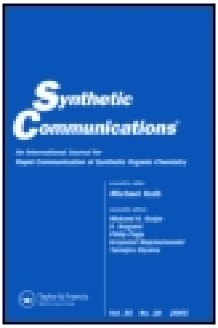

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An Efficient Method for the Oxidation of Hantzsch 1,4-Dihydropyridines to their Corresponding Pyridine Derivatives Under Mild and Heterogeneous Conditions

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AN EFFICIENT METHOD FOR THE OXIDATION OF HANTZSCH 1,4-DIHYDROPYRIDINES TO THEIR CORRESPONDING PYRIDINE DERIVATIVES UNDER MILD AND HETEROGENEOUS CONDITIONS

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Abstract: *A combination of oxalic acid dihydrate and sodium nitrite in the presence of wet* SiO_2 *was used as an effective oxidizing agent for the oxidation of dihydropyridines to their corresponding pyridine derivatives at room temperature with excellent yields.*

The oxidation of Hantzsch dihydropyridines (1) is an old reaction in general organic chemistry.[1] Even in recent years, several groups have reported new methods for aromatization including oxidations with ferric or cupric nitrates on a solid support,[2] ceric ammonium nitrate,[3] clay-supported cupric nitrate

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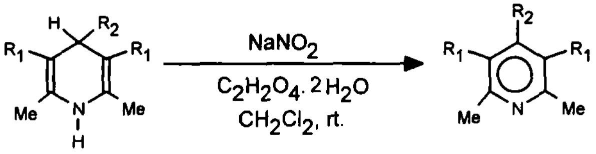
* Corresponding author.

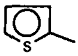
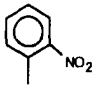
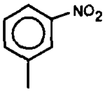
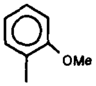
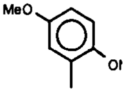
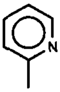
accompanied by ultrasound-promotion,[4] pyridinium chlorochromate,[5] *tert*-butylhydroperoxide,[6] photochemical oxidation.[7] There has also been a general method using nitric acid.[8] Very recently Ohsawa *et al,* reported an excellent procedure for this transformation. They have demonstrated the remarkably practical use of NO gas as a clean and efficient oxidant for this purpose.[1]

Although a variety of reagents is capable of effecting these oxidations,[1-8] as far as we know this transformation is not so easy and is a tricky step because these compounds (they have different functional groups within the molecule) are very sensitive to the oxidizing agents and reaction conditions. Most of the reported reagents produce by-products which makes difficult to remove from desired products. Another major drawback to the older procedures is their use of reagents which are either highly toxic or present serious disposal problems (or both). For example, we know that the NO gas is corrosive and highly toxic and must be used under Ar atmosphere and effective hood with caution. Therefore, we decided to choice a new reagent or reagent systems to overcome the above limitations. In addition, for our propose both clean and easy work-up were also important. Since the heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions and to minimize chemical wastes as compared to the liquid phase counterparts. Consequently , in this article we would like to report a simple , cheap and convenient method for the effective conversion of 1,4-dihydropyridines (**1**) to their corresponding pyridine derivatives (**2**) under mild and heterogeneous conditions (Scheme 1).



1

2

1	R_1	R_2
a	COOEt	H
b	COOEt	Me
c	COOEt	Ph
d	COOEt	
e	COOEt	
f	COOEt	
g	COOEt	
h	COOEt	
i	COOEt	

Scheme 1

Table. Oxidation of 1,4-Dihydropyridines (1) to Their Corresponding Pyridine Derivatives with a Combination of $NaNO_2$ (I), $C_2H_2O_4.2H_2O$ (II) and Wet SiO_2 (50% *w/w*) in Dichloromethane at Room Temperature.

