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Oxidation of 1,4-Dihydropyridines under Mild and Heterogeneous Conditions Using Solid Acids

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A combination of solid acids, including Oxone®, HIO_3, H_5IO_6, and polystyrenesulfonic acid and sodium nitrite, in the presence of wet SiO_2 were used as an effective oxidizing agents for the oxidation of dihydropyridines to their corresponding pyridine derivatives under mild and heterogeneous conditions in good to excellent yields.

Keywords: Oxidation, 1,4-Dihydropyridines, Pyridines, Solid acids

INTRODUCTION

Six-membered heterocyclic compounds are important constituents that often exist in biologically active natural products and synthetic compounds of medicinal interest [1]. Among them, 4-substituted Hantzsch dihydropyridines (**1**), analogues of NADH coenzymes, are an important class of drugs [2]. For example, amlodipine besylate, nifedipine 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, 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 synthetic sequences, and must then be oxidized to pyridines [3]. Numerous reagents and procedures have been recommended for this purpose, such as ferric or cupric nitrates on a solid support (clayfen or claycop) [4], ceric ammonium nitrate [5], clay-supported cupric nitrate accompanied by ultrasound-promotion [6], manganese dioxide or DDQ [7], nitric oxide [8], bismuth nitrate pentahydrate [9], PCC [10], tetrakis-pyridine cobalt(II) dicromate (TPCD) [11], nicotinium dichromate [12], S-nitrosoglutathion [13], N_2O_4 complex of 18-crown-6 [14], diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidizing agents [15], $KMnO_4$ [16], CrO_3 [17], HNO_3 [18], HNO_2 [19], *tert*-butylhydroperoxide [20], silica gel-supported ferric nitrate (silfen) [21], N_2O_3 [22], photochemical oxidation [23], $H_2O_2/Co(OAc)_2$ [24], peroxydisulfate-cobalt(II) [25], $Zr(NO_3)_4$ [26], hypervalent iodine reagents [27], Co(II) catalyzed auto oxidation [28], anodic oxidation [29], I_2-MeOH [30], inorganic acidic salts or

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heteropoly acid and sodium nitrite or nitrate [31-40], and selenium dioxide [41].

Here we present a method for the oxidation of dihydropyridines to their corresponding pyridine derivatives that overcomes the disadvantages of many of the previous methods.

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck, Riedel-dehaen AG and Aldrich chemical companies. Yields refer to isolated products. The oxidation products were characterized by comparison of their spectral data (IR, ^{1}H NMR) with the physical data reported in the literature [30-41]. All Hantzsch 1,4-dihydropyridines were synthesized according to our recently reported procedure [42]. See Scheme 1 for molar ratios.

Typical procedure

A suspension of compound **1** (1 mmol), solid acid (**I-IV**), wet SiO_2 (50% *w/w*) and $NaNO_2$ in CH_2Cl_2 (6 ml) was stirred at room temperature for the specified time (see Tables 1-4). The progress of the reaction was monitored by TLC. When the reaction was complete the suspension was filtered. The residue was washed with CH_2Cl_2 (20 ml). Anhydrous Na_2SO_4 (3 g) was added to the filtrate and filtered off after 20 min. The crude products were obtained after evaporation *in vacuo* and purified by re-crystallization from petroleum ether except for **2b-c**, which were oils and were purified by column chromatography.

RESULTS AND DISCUSSION

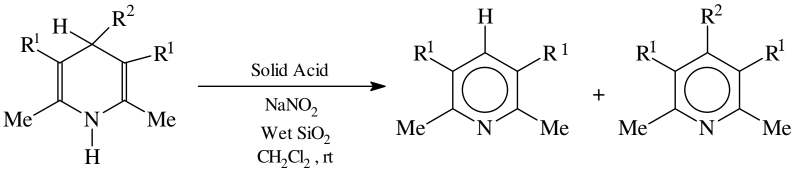
Recently A variety of reagents is capable of effecting the oxidation of dihydropyridines to their corresponding pyridine derivatives [1-41]. However, transformations using most reagents are problematic due to the different functional groups of these compounds that are very sensitive to oxidizing agents and reaction conditions. Most of the reported reagents produce by-products which are difficult to remove from the desired products. Another major drawback to the older procedures is their use of reagents that are either highly toxic or present serious disposal problems (or both). One example is NO gas, which is corrosive, highly toxic and must therefore be used under Ar atmosphere in an effective hood with great caution [3]. Exceptions are the recent reports by Hayashi *et al.*, who reported the remarkably practical use of O_2 gas and NO gas as clean and efficient oxidants for this purpose [1,3].

