SHORT PAPER

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An efficient method for the oxidation of 1,4-dihydropyridines under mild and heterogeneous conditions via *in situ* generation of NOCl†

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A combination of inorganic chloride salts [e.g. $AlCl_3$, $ZrCl_4$, and $ZnCl_2$] and sodium nitrite in the presence of wet SiO_2 was used as an effective oxidising agent for the oxidation of dihydropyridines to their corresponding pyridine derivatives under mild and heterogeneous conditions in moderate to excellent yields.

Keywords: dihydropyridines, inorganic chloride salts, sodium nitrite

4-Substituted Hantzsch dihydropyridines (**1**) are analogues of NADH coenzymes and an important class of drugs.[1] For example, 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 oxidised compounds are largely devoid of the pharmacological activity of the parent compounds.

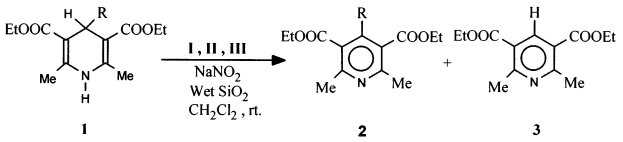
Additionally, dihydropyridines are often produced in a synthetic sequence, and have to be oxidised to pyridines.[2] Numerous reagents and procedures have been recommended for this purpose, such as ferric or cupric nitrates on a solid support (clayfen or claycop),[3] ceric ammonium nitrate,[4] clay-supported cupric nitrate accompanied by ultrasound-promotion,[5] manganese dioxide or DDQ,[6] nitric oxide[7], bismuth nitrate pentahydrate[8], PCC[9], tetrakis-pyridine cobalt(II) dicromate (TPCD),[10] nicotinium dichromate[11], *S*-nitrosoglutathion,[12] N_2O_4 complex of 18-crown-6,[13] diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidising agents,[14] $KMnO_4$,[15] CrO_3,[16] HNO_3,[17] HNO_2,[18] *tert*-butylhydroperoxide,[19] silica gel supported ferric nitrate (silfen),[20] N_2O_3[21] and photochemical oxidation.[22]

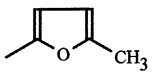
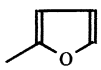
Very recently, Ohsawa and coworkers reported an excellent procedure for this transformation. They have demonstrated the remarkably practical use of NO gas as a clean and efficient oxidant for this purpose.[2]

Although a variety of reagents is capable of effecting these oxidations,[1–22] 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 oxidising agents and reaction conditions. Most of the reported reagents produce by-products which are 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 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.

Heterogeneous reagent systems (applications of NO^+ and NO_2^+ in organic synthesis) have many advantages such as simple experimental procedures, mild reaction conditions and the minimisation of chemical wastes as compared to their liquid phase counterparts.[23-38] Therefore, we decided to apply a heterogeneous system and we have investigated a number of different reaction conditions based upon the *in situ* generation of NOCl (as an efficient oxidising agent) by one of the inorganic chloride salts [*e.g.* $AlCl_3$, $ZrCl_4$, and $ZnCl_2$] and sodium nitrite. In this article, we report a simple, cheap and convenient method for the effective conversion of 1,4-dihydropyridines (**1**) in to their corresponding pyridine derivatives (**2**) under mild and heterogeneous conditions, although in the case of **1**m the reaction involves additional dealkylation.

