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Catalytic aromatization of Hantzsch 1,4-dihydropyridines by ferric perchlorate in acetic acid

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Abstract—Catalytic oxidation of Hantzsch 1,4-dihydropyridines is described using a catalytic amount of ferric perchlorate in acetic acid at room temperature.

1. Introduction

The chemistry of dihydropyridines was reviewed in 1972 by Eisner and Kuthan,[1] and in 1988 by Stout and co-workers.[2] A considerable portion of today's efforts in dihydropyridine chemistry is expanded in synthesizing NADH mimics, exploring the reactions and mechanisms of these compounds, and utilizing them in a variety of synthetic reactions. In addition, recently preceding studies have suggested[3–8] that 1,4-DHP derivatives also provide an antioxidant protective effect that may contribute to their pharmacological activities. This effect is not due to the Ca^{2+} antagonist effect, but is related to the reactivity of these compounds toward radical species.[4]

On the other hand, the oxidation of the dihydropyridine ring is the main metabolic route for these compounds. The aromatization of 1,4-DHP is also one of the ubiquitous problems in organic chemistry, and several researchers have reported oxidation methods including chemical oxidation with ferric or cupric nitrates on a solid support,[9] oxidation with ceric ammonium nitrate,[10] ultrasound-promoted oxidation by clay-supported cupric nitrate,[11] oxidation with pyridinium chlorochromate,[12] and oxidation with nitric acid,[13] RuCl$_3$,[14] Mn(OAc)$_3$,[15] voltammetric oxidation of 1,4-DHP in protic[16] and in aprotic media.[17] In spite of these waves of interest most of the reagents that have oxidized 1,4-dihydropyridines are stoichiometric rather than catalytic. RuCl$_3$ has been used for this purpose in catalytic amount. However this reaction must be performed under pressure of oxygen.[14] Aromatization of 1,4-Hantzsch DHPs have also been performed effectively by the treatment of a catalytic amount of Pd/C in acetic acid[18] and in the presence of activated carbon with molecular oxygen.[19] We have recently reported, ferric perchlorate as a mild, efficient, and inexpensive catalyst for ring opening of epoxides,[20] etherification of alcohols,[21] transetherification of ethers,[22] and tetrahydropyranylation of alcohols.[23] In this communication, we wish to report an improved catalytic and general approach for oxidation of Hantzsch 1,4-DHPs using ferric perchlorate in acetic acid.

2. Experimental

1,4-Dihydropyridines were synthesized according to Arthur Hantzsch procedure.[24] All products were known and their physical and spectroscopic data were compared with those of authentic samples. Melting points were measured using Barenstead Electrothermal. IR spectra were recorded on Bruker 4000–400 cm^{-1}. ^{1}H NMR spectra were obtained on 90 MHz NMR instrument. Yields are based on GC/mass analysis using Agilent 6890 GC system Hp-5 capillary 30 m × 530 μm × 1.5 μm nominal.

2.1. Catalytic oxidation of 1,4-dihydropyridines: general procedure

A solution of an appropriate 1,4-dihydropyridine (1 mmol), ferric perchlorate (0.2 mmol, 2 mol%), and acetic acid (5 mL) was stirred at room temperature until

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Keywords: Aromatization; Oxidation of Hantzsch 1,4-dihydropyridines; Ferric perchlorate; 1,4-DHP.

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Table 1. Oxidation of 1,4-dihydropyridines to pyridine derivatives by ferric perchlorate in acetic acid at room temperature

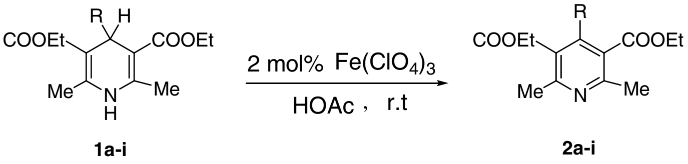
Entry	R (substrate)	Time (h)	Yield (%)	R (product)
a	H	1.5	88	H
b	CH_3	0.75	92	CH_3
c	CH_3CH_2	0.3	96	CH_3CH_2
d	C_6H_5	1.5	93	C_6H_5
e	3-NO_2–C_6H_5	2.0	91	3-NO_2–C_6H_5
f	3-MeO–C_6H_5	1.5	90	3-MeO–C_6H_5
g	4-MeO–C_6H_5	1.0	97	4-MeO–C_6H_5
h	2-Furyl	3.0	87	2-Furyl
I	$(CH_3)_2CH$	1.0	78	H

no dihydropyridine was detected by TLC (eluent, petroleum ether:ethyl acetate, 4:1). Upon completion of the reaction aqueous $NaHCO_3$ 10% (15 mL) was added. The reaction mixture was then extracted with CH_2Cl_2. The organic phase was dried and evaporated under reduced pressure to afford the pure corresponding pyridines (Table 1).

