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Short Communication

Aromatization of *Hantzsch* 1,4-Dihydropyridines by Hydrogen Peroxide in the Presence of Cobalt(II) Acetate

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Summary. Hydrogen peroxide readily oxidizes *Hantzsch* type 1,4-dihydropyridines in the presence of cobalt(II) acetate as catalyst at room temperature. No evidence of a dealkylation process for 4-alkyl 1,4-dihydropyridines has been observed.

Keywords. *Hantzsch* type 1,4-dihydropyridines; Hydrogen peroxide; Cobalt(II) acetate; Aromatization; Catalytic oxidation.

Introduction

The oxidation of 1,4-dihydropyridines has gained interest in recent years due to the fact that 1,4-dihydropyridines based antihypertensive drugs (calcium antagonists) are oxidatively converted to pyridine derivatives by cytochrom P-450 in liver [1, 2]. Consequently, this oxidation reaction continues to attract the attention of researchers for the discovery of milder and general procedure applicable to a wide range of 1,4-dihydropyridines. Many of the reported oxidation procedures either suffer from the use of strong oxidants (HNO_3 [2], $KMnO_4$ [3], CrO_3 [4], $Bi(NO_3)_3$ [5], nicotinium dichromate [6]), require severe conditions (S [7], Pd/C dehydrogenation [8]), or need excess of the oxidants (CAN [9], PCC [10]).

In connection with our interest in the chemistry of 1,4-dihydropyridines and oxidation procedures, we have used zinc chlorochromate [11], molecular oxygen in the presence of cobalt and manganese salts of 4-amino benzoicacid supported on silica gel [12], and sodium hypochlorite/Dowex 1X8-200 [13]. We became

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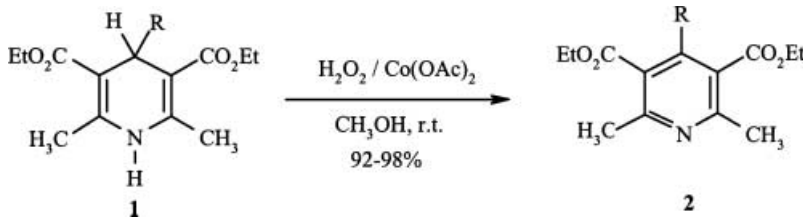
Table 1. Oxidation of 1,4-dihydropyridines to pyridine derivatives using hydrogen peroxide[a]



1,4-DHP	*R*	Time (min)	Oxidized product	Yield (%)
1a	H	15	**2a**	98
1b	CH_3	90	**2b**	95
1c	CH_3CH_2	60	**2c**	97
1d	C_6H_5	30	**2d**	97
1e	3-$NO_2C_6H_4$	150	**2e**	92
1f	2-furyl	75	**2f**	96
1g	4-ClC_6H_4	60	**2g**	97
1h	2-ClC_6H_4	70	**2h**	96
1i	$C_6H_5CH{=}CH$	65	**2i**	98
1j	4-$CH_3C_6H_4$	65	**2j**	98

[a] All reactions were carried out at room temperature in methanol using a molar ratio of 1:1 for DHP:cobalt(II) acetate

interested in developing another convenient and environmentally friendly method for the oxidation of 1,4-dihydropyridines.

Results and Discussion

A commercially available 30% solution of hydrogen peroxide serves as an excellent oxidant for a variety of 1,4-dihydropyridines as shown in the formula scheme. The results are collected in Table 1.

Following experiments have been performed to check the efficiency of our method. Cobalt(II) acetate alone does not oxidize dihydropyridines. When reaction of dihydropyridines and hydrogen peroxide is done without cobalt(II) acetate, it is a slow and low yield reaction. When cobalt acetate is used as catalyst, oxidation of dihydropyridines with hydrogen peroxide occurrs in excellent yields.

The data provided are optimum conditions such as quantity of catalyst, time and solvent, for all the reactions. Hydrogen peroxide in the presence of cobalt(II) acetate is a mild and effective alternative for the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives in high yields without formation of side products.

Experimental

Chemicals were purchased from Merck, Aldrich and Riedel Dehaen AG chemical companies and were used without further purification. IR spectra were recorded on FT-IR Unicam Mattson 1000 Spectrophotometer. ^{1}H-NMR spectra were recorded on Brucker AC-80 (80 MHz) spectrometer in $CDCl_3$ and

chemical shifts are listed in δ ppm. All products are known compounds and they were identified by their mp, IR, and ^{1}H-NMR spectroscopic properties. All yields refer to the isolated products and all reactions were stirred at room temperature until the substrates were completely consumed. The crude products obtained upon extractive work-up were purified by short silica gel column chromatography or crystallization. *Hantzsch* 1,4-dihydropyridines were synthesized according to the standard procedure [14].

