SHORT PAPER

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An efficient and chemoselective method for the oxidation of 1,4-dihydropyridines under mild and heterogeneous conditions†

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A combination of inorganic acidic salts or oxalic acid dihydrate and sodium nitrate in the presence of wet SiO_2 was used as an effective oxidising agent for the oxidation of dihydropyridines to their corresponding pyridine derivatives at 40–50 °C with excellent yields.

Amlodepine besylate, nifedepine and related dihydropyridines are Ca^{2+} channel blockers, and are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular diseases including hypertension. In the human body, it has been observed that these compounds undergo oxidation to form pyridine derivatives. These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds. Additionally, dihydropyridines are often produced in a synthetic sequence, and have to be oxidized to pyridines.[1]

The oxidation of Hantzsch dihydropyridines (**1**) is an old reaction in general organic chemistry.[2] In recent years, several groups have reported new methods for aromatization including oxidations with ferric or cupric nitrates on a solid support,[3] ceric ammonium nitrate,[4] clay-supported cupric nitrate accompanied by ultrasound-promotion,[5] pyridinium chlorochromate,[6] *tert*-butylhydroperoxide[1] and photochemical oxidation.[7]

Itoh *et al.* have 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.[2]

Although a variety of reagents is capable of effecting these oxidations,[1–7] 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 are difficult to remove from desired products. Another major drawback of 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 an argon atmosphere and effective hood with caution.[2] Therefore, we decided to choose a new reagent or reagent systems to overcome the above limitations. In addition, for our purpose both clean and easy work-up were also important.

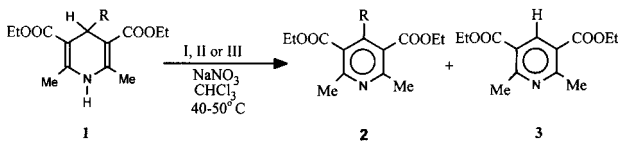
We among many others have recently demonstrated that heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions and the minimization of chemical wastes as compared to their liquid phase counterparts.[8,9] We decided to seek a completely heterogeneous system for dihydropyridine oxidation, and we have investigated a number of different reaction conditions based upon the *in situ* generation of HNO_3 by relatively strong solid inorganic acidic salts or oxalic acid dihydrate [$NaHSO_4.H_2O$, $Mg(HSO_4)_2$, $C_2H_2O_4.2H_2O$, pK_a~2] and sodium nitrate. In this article, we would like to report a simple, cheap and convenient method for the effective conversion of 1,4-dihydropyridines (**1**) into their corresponding pyridine derivatives (**2** or **3**) under mild and heterogeneous conditions.

Different types of dihydropyridines (**1**) were subjected to oxidation in the presence of $NaNO_3$, wet SiO_2 (50% *w/w*) and inorganic acidic salts *e.g.* $NaHSO_4.H_2O$ and $Mg(HSO_4)_2$ or $C_2H_2O_4.2H_2O$ in chloroform (Scheme 1). The oxidation reactions were performed under mild and completely heterogeneous conditions at 40–50 °C with excellent yields (Table 1). Unlike $NaHSO_4.H_2O$ and $Mg(HSO_4)_2$, the molar ratio of oxalic acid dihydrate ($C_2H_2O_4.2H_2O$) is high. Thus, $NaHSO_4.H_2O$ and $Mg(HSO_4)_2$ are superior to the oxalic acid dihydrate, in convenience, molar ratio, and purity of isolated pyridine derivatives (**2** or **3**).

It was also observed that the oxidation of 1,4-dihydropyridines (entries 25–30) bearing alkyl substituents (alkyl moieties may be responsible for generating stable carbocations) at the 4-position gives only the dealkylated pyridine derivative (**3**). This is in agreement with the observation made by others employing different oxidative conditions.[1,2] However, aryl substituted 1,4-dihydropyridines (entries 7–24) furnished the corresponding pyridine derivatives (Table 1).