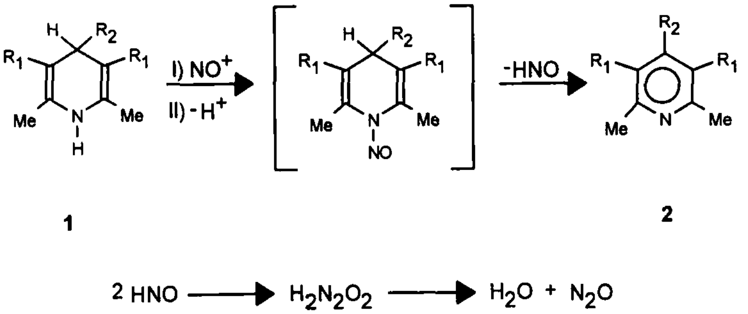
Entry	Substrate	Produc	(Reagent/Substrate)[a]		Time (Min)	Yield[b] (%)
			I	II		
1	**1a**	**2a**	4	2	30	98
2	**1a**[c]	**2a**	4	2	270	91
3	**1a**[d]	**2a**	4	2	120	82
4	**1a**[e]	**2a**	8[f]	4	150	86
5	**1b**	**2b**	4	2	30	90
6	**1c**	**2c**	4	2	30	97
7	**1d**	**2d**	6[f]	3	30	98
8	**1e**	**2e**	8[f]	4	90	97
9	**1f**	**2f**	8[f]	4	90	92
10	**1g**	**2g**	8[f]	4	60	95
11	**1h**	**2h**	8[f]	4	90	90
12	**1i**	**2i**	8[f]	4	60	90

[a] Wet SiO_2: substrate (0.2 g : 1 mmol). [b] Isolated yields. [c] Reaction was occurred in the absence of SiO_2 (both dry SiO_2 and wet SiO_2). [d] Reaction was occurred in the presence of dry SiO_2. [d] Reaction was occurred under two phase system (CH_2Cl_2-H_2O). [f] $NaNO_2$ was added in four portion (each addition after 15 minutes).

Present oxidation reaction can be readily carried out only by placing, $NaNO_2$, $C_2H_2O_4.2H_2O$, **1**, wet SiO_2 (50% *w/w*) and dichloromethane as the inert usable solvent in a reaction vessel and efficiently stirring the resultant heterogeneous mixture at room temperature for 30-90 minutes and the pyridine derivatives (**2**) can be obtained by simple filtration and evaporation of the solvent. The results and reaction conditions are tabulated in Table.

Very recently, we have demostrated that this reagent system acts as N_2O_4 because a number of reactions are known in which nitrogen tetroxide

$(N_2O_4 \Leftrightarrow NO^+NO_3^-)$ acts as a nitrosating agent.[9] Therefore, on the basis of our previously reported results about the applications of N_2O_4[10], $NaNO_2$, $C_2H_2O_4.2H_2O$[11] and the above fact the following mechanism could be proposed (Scheme 2).



Scheme 2

In conclusion, practical and efficient oxidation of 1,4-dihydropyridines were achieved by the present methodology. The cheapness and the availability of the reagents, easy procedure and work-up make this method attractive for the large-scale operations. The present method could be an useful addition to the available methods in organic synthesis.

EXPERIMENTAL SECTION

General: Chemicals were purchased from Fluka, Merck, Riedel-dehaen AG and Aldrich chemicals companies. Yields refer to isolated products. The oxidation products were characterized by comparison of their spectral (IR, $^{1}H-NMR$, and $^{13}C-NMR$) and physical data with the authentic samples. All Hantsch 1,4-dihydropyridines were synthesized by the reported procedures.[4,12]

Oxidation of Dihydropiridine (1a) to Substituted Pyridine (2a). A Typical Procedure.

A suspension of compound **1a** (o.331 g, 1 mmol), $C_2H_2O_4.2H_2O$ (0.252 g, 2 mmol), wet SiO_2 (50% *w/w)* (0.2 g) and $NaNO_2$ (0.276 g, 4 mmol) in dichloromethane (4 ml) was stirred at room temperature for 30 minutes (the progressof the reaction was monitored by TLC) and then filtered. Anhydrous Na_2SO_4 (5 g) was added to the filtrate. After 15 minutes dichloromethane (20 ml) was added to the resulting mixture and filtered. Dichloromethane was removed by water bath (40-50 °C) and simple distillation. The yield was 0.322 g, (98%) of crystalline pale yellow solid (**2a**).[1-8]

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