

Oxidative aromatization of some 1,4-dihydropyridines by aqueous hydrogen peroxide in ethanol

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Abstract

Some 3,5-diacyl or 3,5-diester 1,4-dihydropyridines were oxidized to the corresponding pyridine derivatives using hydrogen peroxide in aqueous ethanol in the presence of potassium bromide and acetic acid as the catalysts. The reaction was carried out in ethanol and the products were isolated in high to excellent yields. However, oxidation of 3,5-diacetyl 1,4-dihydropyridines is slower than 3,5-diester 1,4-dihydropyridines under the same condition. Furthermore, the reaction is facilitated by electron releasing groups on 4-substituent of dihydropyridine ring. The cheapness of reagent, high yielding, easy workup and mild condition makes this method a useful addition to the available method in organic synthesis. In addition, employment of clean oxidant H₂O₂ together with nontoxic solvent ethanol makes it friendly to the environment.

Keywords: 3,5-Diester 1,4-dihydropyridines; 3,5-diacetyl 1,4-dihydropyridine; aromatization; hydrogen peroxide.

Introduction

1,4-Dihydropyridines are interesting compounds and play an important role in synthetic, therapeutic and bioorganic

chemistry [1-4]. In the human body, these compounds are oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver [5 and 6]. The aromatization

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of 1,4-dihydropyridines provides an easy access to 4-substituted pyridine which are difficult to access *via* the Friedel-Crafts alkylation. So, various reagents have been developed for aromatization of 1,4-dihydropyridines.

In the course of our study with 1,4-dihydropyridines [7-12], we investigate oxidation of some 3,5-diacetyl or 3,5-diester 1,4-dihydropyridines using aqueous hydrogen peroxide in the presence of KBr in ethanol. Hydrogen peroxide has been used for the oxidation of a variety of substrates [13] and it is relatively non-toxic and breaks down in the environment to non-toxic by-products.

Oxidation of some 3,5-diester 1,4-dihydropyridines by H₂O₂ in the presence of NaI [14], AlCl₃ [15], urea [16, 17] and acetic acid [18] have been reported. Although some of reported procedures have been successfully used for this purpose, most of them have several disadvantages such as long reaction times, low yields of products, low selectivity, and cumbersome workup. In addition, in this study, we investigate the effect of the type and the nature of the 4 or 3,5-substituents on the rate of oxidation. So, the present study describes a convenient and efficient method for the oxidation of 3,5-diester or 3,5-diacetyl 1,4-dihydropyridines

with H₂O₂ in the presence of KBr in aqueous ethanol.

Experimental

General

All Hantzsch 1,4-dihydropyridines have been synthesized according to the known procedure [19-21]. All products were known and their physical and spectroscopic data were compared with those of authentic samples [21-27]. Melting points were determined with Barnstead Electrothermal and are uncorrected. IR spectra were recorded on Shimadzu IR-470 spectrometer; and ¹H NMR data were obtained using a Bruker 300 MHz spectrometer in CDCl₃. UV spectra were measured on a R.R. China, Agilent 8453 spectrometer.

General procedure for oxidation of 1,4-dihydropyridines using aqueous hydrogen peroxide in ethanol in the presence of potassium bromide

1,4-Dihydropyridine (1 mmol), KBr (0.4 mmol), acetic acid (0.1 mL) and hydrogen peroxide (30%, 2 cc) were added to a round bottom flask in aqueous ethanol (EtOH/H₂O = 5 : 2.5). The mixture was refluxed and the progress of reaction was followed by TLC. After the reaction was completed, the combined organic layer was extracted with methylene dichloride (2 × 20 mL), dried over MgSO₄ and, after filtration, the solvent was

evaporated. The product was purified by recrystallization from petroleum ether / ethyl acetate (4:1). The structures of the products were confirmed by ¹HNMR, UV and IR spectroscopy and comparison with authentic samples prepared according to the literature methods [21-27].

Results and discussion

A long series of 1,4-dihydropyridines were synthesized to investigate their conversion to the corresponding pyridines with hydrogen peroxide. For optimization of the reaction condition, we accomplish some experimental, with diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **1b** as a typical compound (Table 1). As we show in Table 1, the reaction in the absence of KBr as catalyst did not yield any product after 24 h (Table 1: Entries 1, 2 ,3) or it was very slow (Table 1: Entry 12). In addition, it was found that the reaction was very slow in the absence of acetic acid as catalyst (Table 1: Entries 1-10).

