gel plate or a silica gel column (eluent: CCl_4–Et_2O) and was analyzed by spectroscopic methods.

RESULTS AND DISCUSSION

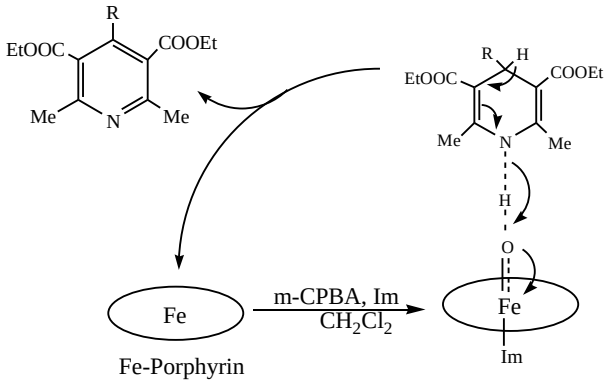
The structural analogy between synthetic metalloporphyrins and natural enzymes like cytochrome P-450 provides a valuable pathway for organic and inorganic chemists to construct transition metal-porphyrin complexes with catalytic, optoelectronic and photodynamic properties. Organic compounds could be effectively and highly selectively oxidized by oxygen donors such as PhIO, ClO^-, H_2O_2, ROOH or IO_4^- in the presence of metalloporphyrins [16].

In continuation of our earlier work on the oxidative dehydrogenation of 1,4-dihydropyridins by Tryp–Mn/*n*–Bu_4NIO_4 [17], we report here a facile and efficient procedure for conversion of various 1,4-DHPs into the respective pyridine derivatives by Fe(TPP)Cl and m-CPBA with 95–100% yields in a few minutes at ambient conditions (Scheme 1).

In the initial experiment, 4-methyl substituted DHP was oxidized by m-CPBA in CH_2Cl_2 at room temperature. We found that the oxidation does not efficiently proceed in the absence of catalyst (<15% yield). Moreover, simple Fe(II) and Fe(III) salts have not enough capability to improve the oxidation.

In the further experiments, different molar ratios of reagents and catalyst were examined to attain the optimum conditions for oxidation of 1,4-DHPs. The maximum yield with the starting 1,4-DHP was obtained at a molar ratio of Fe(TPP)Cl: Im: 1,4-DHP: m-CPBA = 1: 15 :50 : 60 (see Experimental).

It is notable that the catalytic activity of Fe(TPP)Cl increased during the reactions. It seems that the produced pyridine derivatives act as axial ligands for the catalyst, accelerating the oxidation during the course of the reactions. This hypothesis was confirmed by adding a nitrogenous donor such as imidazole into the reaction mixture. In this case the oxidation rate was 4.5 times higher than without imidazole. Nitrogenous ligands such as imidazoles and pyridines are reported to improve selectivity, reactivity and turnover number of metalloporphyrin-mediated reactions, by weakening of the M–O bond in the oxidized form of the porphyrin catalysts by donating electron density into the M–O antibonding orbitals [18].

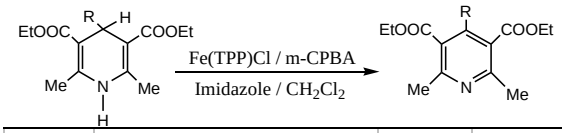


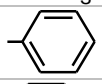
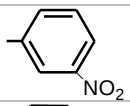
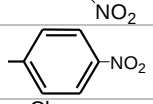
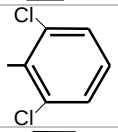
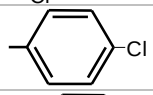
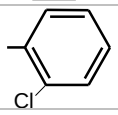
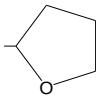
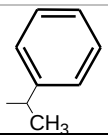
Scheme 2

The coordinated nitrogenous bases (*i.e.* imidazole and/or the produced pyridines) assist the possible electronic changes in the Fe centre and lead to the facile formation of a metal-oxo intermediate [19]. Also, the nitrogenous bases facilitate the transfer of oxygen atom from the metal-oxo intermediate to the substrates. It is plausible to assume that the oxidations occurs by an electrophilic attack of oxo iron porphyrin [19] to the N–H hydrogen atom, followed by concomitant elimination of the hydrogen atom on the 4-position of the 1,4-DHPs, as shown in Scheme 2. It may be assumed that the metabolism of 1,4–DHPs in the liver may take place by a similar pathway in the presence of cytochrome P–450.

The iron(III) porphyrin/m-CPBA catalytic system can be used for oxidizing a wide variety of 1,4-dihydropyridine derivatives bearing an alkyl or an aryl group to their corresponding pyridine derivatives in excellent yields at room temperature in the presence of imidazole as axial ligand. The results are summarized in Table 1. The formation of the products is very rapid, so it is not possible to evaluate the effect of structural parameters (i. e. steric and electronic) on the reaction mechanism and rate.

Table 1. Oxidative dehydrogenation of Hantzsch 1,4-dihydropyridines with m-CPBA catalyzed by Fe(TPP)Cl/m-CPBA-Im in CH_2Cl_2



Entry	R	Time (min)	Yield (%)
1	H	1	100
2	-CH_3	1	100
3	-CH-CH_3	2	98
4	-CH-CH_2-CH_3	2	96
5	-OCH_3	1	100
6		2	100
7		1	100
8		1	100
9		6	95
10		2	100
11		5	98
12		4	98
13		5	100

[a]All products were identified by comparison with authentic samples (IR, 1H NMR, m.p.).

CONCLUSIONS

This paper describes a convenient and efficient process for oxidative decarboxylation of 1,4-dihydropyridines to the corresponding pyridine derivatives with m-CPBA by a biomimetic Fe(TPP)Cl catalyst. This biomimetic catalytic methodology offers very attractive features such as mild reaction conditions, high efficiency of the catalyst and 95–100% yield with ~100% selectivity in less than 5 minutes. Therefore, the present method could be used in organic synthesis.

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БИОМИМЕТИЧНО ОКСИДАТИВНО ДЕХИДРОГЕНИРАНЕ НА 1,4-ДИХИДРОПИРИДИНИ С М-ХЛОРПЕРОКСИБЕНЗОЕНОВА КИСЕЛИНА (М-CPBA) В ПРИСЪСТВИЕ НА ЖЕЛЕЗЕН(III)ТЕТРАФЕНИЛПОРФИРИНАТ ХЛОРИД [FE(TPP)CL]

Г. Каримипур[1], Т. Мусавинеджад[2]

[1]*Катедра по химия, Университет Иасудж, Иасудж 75918-74831, Иран; факс: (+98) 741 3342172*

[2]*Катедра по изследване на покрития, Подразделение по индустрия и опазване на околната среда, Изследователски институт по нефтопреработване (RIPI), P.O.BOX 14665-137, Техеран, Иран*

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(Резюме)

Представена е проста и ефективна методология за оксидативно дехидрогениране на Hantzsch на 1,4-дихидропиридини (1,4-DHP) до техните съответни производни на пиридин с *m*-хлорпероксибензоенова киселина (m-CPBA) в присъствието на железен(III)тетрафенилпорфиринат хлорид [Fe(TPP)Cl]. Получаването на продуктите става в рамките на само няколко минути с ~100% селективност при 95-100% добив. Методът може да предостави полезна информация за оценка на окислителната пътека на 1,4-DHP с цитохром P-450 в човешкото тяло.