Different types of dihydropyridines (**1**) were subjected to the oxidation reaction in the presence of inorganic chloride salts [*e.g.* $AlCl_3$ (**I**), $ZrCl_4$ (**II**), and $ZnCl_2$ (**III**)], $NaNO_2$ (**IV**) and wet SiO_2 (50% w/w) in dichloromethane (Scheme)]. The oxidation reactions were performed under mild and completely heterogeneous conditions at room temperature and take place with moderate to excellent yields (Table 1). Unlike



1, 2	R	1, 2	R	1, 2	R
a	H	**f**	2-NO_2-C_6H_4-	**k**	
b	Me	**g**	3-NO_2-C_6H_4-	**l**	
c	Et	**h**	2-CH_3O-C_6H_4-		
d	Ph	**i**	2, 5-$(CH_3O)_2$-C_6H_4-		
e	2-Thienyl-	**j**	4-Br-C_6H_4-		

For **Im** R=$(CH_3)_2CH$-

Scheme 1

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

Table 1. Oxidation of 1,4-dihydropyridines **(1)** to corresponding pyridine derivatives **(2)** with a combination of $AlCl_3$ **(I)**, $ZrCl_4$ **(II)** or $ZnCl_2$ **(III)**, $NaNO_2$ **(IV)** and wet SiO_2 (50% *w/w*) in dichloromethane at room temperature

Entry	Substrate	Product	(Reagent/substrate)[a]				Time	Yield
			I	**II**	**III**	**IV**	/min	/%
1	**1a**	**2a**	1.5	–	–	6	30	90
2	**1a**	**2a**	–	1.5	–	6	45	99
3	**1a**	**2a**	–	–	3.75	7.75	30	91
4	**1b**	**2b**	2.5	–	–	7.5	270	60[c]
5	**1b**	**2b**	–	1.5	–	6	120	99
6	**1b**	**2b**	–	–	3	6	30	99
7	**1c**	**2c**	1	–	–	3	60	97
8	**1c**	**2c**	–	1.5	–	6	45	99
9	**1c**	**2c**	–	–	2.5	5	105	91
10	**1d**	**2d**	2	–	–	6	30	91
11	**1d**	**2d**	–	4	–	16	80	99
12	**1d**	**2d**	–	–	7.5	15	120	99
13	**1e**	**2e**	2.5	–	–	7.5	75	99
14	**1e**	**2e**	–	4	–	16	90	99
15	**1e**	**2e**	–	–	7	14	30	99
16	**1f**	**2f**	3	–	–	9	75	98
17	**1f**	**2f**	–	4	–	16	75	92
18	**1f**	**2f**	–	–	7.5	15	75	99
19	**1g**	**2g**	3	–	–	9	75	95
20	**1g**	**2g**	–	4	–	16	75	96
21	**1g**	**2g**	–	–	7.5	15	75	96
22	**1h**	**2h**	2	–	–	6	45	92
23	**1h**	**2h**	–	2.5	–	10	75	96
24	**1h**	**2h**	–	–	7	14	135	90
25	**1i**	**2i**	2	–	–	6	75	90
26	**1i**	**2i**	–	1.5	–	6	70	93
27	**1i**	**2i**	–	–	5	10	50	95
28	**1j**	**2j**	2.5	–	–	7.5	60	92
29	**1j**	**2j**	–	3	–	12	75	99
30	**1j**	**2j**	–	–	7	14	45	99
31	**1k**	**2k**	3	–	–	9	75	99
32	**1k**	**2k**	–	3.5	–	14	45	98
33	**1k**	**2k**	–	–	7	14	60	99
34	**2l**	**2l**	3	–	–	7.5	45	99
35	**2l**	**2l**	–	4	–	16	75	92
36	**2l**	**2l**	–	–	7	14	45	97
37	**2m**	**2a**	1	–	–	3	45	92
38	**2m**	**2a**	–	1.5	–	6	45	97
39	**2m**	**2a**	–	–	2.5	5	90	98

[a]Wet SiO_2: substrate (0.4 g: 1 mmol), **I–IV** refer to mmol of the inorganic chloride salts and $NaNO_2$. [b]Isolated yields. [c]Reaction was repeated several times without increasing the yield.

$AlCl_3$, $ZrCl_4$, and $ZnCl_2$, the tungsten hexachloride (WCl_6) is not suitable for this purpose.