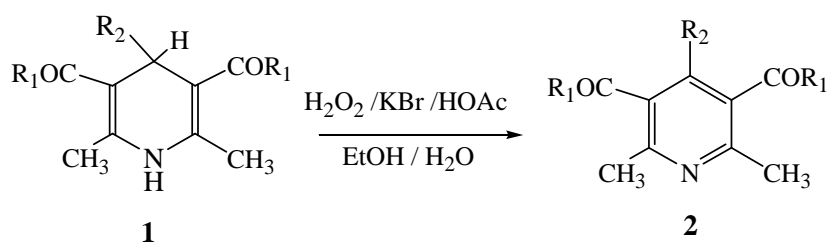
According to the data of Table 1, 19.5 mmol of H₂O₂ 30% (2 mL), 0.4 mmol of KBr, and 0.1 mL of AcOH in 7.5 mL of

aqueous ethanol (EtOH /H₂O = 5 : 2.5) were chosen as the optimized reaction conditions for oxidation of 1 mmol of 1,4-dihydropyridines (Scheme 1). Under the same condition, various substituted 1,4-dihydropyridines were readily oxidized to the corresponding pyridines in high yields with short reaction times (Table 2). As can be seen from Table 2, oxidation of **1a-1j** yields **2a-2j** with retention of the substituent in position 4 of dihydropyridine ring. The presented data in Table 2 indicate that hydrogen peroxide, in the presence of potassium bromide and acetic acid in aqueous ethanol, is able to convert 1,4-dihydropyridines to their corresponding pyridines in good yields. As can be seen from this table, oxidation of 3,5-diacetyl 1,4-dihydropyridines is slower than 3,5-diester 1,4-dihydropyridines under the same condition. However, compounds **1a** and **1f** with no substituent in position 4 of dihydropyridine ring convert to the corresponding pyridines in very short reaction time. In addition, the reaction is facilitated by electron releasing groups on 4-substituent of dihydropyridine ring.

Table 1. Optimization of reaction condition for 1mmol of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **1b**.

Entry	Solvent (mL)	H ₂ O ₂ 30% (mL)	Cat. (mmol)	AcOH (mL)	Time (h)	Conversion (%)
1	EtOH (7.5)	1	-	0	24	0

2	EtOH (7.5)	2	-	0	24	0
3	EtOH (7.5)	3	-	0	24	0
4	EtOH (7.5)	1	KBr (0.2)	0	16	90
5	EtOH (7.5)	2	KBr (0.2)	0	15	100
6	EtOH (7.5)	3	KBr (0.2)	0	12	100
7	EtOH (7.5)	2	KBr (0.3)	0	9	100
8	EtOH (7.5)	2	KBr (0.4)	0	7.5	100
9	EtOH /H ₂ O (5 : 2.5)	2	KBr (0.4)	0	6.5	100
10	H ₂ O (7.5)	2	KBr (0.4)	0	24	0
11	EtOH /H ₂ O (5 : 2.5)	2	KBr (0.4)	0.1	5	100
12	EtOH /H ₂ O (5 : 2.5)	2	-	0.1	13	60
13	EtOH /H ₂ O (5 : 2.5)	2	KCl (0.4)	0.1	14	70
14	EtOH /H ₂ O (5 : 2.5)	2	NaCl (0.4)	0.1	8	60



Scheme 1. Oxidative aromatization of some 1,4-dihydropyridines by aqueous hydrogen peroxide in ethanol

Table 2. Oxidative aromatization of some 1,4-dihydropyridines using aqueous hydrogen peroxide in ethanol

Comp.	R ₁	R ₂	Product (%) ^a	Time (h)
1a	OC ₂ H ₅	H	73	1.16
1b	OC ₂ H ₅	C ₆ H ₅	97	5
1c	OC ₂ H ₅	4-ClC ₆ H ₄	67	9
1d	OC ₂ H ₅	3-NO ₂ C ₆ H ₄	90	10
1e	OC ₂ H ₅	4-OCH ₃ C ₆ H ₄	65	5.5
1f	CH ₃	H	80	0.51
1g	CH ₃	C ₆ H ₅	90	4
1h	CH ₃	4-ClC ₆ H ₄	72	6.2
1i	CH ₃	3-NO ₂ C ₆ H ₄	87	8
1j	CH ₃	4-OCH ₃ C ₆ H ₄	75	5.25

^a Isolated yield

Conclusion

In conclusion, we have discovered an efficient and convenient method for the oxidation of 1,4-dihydropyridines to the corresponding pyridines. The cheapness of reagent, high yielding, easy workup and mild condition makes this method a useful addition to the available method in organic synthesis. In addition, employment of clean oxidant H₂O₂ together with nontoxic solvent ethanol makes it friendly to the environment.

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