Oxidation of diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate

Typical procedure

The *Hantzsch* 1,4-dihydropyridine **1**, (0.253 g, 1 mmol) was dissolved in 25 ml methanol and cobalt(II) acetate tetrahydrate (0.249 g, 1 mmol) was added to this solution and then 0.15 ml hydrogen peroxide 30% was added in portions over 15 min at room temperature along with stirring of the reaction mixture. Then 25 ml water was added to the reaction mixture and it was treated by 10% sodium bicarbonate solution. The product was extracted with 3×10 ml Et_2O, dried over Na_2SO_4 and evaporated to dryness. After crystallization of the product in ethanol, 0.250 g (99% yield) of diethyl-2,6-dimethyl-3,5-pyridine dicarboxylate was obtained.

The oxidations of the other 1,4-dihydropyridines were carried out in a similar procedure. The time of reactions and the yields of the isolated products are compiled in Table 1.

Diethyl-2,6-dimethyl-3,5-pyridine dicarboxylate (**2a**; $C_{13}H_{17}NO_4$)

Mp 68–70°C (Ref. [15], 71°C); FT-IR (KBr): 2976, 1723, 1592, 1446, 1222 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 8.6 (s, 1H).

Diethyl-2,6-dimethyl-4-methyl-3,5-pyridine dicarboxylate (**2b**; $C_{14}H_{19}NO_4$)

Oil (Ref. [15], oil); FT-IR (neat): 2984, 1730, 1569, 1453, 1238 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 2.1 (s, 3H).

Diethyl-2,6-dimethyl-4-ethyl-3,5-pyridine dicarboxylate (**2c**; $C_{15}H_{21}NO_4$)

Oil (Ref. [15], oil); FT-IR (neat): 2974, 1730, 1569, 1453, 1238 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 2.8 (2H), 1.2–0.8 (3H).

Diethyl-2,6-dimethyl-4-phenyl-3,5-pyridine dicarboxylate (**2d**; $C_{19}H_{21}NO_4$)

Mp 60–61°C (Ref. [16], 60–61°C); FT-IR (KBr): 2976, 1723, 1561, 1230, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 7.2 (s, 5H).

Diethyl-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylate (**2e**; $C_{19}H_{20}N_2O_6$)

Mp 62–64°C (Ref. [16], 61–62°C); FT-IR (KBr): 3061, 2984, 1730, 1530, 1246 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 7.9 (m, 2H), 7.3 (m, 2H).

Diethyl-2,6-dimethyl-4-(2-furyl)-3,5-pyridine dicarboxylate (**2f**; $C_{17}H_{19}NO_5$)

Mp 40–42 (Ref. [15], oil); FT-IR (neat): 3123, 2984, 1730, 1561, 1107, 1046 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 7.3 (m, 1H), 6.5–6.2 (m, 2H).

Diethyl-2,6-dimethyl-4-(4-chlorophenyl)-3,5-pyridine dicarboxylate (**2g**; $C_{19}H_{20}ClNO_4$)

Mp 66–68°C (Ref. [17], 65–67°C); FT-IR (KBr): 2976, 1730, 1561, 1238, 1107 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 7.2–7.3 (m, 4H).

Diethyl-2,6-dimethyl-4-(2-chlorophenyl)-3,5-pyridine dicarboxylate (**2h**; $C_{19}H_{20}ClNO_4$)

Mp 61–63°C (Ref. [16], 61–62°C); FT-IR (KBr): 2984, 1730, 1561, 1238, 1115 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 7.1–7.2 (m, 4H).

Diethyl-2,6-dimethyl-4-(4-cinamyl)-3,5-pyridine dicarboxylate (**2i**; $C_{21}H_{23}NO_4$)

Mp 162–164°C (Ref. [15], 162–163°C); FT-IR (KBr): 2930, 1730, 1561, 1115, 1046 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 7.1–7.2 (m, 7H).

Diethyl-2,6-dimethyl-4-(4-methylphenyl)-3,5-pyridine dicarboxylate (**2j**; $C_{20}H_{23}NO_4$)

Mp 72–73°C (Ref. [15], 72–73°C); FT-IR (KBr): 2976, 1730, 1561, 1246, 1107 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4-R: 7.1 (s, 4H), 2.3 (s, 3H).

^{1}H-NMR ($CDCl_3$) δ 2,6-CH_3: 2.4 (s, 6H) for **2b–j** and 3.0 (s, 6H) for **1a**, δ $COOC_2H_5$: 4.2 (q, 4H) and 1.2 (t, 6H) for **2a–j**.

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