Here we chose a new reagent system to overcome the above limitations. In addition, this system offers a clean and easy work-up. Furthermore, the reduction in the amount of liquid acids needed and simplification in handling procedures reduces personal risk in the laboratory/manufacturing area, cost of the procedure and improves environmental safety. Presently, research and general interest in heterogeneous systems is intense due to the opportunities such systems present for basic research, industry and in developing technologies. In continuation of our studies on the application of heterogeneous systems [42], we applied inorganic solid acids, including Oxone® ($KHSO_4.2KHSO_5$. **I**), HIO_3 (**II**), H_5IO_6 (**III**) and the organic polymeric reagent polystyrenesulfonic acid (poly-SO_3H, IV), in conjunction with $NaNO_2$, wet SiO_2 for the *in situ* generation of NOX (X = IO_4, IO_3, KSO_5^-, poly-SO_3^-). Here we report a simple method for the effective oxidation of 1,4-dihydropyridines (**1**) to their corresponding pyridine derivatives (**2** or **3**) under mild and heterogeneous conditions via in-situ generation of NOX (Scheme 1).

A good range of dihydropyridines (**1**) were subjected to the oxidation reaction in the presence of solid acids (**I-IV**), $NaNO_2$ and wet SiO_2 (50% *w/w*) in dichloromethane (Scheme 1). The oxidation reactions were performed under mild and completely heterogeneous conditions at room temperature and took place with good to excellent yields (Tables 1-4).

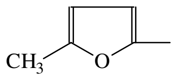
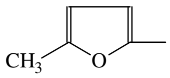
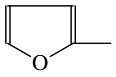
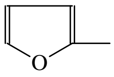
It was also observed that the oxidation of 1,4-dihydropyridines (Entry 13) bearing alkyl substituents (alkyl moieties may be responsible for generating stable carbocations) at the 4-position gives only the dealkylated pyridine derivative (**2**). This is in agreement with the observation made by others employing different oxidative conditions [3]. However, aryl substituted 1,4-dihydropyridines (Entries 4-12, 14, 15 and 18-24) furnished the corresponding pyridine derivatives (Tables 1-4).

The oxidation reaction did not occur in the absence of wet SiO_2. This observation suggests that the water is essential for



1 **2** **3**

Solid Acid: Oxone® (**I**), HIO_3 (**II**), H_5IO_6 (**III**), Poly-SO_3H (**IV**).

1,2,3	**R¹**	**R²**	**1,3**	**R¹**	**R²**
a	COOEt	H	**m**	COOEt	CH_3-CH-CH_3
b	COOEt	Me	**n**	COOEt	2-Py
c	COOEt	Et	**o**	COOEt	4-Py
d	COOEt	Ph	**p**	$COCH_3$	H
e	COOEt	2-Thienyl	**q**	$COCH_3$	Me
f	COOEt	2-NO_2-C_6H_4-	**r**	$COCH_3$	Ph
g	COOEt	3-NO_2-C_6H_4-	**s**	$COCH_3$	4-CH_3O-C_6H_4-
h	COOEt	2-CH_3O-C_6H_4-	**t**	$COCH_3$	2-CH_3O-C_6H_4-
i	COOEt	2,5-$(CH_3O)_2$-C_6H_3-	**u**	$COCH_3$	2,5-$(CH_3O)_2$-C_6H_3-
j	COOEt	4-Br-C_6H_4-	**v**	$COCH_3$	2-Thienyl
k	COOEt		**w**	$COCH_3$	
l	COOEt		**x**	$COCH_3$	

Scheme 1

such processes. The presence of wet SiO_2 thus provides an effective heterogeneous surface area for the *in situ* generation of NOX. It also simplifies the reaction work-up.

The oxidation reactions using HIO_3, H_5IO_6, and Oxone® without the application of $NaNO_2$, resulted in very long reaction times and the yield using Oxone® was negligible (Scheme 2). In these reactions the molar ratio of solid acid was the same as in Tables 1-3.