The present oxidation reaction can be readily carried out only by placing $NaNO_3$, $NaHSO_4.H_2O$, $Mg(HSO_4)_2$ or $C_2H_2O_4.2H_2O$, **1**, wet SiO_2 (50% w/w) and chloroform as the solvent in a reaction vessel and efficiently stirring the resulting heterogeneous mixture at 40–50 °C for 15–80 minutes. The pyridine derivatives (**2** or **3**) can be obtained by simple filtration and evaporation of the solvent. The results and reaction conditions are shown in Table 1.

This new system of solid acids (*e.g.* $NaHSO_4.H_2O$, $Mg(HSO_4)_2$ and $C_2H_2O_4.2H_2O$) , $NaNO_3$ and wet SiO_2 *in situ* generates HNO_3 (equation 1). The autoionization of generated



1 **2** **3**

1,2: a: R = H **b:** = Me **c:** R = Ph **d:** R = 2-Thienyl
e: R = 2-NO_2–C_6H_4 **f:** R = 3-NO_2–C_6H_4 **g:** R = 2-CH_3O-C_6H_4
h: R = 2, 5-$(CH_3O)_2$–C_6H_3 **i:** R = $CH_3CHC_6H_5$ **j:** R = CH_3CHCH_3

Scheme 1

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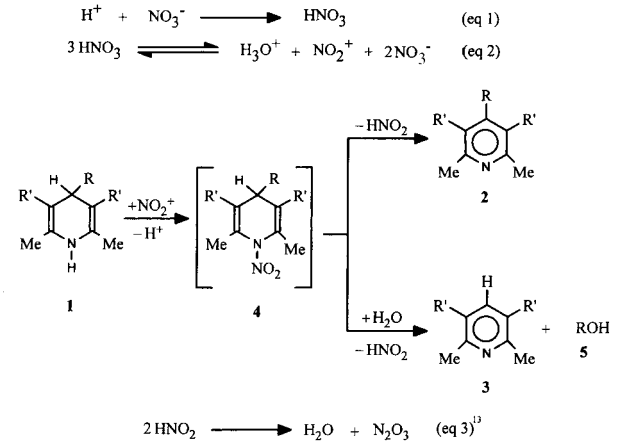
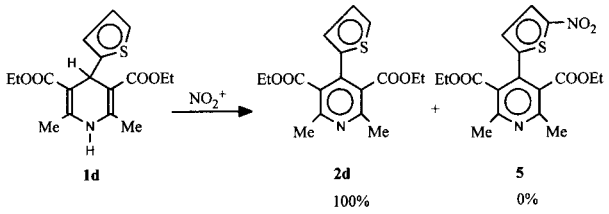
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2

nitric acid produces NO_2^+ (equation 2), the reactions of which are similar to those of the nitrosonium ion (NO^+).[9,10] Therefore, on the basis of our observations, the previously reported results concerning the *in situ* generation of HNO_3 or $HNO_3.NO_2$ and their applications on the nitration of phenolic compounds,[10,11–12] and the products which are obtained, the following mechanism could be proposed (Scheme 2).

In the case of 1,4-dihydropyridines (**1d**, **1g** and **1h**, entries 10–12 and 19–24) bearing electron rich aryl or thienyl substituents (these compounds are also very susceptible to nitration) at the 4-position give only the pyridine derivative (**2**) confirming that these compounds have not been nitrated during the oxidation reaction. Therefore, this system behaves



Scheme 3

chemoselectively and NO_2^+ (equations (1) and (2) attacks only) the nitrogen site of the secondary amines in 1,4-dihydropyridines (Scheme 3).

In conclusion, the cheapness and the availability of the reagents, easy and clean work-up, and high yields make this an attractive methodology. This simple procedure is highly selective and contamination by nitration side-products is avoided. Moreover, the new element here is that the reaction is heterogeneous. This could be worthwhile in an industrial setting. We believe that the present methodology could be an important addition to existing methodologies.

