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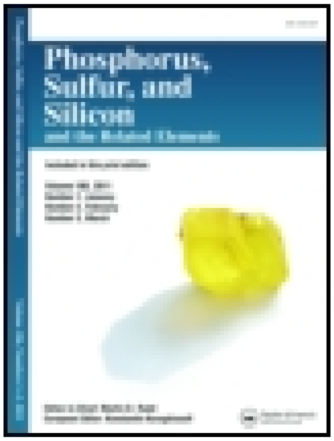

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Silica Chloride/NaNO 2 as a Novel Heterogeneous System for the Oxidation of 1,4-Dihydropyridines Under Mild Conditions via In Situ Generation of NOCl

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SILICA CHLORIDE/$NaNO_2$ AS A NOVEL HETEROGENEOUS SYSTEM FOR THE OXIDATION OF 1,4-DIHYDROPYRIDINES UNDER MILD CONDITIONS VIA IN SITU GENERATION OF NOCl

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A combination of silica chloride and sodium nitrite in the presence of wet SiO_2 were used as an effective oxidizing agent for the oxidation of dihydropyridines to their corresponding pyridine derivatives under mild and heterogeneous conditions in moderate to excellent yields.

Keywords: 1,4-Dihydropyridines; oxidation; pyridines; silica chloride

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 oxidized compounds largely are devoid of the pharmacological activity of the parent compounds. Additionally, dihydropyridines often are produced in a synthetic sequence and have to be oxidized 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]

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bismuth nitrate pentahydrate,[8] PCC,[9] tetrakis-pyridine cobalt(II) dichromate (TPCD),[10] nicotinium dichromate,[11] S-nitrosoglutathion,[12] N_2O_4 compelex of 18-crown-6,[13] diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidizing 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] photochemical oxidation,[22] inorganic acidic salts and sodium nitrite or nitrate.[23–26]

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.[2]

Although a variety of reagents is capable of effecting these oxidations,[1–26] as far as we know this transformation is not easy and is a complicated step because these compounds (which 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 the 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 an 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 propose both clean and easy work-up were also important.

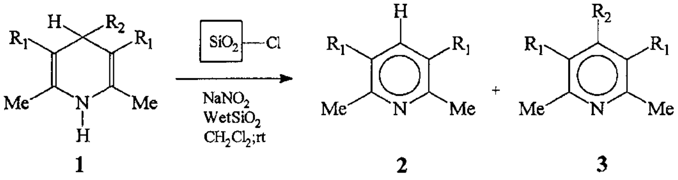
On the other hand, any reduction in the amount of liquid acids needed and any simplification in handling procedures would be highly convenient in terms of risk reduction, economic advantage, and environment protection.[27] Also there is intense current research and general interest in heterogeneous systems because of the perceived opportunities such systems present for basic research and because of the unquestioned importance such systems have in industry and in developing technologies.[28] In continuation of our studies on the application of heterogeneous systems,[29,30] we found that the silica chloride[31] **(I)** is an excellent source for generation of HCl. It is interesting to note that the addition of wet SiO_2 to the reaction mixture containing of silica chloride could in situ generate HCl. Therefore, we were interested in using this inorganic acidic resin (**I**) as a new hydrochloric acid function immobilized on the surface of silica gel via covalent bonding for the in situ generation of NOCl (as an efficient oxidizing agent) when used in conjunction with $NaNO_2$, wet SiO_2 (Scheme 1). 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 NOCl (Scheme 2).

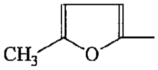
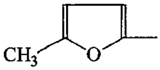
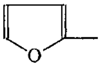
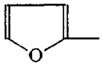
$$\underset{\textbf{I}}{\boxed{SiO_2}\text{–Cl}} + H_2O\ (\text{wet } SiO_2) \longrightarrow \boxed{SiO_2}\text{–OH} + HCl$$

$$HCl + \underset{\textbf{II}}{NaNO_2} \longrightarrow NaCl + HNO_2$$

$$HNO_2 + HCl \longrightarrow NO^+ + H_2O + Cl^-$$

SCHEME 1



1,2	R_1	R_2	1,2	R_1	R_2
a	COOEt	H	m	COOEt	$CH_3\text{-}CH\text{-}CH_3$
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	$2\text{-}NO_2\text{-}C_6H_4\text{-}$	r	$COCH_3$	Ph
g	COOEt	$3\text{-}NO_2\text{-}C_6H_4\text{-}$	s	$COCH_3$	$4\text{-}CH_3O\text{-}C_6H_4\text{-}$
h	COOEt	$2\text{-}CH_3O\text{-}C_6H_4\text{-}$	t	$COCH_3$	$2\text{-}CH_3O\text{-}C_6H_4\text{-}$
i	COOEt	$2,5\text{-}(CH_3O)_2\text{-}C_6H_3\text{-}$	u	$COCH_3$	$2,5\text{-}(CH_3O)_2\text{-}C_6H_3\text{-}$
j	COOEt	$4\text{-}Br\text{-}C_6H_4\text{-}$	v	$COCH_3$	2-Thienyl
k	COOEt		w	$COCH_3$	
l	COOEt		x	$COCH_3$	

