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

Masumeh Abdoli-Senejani*, Maryam Hajibabaei

Department of Chemistry, Islamic Azad University-Arak Branch, P.O. BOX 38135-567, Arak, Iran

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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 H_2O_2 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 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 H_2O_2 in the presence of NaI [14], $AlCl_3$ [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

*Corresponding author: Masumeh Abdoli-Senejani
Tel: +98 (86) 3663041, Fax: +98 (86) 33670017
E-mail: mabdoli@iau-arak.ac.ir

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 H_2O_2 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 ^{1}HNMR data were obtained using a Brüker 300 MHz spectrometer in $CDCl_3$. 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/H_2O =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 $MgSO_4$ 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 ^{1}HNMR, UV and IR spectroscopy and comparison with authentic samples prepared according to the literature methods [21-27].

Results and discussion

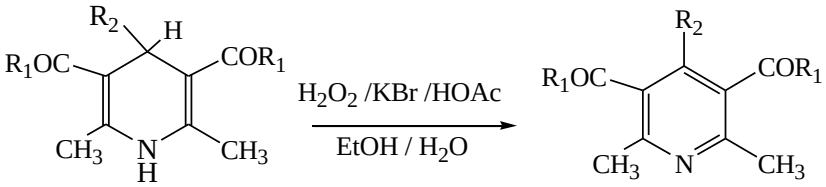
A long series of 1,4-dihydropyridines were synthesized to investigate their conversion to the corresponding pyridines with hydrogen peroxide. For optimization of the reaction condition, we accomplish some experimental, with diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **1b** as 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 H_2O_2 30% (2 mL), 0.4 mmol of KBr, and 0.1 mL of AcOH in 7.5 mL of aqueous ethanol (EtOH /H_2O = 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_2O_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_2O (5 : 2.5)	2	KBr (0.4)	0	6.5	100
10	H_2O (7.5)	2	KBr (0.4)	0	24	0
11	EtOH /H_2O (5 : 2.5)	2	KBr (0.4)	0.1	5	100
12	EtOH /H_2O (5 : 2.5)	2	-	0.1	13	60
13	EtOH /H_2O (5 : 2.5)	2	KCl (0.4)	0.1	14	70
14	EtOH /H_2O (5 : 2.5)	2	NaCl (0.4)	0.1	8	60



1 **2**

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_2H_5	H	73	1.16
1b	OC_2H_5	C_6H_5	97	5
1c	OC_2H_5	4-ClC_6H_4	67	9
1d	OC_2H_5	3-$NO_2C_6H_4$	90	10
1e	OC_2H_5	4-$OCH_3C_6H_4$	65	5.5
1f	CH_3	H	80	0.51
1g	CH_3	C_6H_5	90	4
1h	CH_3	4-ClC_6H_4	72	6.2
1i	CH_3	3-$NO_2C_6H_4$	87	8
1j	CH_3	4-$OCH_3C_6H_4$	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 H_2O_2 together with nontoxic solvent ethanol makes it friendly to the environment.

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