AROMATIZATION OF 1,4-DIHYDROPYRIDINES IN THE PRESENCE OF TOLUENESULFONYL CHOLORIDE/ $NaNO_2$/ WET-SiO_2 UNDER MICROWAVE IRRADIATION

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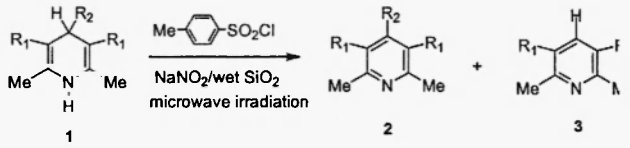
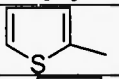
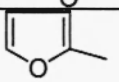
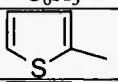
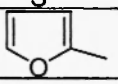
Abstract: A combination of toluenesulfonyl chloride and sodium nitrite in the presence of wet SiO_2 was used as an effective oxidizing agent for the aromatization of 1,4-dihydropyridines to the corresponding pyridine derivatives under microwave irradiation in excellent yields. The oxidizing agent (NOX) in-situ generated in the presence of wet SiO_2 that provided an effective heterogeneous surface area in this system.
Keywords: Aromatization, 1,4-dihydropyridines, oxidation, toluenesulfonyl chloride, sodium nitrite, microwave irradiation, wet-SiO_2

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** are analogues of NADH coenzymes and an important class of drugs (2). 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 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 (3). Although a variety of reagents is capable of effecting these oxidations (1, 3-8), 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 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 causion (3). 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/or any simplification in handling procedures would be highly convenient in terms of risk reduction, economic advantage and environment protection. Also there is intense current research and general interest in microwave radiation because of the provided an alternative to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. The use of microwave irradiation has introduced several new concepts in chemistry, since the absorption and transmission of the energy is completely different from the conventional mode of heating. The microwave technology has been applied to a number of useful research and development processes such as polymer technology, organic synthesis, application to waste treatment; drug release/targeting; ceramic and alkane decomposition (9).

In continuation of our work in the oxidation of 1,4-dihydropyridines (10-13), we report here the microwave-assisted oxidation of 1,4-dihydropyridines **1** to their corresponding pyridine derivatives **2** or **3** under mild and heterogeneous reagent via in-situ generation of NOCl (Scheme 1).

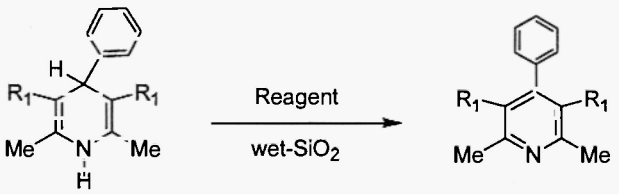


1,2	R_1	R_2	1,2	R_1	R_2	1,2	R_1	R_2
a	COOEt	H	**h**	COOEt	2-MeO-C_6H_4-	**o**	COMe	Me
b	COOEt	Me	**i**	COOEt	2,5-$(MeO)_2$-C_6H_3-	**p**	COMe	Ph
c	COOEt	Et	**j**	COOEt		**q**	COMe	4-MeO-C_6H_4-
d	COOEt	Ph	**k**	COOEt		**r**	COMe	2-MeO-C_6H_4-
e	COOEt	4-Br-C_6H_4-	**l**	COOEt		**s**	COMe	2,5-$(MeO)_2$-C_6H_3-
f	COOEt	2-NO_2-C_6H_4-	**m**	COOEt	i-Pr	**t**	COMe	
g	COOEt	3-NO_2-C_6H_4-	**n**	COMe	H	**u**	COMe	

Scheme-1

Different type of dihydropyridines **1** were subjected to oxidation in the presence of toluenesulfonyl chloride (**I**), $NaNO_2$ (**II**), and wet SiO_2 (50% w/w) under microwave irradiation (Scheme 1). Microwave-assisted aromatization reactions were performed by using heterogeneous oxidant with excellent yields (Table 1).