SCHEME 2

Different types of dihydropyridines (**1**) were subjected to the oxidation reaction in the presence of silica chloride (**I**), $NaNO_2$ (**II**), and wet SiO_2 (50% *w/w*) in dichloromethane (Scheme 2). The oxidation reactions were performed under mild and completely heterogeneous conditions at room temperature and take place with moderate to excellent yields (Table I).

It also was observed that the oxidation of 1,4-dihydropyridines (Table I, entry 13) bearing alkyl substituent (alkyl moieties may be responsible for generating stable carbocations) at the 4-position gives only dealkylated pyridine derivative (**2**). This is in agreement with the observation made by other employing different oxidative conditions.[2,19,23–26]

TABLE I Oxidation of 1,4-Dihydropyridines (**1**) to Their Corresponding Pyridine Derivatives (**2** or **3**) with a Combination of Silica Chloride (**I**), $NaNO_2$ (**II**), and wet SiO_2 (50% *w/w*) in Dichloromethane at Room Temperature

			Reagent/Substrate[a] (mmol)			
Entry	Substrate	Product	**I**	**II**	Time (min)	Yield[b]
1	1a	2a	0.2	1.5	30	92
2	1b	2b	0.25	1.75	30	92
3	1c	2c	0.25	1.75	30	99
4	1d	2d	0.55	4.125	60	92
5	1e	2e	0.6	4.5	45	99
6	1f	2f	0.75	5.5	45	96
7	1g	2g	0.75	5.5	30	99
8	1h	2h	0.2	1.5	90	90
9	1i	2i	0.3	2.25	45	90
10	1j	2j	0.5	3.75	45	99
11	1k	2k	0.6	4.5	45	92
12	1l	2l	0.6	4.5	45	95
13	1m	2m	0.25	1.75	30	99
14	1n	2n	1.05	7.875	135	86
15	1o	2o	0.95	7.125	75	90
16	1p	2p	0.2	1.5	30	91
17	1q	2q	0.25	1.75	45	98
18	1r	2r	0.55	4.125	120	91
19	1s	2s	0.4	3	75	99
20	1t	2t	0.4	3	60	98
21	1u	2u	0.4	3	45	97
22	1v	2v	0.6	4.5	75	96
23	1w	2w	0.6	4.5	75	96
24	1x	2x	0.6	4.5	75	96

[a] Wet SiO_2: substrate (0.4 g: 1 mmol), **I**–**II** refer to mmol of the silica chloride and $NaNO_2$.

[b] Isolated yields.

However, aryl substituted 1,4-dihydropyridines (Table I, entries 4–12, 14, 15, 18–24) furnished the corresponding pyridine derivatives.

This present oxidation reaction can be carried out readily by placing silica chloride (**I**), NaNO$_2$ (**II**), 1,4-dihydropyridine (**1**), wet SiO$_2$ (50% *w*/*w*), and CH$_2$Cl$_2$ as the solvent in a reaction vessel and efficiently stirring the resulting heterogeneous mixture at room temperature. The pyridine derivatives (**2** or **3**) can be obtained simply by filtration and evaporation of the solvent. The results and reaction conditions are given in the Table I.

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.[32] It also eases the reaction work-up.

1,4-Dihydropyridines (Table I, entries 5, 8–9, 19–22) bearing very electron rich aryl or thienyl substituents (these compounds also are 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-dihydropyridines.[24]

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 and contamination by nitration side-products is avoided. We believe that the present methodology could be an important addition to existing methodologies.

EXPERIMENTAL SECTION

General: Chemicals were purchased from Fluka, Merck, Riedel-de Haen AG and Aldrich chemical companies. Yields refer to isolated products. Silica chloride was synthesised according to the reported prosedures.[33,34] The oxidation products were characterized by comparison of their spectral data (IR, ^{1}H-NMR) with the reported physical data in the literature. All Hantzsch 1,4-dihydropyridines were synthesized 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), silica chloride (0.2 g), wet SiO$_2$ (50% *w*/*w*, 0.4 g), and NaNO$_2$ (0.1035 g, 1.5 mmol) in CH$_2$Cl$_2$ (6 mL) was stirred at room temperature for 30 min (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 20 min. Dichloromethane was removed. The yield was 0.3312 g, (92%) of crystalline pale yellow solid (**2a**), m.p. 70–72°C [Lit.[3] m.p. 72–73°C]. ^{1}H-NMR (FT-NMR 90 MHz, $CDCl_3$)/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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