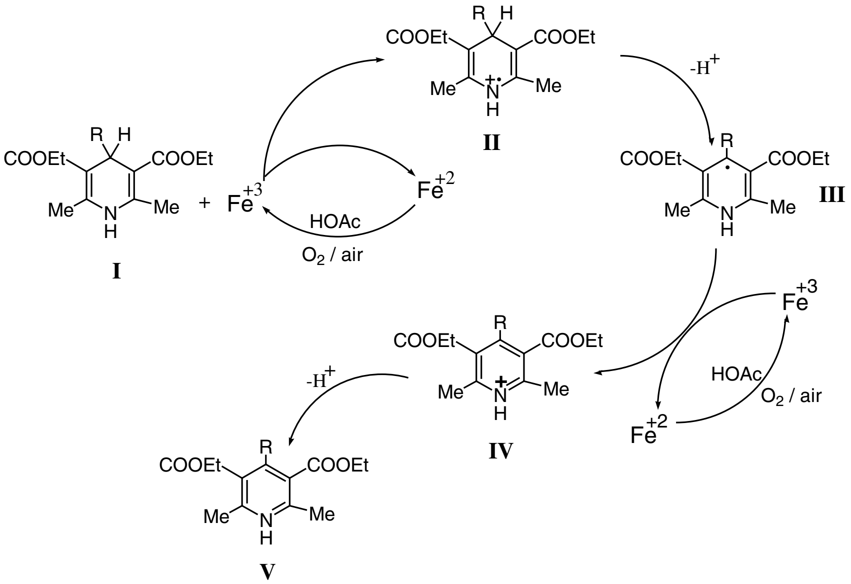
3. Results and discussion

A long series of 1,4-DHP derivatives were synthesized to investigate their catalytic conversion to the corresponding pyridines. We have used ferric perchlorate as catalyst to affect various organic transformations.[20–23] Armed with these experiences, we wish to report that ferric perchlorate, a compound which is readily available and inexpensive serves as an excellent oxidative catalyst for a variety of 4-substituted Hantzsch 1,4-DHPs system as shown in the generalized Scheme 1. Our results are reported in Table 1. Our initial attempts to affect the oxidation of the simple 1,4-DHP as test case with **1a** and stoichiometric amount of ferric perchlorate in various solvents such as CH_2Cl_2, CH_3COCH_3, CH_3CN, and CH_3OH at ambient and thermal conditions produced non or insignificant amount of the corresponding pyridine (entry **a**). However to our delight, oxidation of **1a** to **2a** occurred smoothly with the stoichiometric amount of ferric perchlorate in acetic acid at room temperature. The success of this reaction prompted us to study the catalytic oxidation of 1,4-dihydropyridines with ferric perchlorate mediated by acetic acid. Indeed 2 mol% ferric perchlorate in acetic acid converted **1a** to **2b** in 88% yield (quantitative conversion by TLC). 1,4-Dihydropyridines were stable in acetic acid proving the catalytic ability and effect of ferric perchlorate.

To establish the generality of this catalytic method, various alkyl, aryl, and heterocycle Hantzsch 1,4-DHP were oxidized under the above conditions. Apart from being catalytic, one of the other salient feature of this reaction is the stability of the substituents at 4-position which are normally dealkylated during aromatization by existing methods, for example, oxidants such as $KMnO_4$[25] and clay–MnO_2.[26] The general exception, typical of all known oxidants described in the modern literature is the case of secondary alkyl (isopropyl) and benzyl



Scheme 1.



Scheme 2. Plausible mechanism for the catalytic oxidation of 1,4-dihydropyridines.

groups. In view of their electron releasing ability of the corresponding radicals these substituents are expelled with the formation of dealkylated products.[15]

We believe the catalytic oxidation of 1,4-DHP with ferric perchlorate mediated by acetic acid proceeds the pathways illustrated in Scheme 1. Presumably the oxidation of 1,4-DHPs is initiated by a single electron transfer to Fe(III) that produces Fe(II) and a radical cation which subsequently loses a proton to generate a radical **III**. With air present and because acid is used, Fe(II) goes back to Fe(III). This phenomenon has been already established.[27] The regenerated iron(III) then oxidizes radical **III** to the protonated pyridine **IV**. Ultimately the pyridinium species **IV** loses a proton to give the desired pyridine derivative **V** (Scheme 2).

In summary we have described a general and practical route for the catalytic oxidation of 1,4-dihydropyridines in excellent yields using catalytic amount of available and relatively nontoxic ferric perchlorate and inexpensive acetic acid. Since the concentration of oxygen in the air is good enough to facilitate catalyst turn over, we believe our method is an improvement in comparison to other catalytic methods.[14,18,19] The salient feature of this catalytic oxidation is that we do not have to use pure oxygen to affect oxidation and oxygen in the air will do the job.

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