It was also observed that the oxidation of the 1,4-dihydropyridine (entries 37–39) bearing the 1-methylethyl substituent (some alkyl moieties may be responsible for generating stable carbocations) at the 4-position gave only the dealkylated pyridine derivative (**2a**). This is in agreement with the observation made by others employing different oxidative conditions.[2, 19, 23-26] However, aryl substituted 1,4-dihydropyridines (entries 10–36) furnished the corresponding pyridine derivatives (Tables 1 and 2).

This present oxidation reaction can be readily carried out by placing one of the inorganic chloride salts [*e.g.* $AlCl_3$ (**I**), $ZrCl_4$ (**II**), and $ZnCl_2$ (**III**)], $NaNO_2$ (**IV**), 1,4-dihydropyridine (**1**), wet SiO_2 (50% w/w) and CH_2Cl_2 as the solvent in a reaction vessel and efficiently stirring the resulting heterogeneous mixture at room temperature. The pyridine derivatives (**2**) can be obtained simply by filtration and evaporation of the solvent. The results and reaction conditions are given in Table 1.

The oxidation reaction did not occur in the absence of wet SiO_2. This observation suggests that the water molecule is essential for such processes. The presence of wet SiO_2 thus provides an effective heterogeneous surface area for *in situ* generation of NOCl.[29] It also eases the reaction work-up.

Table 2 Observed and literature melting points and also some typical mass spectra of the oxidation products **(2)**.

Product	M.p. °C		Mass spectrum		Ref.
	Found	Reported	Found (M^+)	Calc. (MW)	
2a	70–72	72–73	265	265	3
2b	Oil	168–170[a]	279	279	10
2c	Oil	112–114[a]			10
2d	62–64	60–62			10
2e	77–78	76–79			6
2f	76–79	75–76			3
2g	61–62	63			3
2h	56–58	57–58	357	357	22a
2i	77–78	75–76	388	388	22b
2j	Oil	Oil	406[c]	406	22b
2k	Oil	Oil	331	331	22b
2l	70–72	72–73			10
2a	70–72	72–73			10

[a]Melting points were reported as their corresponding salts with 2,4,6-trinitrophenol.
[b]Substrate **1m** gives only dealkylated pyridine derivative **2a**.
[c]Peak at M+2 was also observed.

In the case of 1,4-dihydropyridines (Table 1, **1e**, **1h** and **1i**, entries 13–15 and 22–27) bearing very electron-rich aryl or thienyl substituents (these compounds are also very susceptible to electrophilic aromatic substitution) at the 4-position give only the pyridine derivative (**2**) confirming that these compounds have not been nitrosated or nitrated (or both) during the oxidation reaction. Therefore, this system behaves chemoselectively and NO^+ attacks only the nitrogen site of the secondary amines in 1,4-dihydropyridines.[24]

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. We believe that the present methodology could be an important addition to existing methodologies.

Experimental

General: Chemicals were purchased from Fluka, Merck, Riedeldehaen AG and Aldrich chemical 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 authentic samples. All Hantzsch 1,4-dihydropyridines were synthesised by the reported procedures.[18]

Oxidation of dihydropiridine **(1a)** *to substituted pyridine* **(2a)**, *a typical procedure:* A suspension of compound **1a** (0.331 g, 1 mmol), $ZrCl_4$ (0.350 g, 1.5 mmol), wet SiO_2 (50% w/w, 0.4 g) and $NaNO_2$ (0.414 g, 6 mmol) in CH_2Cl_2 (6 ml) was stirred at room temperature for 45 minutes (the progress of the reaction was monitored by TLC) and then filtered. The residue was washed with CH_2Cl_2 (20 ml). Anhydrous Na_2SO_4 (5 g) was added to the filtrate and filtered after off 20 minutes. Dichloromethane was removed. The yield was 0.295 g, (90%) of crystalline pale yellow solid (**2a**), m.p. 70–72 °C [Lit.[3] m.p. 72–73 °C]. ^{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) [Lit.[9]].

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