

AROMATIZATION OF 1,4-DIHYDROPYRIDINES WITH OXYGEN OR AIR USING MANGANESE AND COBALT SALTS OF *p*-AMINOBENZOIC ACID SUPPORTED ON SILICA GEL AS OXIDIZING CATALYSTS

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Abstract

Hantzsch 1,4-dihydropyridines are oxidized to the corresponding pyridine derivatives using oxygen or air and a mixture of the manganese and cobalt salts of *p*-aminobenzoic acid supported on silica gel as the catalysts. Reactions are clean and the catalysts can be recovered easily and reused repeatedly.

Introduction

Performing organic reactions in a similar manner to those which occur in living cells is a fascinating challenge to organic chemists. In this regard, dihydropyridines have had a unique evolutionary history over this past century. First synthesized by Hantzsch [1] dihydropyridines were later discovered to be the active part of NADH, the essential reducing coenzyme in animals.

The oxidation of Hantzsch 1,4-dihydropyridines is one of the ubiquitous problems in organic chemistry and even in recent years several groups have reported new methods for aromatization [23]. In this regard, special attention has been focused on the developing heterogeneous systems in order to support reagents and

to achieve catalytic reactions, e.g. clay-supported cupric nitrate was reported to oxidize 1,4-dihydropyridines, although this is a mild reagent, it cannot be used in the 4-alkyl series even under sonication [4,5]. Oxidation of 1,4-dihydropyridine using pyridinium chlorochromate absorbed on a solid support was also reported. In this method, some dealkylation was also obtained [6]. Similarly, NHO_3 [7], HNO_2 [8] and $\text{NaNO}_2/\text{AcOH}$ [9] have been reported. Oxidation of 4-alkyldihydropyridines was carried out by microwave irradiation in the presence of MnO_2 /bentonites to give a mixture of normal and anomalous pyridines and the trends of $\text{H}>\text{alkyl}>\text{aryl}$ in the case of the oxidation of 4-substituted dihydropyridines were observed [10].

In recent years, other methods have been used such as CAN [11], HNO_3 /bentonite using microwave irradiation [12], supported KMnO_4 [13], nitric oxide [14] and MnO_2 [15]. Several reviews are available on this subject [16,17]. We have recently reported the oxidation of dihydropyridines using zinc chlorochromate [18].

In this work, the oxidation of 4-alkyl and 4-heteroaryldihydropyridines is reported using oxygen or

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air and a mixture of manganese and cobalt salts of *p*-aminobenzoic acid supported on silica gel as a catalyst. The catalysts are prepared easily in the following manner: silica gel is activated in a pyrolysis apparatus at 260°C at 20 mm Hg to lose its water by 5.7%. *p*-Aminobenzoic acid is reacted with the activated silica gel. The reaction of the acid bonded to silica gel with sodium bicarbonate solution afforded sodium salt of the acid, which is then converted to cobalt and manganese salts using cobalt chloride and manganese chloride solutions, respectively [19].

The oxidation of 4-alkyl-1,4-dihydropyridines was carried out in heptane at 93°C whereas that of 4-aryl and 4-heteroaryls 1,4-dihydropyridines was carried out in toluene at 105°C (Table I). The reactions were selective and only 4-alkyl and 4-arylpyridines were isolated. The catalysts were recovered via a simple filtration and dried in an oven at 135°C for 4 h; they can be used again (Table

II). Instead of oxygen, air has been used as the oxidant, which resulted in lower yields and longer reaction times being observed.

In conclusion, mild reaction conditions, good yields, easy work-up, and stability and reusability of the catalysts, are the most significant aspects of this method.

Experimental Section

All products are known compounds. They are identified by comparison of their m.p.s, IR and H NMR spectroscopic properties data with those of authentic samples. 1,4-Dihydropyridines were prepared using the standard procedures [20].

General Procedure for Oxidation of 1,4-Dihydropyridines

To a stirring solution of 1,4-dihydropyridines (1 mmol) in 95 ml of solvent was added the cobalt salt (90

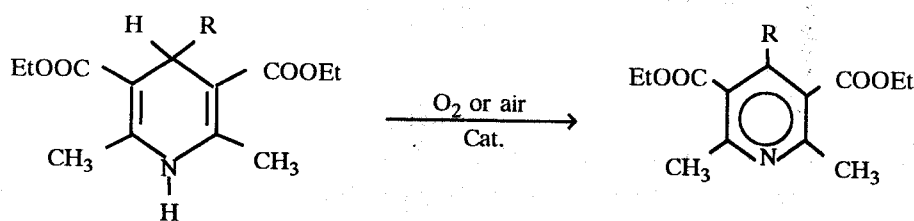


Table I. Oxidation of 1,4-dihydropyridines*

No	R	Yield (Oxygen)	Reaction Time	Yield (Air)	Reaction Time
1	-H	99	3	97	5
2	-CH ₃	92	15	90	20
3	-CH ₂ CH ₃	98	8	96	11
4	-CH ₂ CH ₂ CH ₃	98	8	95	10
5	-CH ₂ -CH(CH ₃) ₂	97	12	95	15
6	-C ₆ H ₅	95	8	93	10
7	-4-(CN)-C ₆ H ₄	91	12	90	15
8	-3-(NO ₂)-C ₆ H ₄	93	12	91	15
9	-2-Furyl	92	10	90	14
10	-2-Thienyl	95	10	93	14

*Reactions 1 through 5 were carried out in *n*-heptane as a solvent at 93°C and the reaction times are in minutes. Reactions 6 through 10 were carried out in toluene at 105°C and the reaction times are in hours.

Table II. Reusability of catalysts*

Experimental Trial	%Yield Compound# 3	%Yield Compound# 6
First	98	95
Second	95	90
Third	93	87
Fourth	91	85
Fifth	90	84

*Oxygen was used as the oxidant and conditions are similar to those in Table I.

mg 0.1 mmol) and manganese salt (90 mg 0.1 mmol). The reaction mixture was refluxed during which oxygen was bubbled at the rate of 15 ml per minute into the solution. Progress of the reaction was monitored by TLC ($\text{CH}_2\text{Cl}_2/\text{ETOAc}$ 98:2). The reaction mixture was then cooled to room temperature and filtered to recover the solid material (Co and Mn salts). The filtrate was evaporated and the residue was purified by preparative TLC on silica gel ($\text{CH}_2\text{Cl}_2/\text{ETOAc}$ 98:2) to obtain the desired products (Table I).

The above experiments were also repeated with air bubbled in at a rate of 40 ml per minute and the recovered catalysts were dried in an oven at 135°C for 4 h. The above experiments were repeated using recovered catalysts; yield drops slightly in each experiment. The catalysts were recovered quantitatively in each experiment.

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