Experimental

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 TLC) and physical data with the authentic samples. All Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures.[14]

Oxidation of dihydropiridine (1a) to substituted pyridine (2a): a typical procedure. A suspension of compound **1a** (0.331 g, 1 mmol), $NaHSO_4.H_2O$ (0.360 g, 3 mmol), wet SiO_2 (50% *w/w)* (0.2 g) and

Table 1 Oxidation of 1,4-dihydropyridines (**1**) to the corresponding pyridine derivatives (**2** or **3**) with a combination of $Mg(HSO_4)_2$ (I), $NaHSO_4.H_2O$ (II) or $C_2H_2O_4{\cdot}2H_2O$ (III), $NaNO_3$ (IV) and wet SiO_2 (50% w/w) in chloroform at 40–50 °C

Entry	Substrate	Product	(Reagent/Substrate)				Time	Yield[b]
			I	II	III	IV	(min)	(%)
1	**1a**	**3**	1	–	–	2	30	98
2	**1a**	**3**	–	3	–	3	20	99
3	**1a**	**3**	–	–	6	12	20	91
4	**1b**	**2b**	1.5	–	–	3	20	99
5	**1b**	**2b**	–	3	–	3	15	97
6	**1b**	**2b**	–	–	6	12	20	81
7	**1c**	**2c**	1.5	–	–	3	20	99
8	**1c**	**2c**	–	3–	–	3	15	98
9	**1c**	**2c**	–	–	6	12	20	98
10	**1d**	**2d**	1	–	–	2	45	99
11	**1d**	**2d**	–	2	–	2	30	81
12	**1d**	**2d**	–	–	6	12	30	98
13	**1e**	**2e**	2.5	–	–	5	30	98
14	**1e**	**2e**	–	5	–	5	20	90
15	**1e**	**2e**	–	–	7	14	45[c]	96
16	**1f**	**2f**	2.5	–	–	5	40	98
17	**1f**	**2f**	–	5	–	5	15	86
18	**1f**	**2f**	–	–	7	14	45[c]	97
19	**1g**	**2g**	1.5	–	–	3	30	97
20	**1g**	**2g**	–	3	–	3	15	98
21	**1g**	**2g**	–	–	7	14	60	95
22	**1h**	**2h**	1.5	–	–	3	60	90
23	**1h**	**2h**	–	3	–	3	50	93
24	**1h**	**2h**	–	–	7	14	80	99
25	**1i**	**3**	1.5	–	–	3	20	90[d]
26	**1i**	**3**	–	3	–	3	10	98[d]
27	**1i**	**3**	–	–	6	12	20	97[d]
28	**1j**	**3**	1.5	–	–	3	20	97[d]
29	**1j**	**3**	–	3	–	3	15	90[d]
30	**1j**	**3**	–	–	6	12	20	98[d]

[a]Wet SiO_2: substrate (0.2 g : 1 mmol), I–IV refer to mmol of the acidic salts, oxalic acid and $NaNO_3$. [b]Isolated yields. [c]Under reflux conditions. [d]After passage through a 5 cm pad of silica gel.

$NaNO_3$ (0.255 g, 3 mmol) in chloroform (4 ml) was stirred at 40–50 °C for 10 minutes (the progress of the reaction was monitored by TLC) and then filtered. The residue was washed with chloroform (20 ml). Anhydrous Na_2SO_4 (5 g) was added to the filtrate and filtered after off 20 minutes. Chloroform was removed. The yield was 0.325 g, (99%) of crystalline pale yellow solid (**2a**), mp 69–72 °C [Lit.[3a] mp 72–73 °C][3a]. ^{1}H-NMR ($CDCl_3$)/TMS): 1.42 (t, 6 H), 2.86 (s, 6 H), 4.36 (q, 4 H), 8.69 (s, 1 H).[6]

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