In the case of 1,4-dihydropyridines (Entries 5, 8-9 and 19-22), bearing very electron-rich aryl or thienyl substituents (compounds which are also very susceptible to electrophilic aromatic substitution) at the 4-position give only the pyridine derivative (**3**) 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-

Table 1. Oxidation of 1,4-dihydropyridines (1) using Oxone® (I)

Entry	Substrate	Product	Reagent/Substrate (mmol)[a]			Time (min)	Yield (%)[b]
			Oxone®	Substrate	$NaNO_2$		
1	**1a**	**2a**	0.5	1	1.5	30	99
2	**1b**	**3b**	1	1	3	150	98
3	**1c**	**3c**	1	1	3	150	95
4	**1d**	**3d**	1	1	3	75	91
5	**1e**	**3e**	2	1	6	90	98
6	**1f**	**3f**	1.5	1	4.5	135	99
7	**1g**	**3g**	1.5	1	4.5	75	99
8	**1h**	**3h**	1	1	3	90	99
9	**1i**	**3i**	4.5	1	13.5	165	99
10	**1j**	**3j**	4.5	1	13.5	165	98
11	**1k**	**3k**	4	1	12	90	97
12	**1l**	**3l**	2.25	1	7.5	90	99
13	**1m**	**2a**	1.75	1	5.25	90	99
14	**1n**	**3n**	5	1	15	120	99
15	**1o**	**3o**	5	1	15	240	98
16	**1p**	**3p**	0.75	1	2.25	30	98
17	**1q**	**3q**	1	1	3	90	96
18	**1r**	**3r**	2	1	6	75	98
19	**1s**	**3s**	1	1	3	90	99
20	**1t**	**3t**	1	1	3	120	98
21	**1u**	**3u**	1	1	3	90	98
22	**1v**	**3v**	4	1	12	165	98
23	**1w**	**3w**	4	1	12	195	90
24	**1x**	**3x**	4	1	12	135	97

[a] Wet SiO_2: substrate (0.4 g: 1 mmol). [b] Isolated yields.

Table 2. Oxidation of 1,4-dihydropyridines (1) using a HIO_3 (II)

Entry	Substrate	Product	Reagent/Substrate (mmol)[a]			Time (min)	Yield (%)[b]
			HIO_3	Substrate	$NaNO_2$		
1	**1a**	**2a**	1.5	1	1.5	15	97
2	**1b**	**3b**	2	1	2	60	99
3	**1c**	**3c**	2	1	2	45	95
4	**1d**	**3d**	3.5	1	3.5	30	95
5	**1e**	**3e**	4.5	1	4.5	90	98
6	**1f**	**3f**	5.5	1	5.5	135	96
7	**1g**	**3g**	5.5	1	5.5	135	99

Table 2. Continued

8	**1h**	**3h**	3	1	3	60	99
9	**1i**	**3i**	2.25	1	2.25	30	98
10	**1j**	**3j**	3.75	1	3.75	90	99
11	**1k**	**3k**	4.5	1	4.5	75	97
12	**1l**	**3l**	4.5	1	4.5	60	99
13	**1m**	**2a**	2	1	2	60	93
14	**1n**	**3n**	8	1	8	310	99
15	**1o**	**3o**	12	1	12	40	93
16	**1p**	**3p**	2	1	2	45	96
17	**1q**	**3q**	2	1	2	130	99
18	**1r**	**3r**	3.5	1	3.5	150	87
19	**1s**	**3s**	3	1	3	60	99
20	**1t**	**3t**	2	1	2	110	97
21	**1u**	**3u**	2	1	2	60	95
22	**1v**	**3v**	4.5	1	4.5	70	93
23	**1w**	**3w**	4.5	1	4.5	60	90
24	**1x**	**3x**	4.5	1	4.5	90	95

[a]Wet SiO_2: substrate (0.4 g: 1 mmol). [b]Isolated yields.

Table 3. Oxidation of 1,4-dihydropyridines (1) using $HIO_4.2H_2O$ or H_5IO_6 (III)

Entry	Substrate	Product	Reagent/Substrate (mmol)[a]			Time (min)	Yield (%)[b]
			H_5IO_6	Substrate	$NaNO_2$		
1	**1a**	**2a**	1.5	1	1.5	7	95
2	**1b**	**3b**	2	1	2	22	96
3	**1c**	**3c**	2	1	2	38	92
4	**1d**	**3d**	2	1	2	17	94
5	**1e**	**3e**	2	1	2	45	93
6	**1f**	**3f**	5.5	1	5.5	10	95
7	**1g**	**3g**	5.5	1	5.5	10	96
8	**1h**	**3h**	2	1	2	15	92
9	**1i**	**3i**	2	1	2	10	95
10	**1j**	**3j**	2	1	2	30	91
11	**1k**	**3k**	2	1	2	20	99
12	**1l**	**3l**	2	1	2	17	99
13	**1m**	**2a**	2	1	2	17	90
14	**1n**	**3n**	6	1	6	20	90
15	**1o**	**3o**	6	1	6	80	96
16	**1p**	**3p**	1.5	1	1.5	6	97
17	**1q**	**3q**	2	1	2	15	94

Table 3. Continued

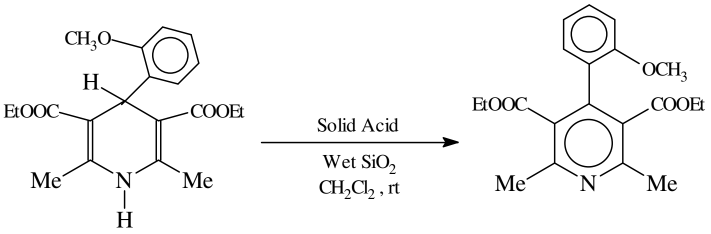
18	**1r**	**3r**	2	1	2	80	99
19	**1s**	**3s**	2	1	2	35	97
20	**1t**	**3t**	2	1	2	60	98
21	**1u**	**3u**	2	1	2	13	99
22	**1v**	**3v**	2	1	2	20	96
23	**1w**	**3w**	2	1	2	35	99
24	**1x**	**3x**	2	1	2	25	91

[a]Wet SiO_2: substrate (0.4 g: 1 mmol). [b]Isolated yields.

Table 4. Oxidation of 1,4-Dihydropyridines Using Poly-SO_3H (IV) in the Presence of Three Drops of Water

Entry	Substrate	Product	Reagent/Substrate (mmol)[a]			Time (min)	Yield (%)[b]
			Poly-SO_3H	Substrate	$NaNO_2$		
1	**1a**	**2a**	3	1	1.5	15	95
2	**1b**	**3b**	6	1	3	15	95
3	**1c**	**3c**	6	1	3	30	92
4	**1d**	**3d**	9	1	4.5	8	96
5	**1e**	**3e**	9	1	4.5	15	92
6	**1f**	**3f**	11	1	5.5	30	93
7	**1g**	**3g**	11	1	5.5	30	92
8	**1h**	**3h**	6	1	3	10	96
9	**1i**	**3i**	6	1	3	5	92
10	**1j**	**3j**	8	1	4	5	97
11	**1k**	**3k**	11	1	5.5	85	93
12	**1l**	**3l**	11	1	5.5	45	93
13	**1m**	**2a**	6	1	3	10	91
14	**1n**	**3n**	11	1	5.5	–	–[c]
15	**1o**	**3o**	11	1	5.5	–	–[c]
16	**1p**	**3p**	3	1	1.5	5	97
17	**1q**	**3q**	8	1	4	40	94
18	**1r**	**3r**	9	1	4.5	5	92
19	**1s**	**3s**	6	1	3	5	91
20	**1t**	**3t**	6	1	3	5	91
21	**1u**	**3u**	6	1	3	30	96
22	**1v**	**3v**	9	1	4.5	40	93
23	**1w**	**3w**	11	1	5.5	85	93
24	**1x**	**3x**	11	1	5.5	20	93

[a]Poly-SO_3H (IV): substrate (1 g: 1 mmol). [b]Isolated yields. [c]Reaction did not occur.



Solid acid	Time (h)	Yield
HIO_3	4	98
H_5IO_6	3	99
Oxone®	24	trace

Scheme 2

dihydropyridines.

In conclusion, the low cost and availability of the reagents, easy and clean work-up and high yields make this an attractive methodology. This simple procedure is highly selective, avoiding contamination by nitration side-products. We believe that the present methodology could be an important improvement over many of the existing methodologies.

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