It also was observed that the oxidation of 1,4-dihydropyridines [Table 1, Entry 13] bearing alkyl substituent (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 other employing different oxidative conditions (3-5, 10-13). However, aryl substituted 1,4-dihydropyridines [Table 1, Entries 4-12, 16-21] furnished the corresponding pyridine derivatives. 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 NOX. It also eases the reaction work-up. Oxidation reaction by using toluenesulfonyl chloride and without applying $NaNO_2$ was proceeded slowly for example; conversion of this oxidation for $\mathbf{1_d}$ was about 70% after 100 s, (Scheme 2). In this reaction the molar ratio of toluenesulfonyl chloride was the same with used in Tables 1.



Reagent	Time(s)	Conversion%
Toluenesulfonyl Chloride	100	70

Scheme 2

1,4-Dihydropyridines [Table 1, Entries 8-12, 17-21] 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 **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 amino group in 1,4-dihydropyridines (11).

In conclusion, this method provides an excellent approach for the safe, rapid, inexpensive, simple, easy and clean work-up, and high yields. This simple procedure is highly selective and contamination by nitration side-products is avoided.

Table-1: Oxidation of 1,4-dihydropyridines **1** to their corresponding pyridine derivatives **2** or **3** with a combination of toluenesulfonyl chloride (**I**), $NaNO_2$ (**II**) and wet-SiO_2 (50% *w/w*) under microwave irradiation.

Entry	Substrate	Product	Reagent/Substrate (1 mmol)[a]		Time (s)	Yeild[b] (%)
			1	**II**		
1	**1a**	**3a**	2	2	50+ 30	92
2	**1b**	**2b**	3	3	50+ 50	91
3	**1c**	**2c +3c**	3	3	50+ 50	88 (70:30)
4	**1d**	**2d**	4	4.5	50+ 50	89
5	**1e**	**2e**	4	4	50+ 50	88
6	**1f**	**2f**	5.5	5.5	50+ 50	89
7	**1g**	**2g**	5.5	5.5	50+ 50	89
8	**1h**	**2h**	3	3	50+ 20	92
9	**1i**	**2i**	3	3	50+20	91
10	**1j**	**2j**	4	4.5	50+ 20	88
11	**1k**	**2k**	5.5	5.5	50+ 20	87
12	**1l**	**2l**	4	4.5	50+ 20	89
13	**1m**	**3m**	3	3	50+ 30	90
14	**1n**	**3n**	2	2	50+ 30	93
15	**1o**	**2o**	3	3	50+ 50	91
16	**1p**	**2p**	4	4.5	50+ 50	90
17	**1q**	**2q**	3	3	50+ 20	90
18	**1r**	**2r**	3	3	50+ 20	91
19	**1s**	**2s**	3	3	50+ 20	88
20	**1t**	**2t**	4	4.5	50+ 20	87
21	**1u**	**2u**	4	4.5	50+ 20	88

[a]substrate:wet SiO_2 (1 mmol: 0.5 g), **1** refer to mmol of toluenesulfonyl chloride and **II** refer to mmol of $NaNO_2$. [b]Isolated yields.

Experimental

Chemicals were purchased from Fluka, Merck and Aldrich chemicals companies. All of the products are known compounds and characterized by comparison of their spectroscopic data (IR, ^{1}H NMR), TLC and physical data with those reported in the literature [3-8, 10-12]. All Hantzsch 1,4-dihydropyridines were synthesized according to our recently reported procedure (14).

General procedure for the oxidation of 1,4-dihydropyridines (1) to the corresponding pyridine derivatives (2 or 3)

A mixture of compound **1** (1 mmol), sodium nitrite, toluenesulfonyl chloride [the molar ratio of toluenesulfonyl chloride (**I**) and the molar ratio of sodium nitrite (**II**) to the substrate **1** was optimized, Table 1] and wet SiO_2 (0.5 g, 50% w/w) were finely ground with a mortar and pestle, which was placed in a screw capped Teflon vessel. Microwave irradiation (MW domestic type oven 900 W with a frequency 2450 MHz, multi wave LG Korea) was applied for time specified in Table 1. The progress of the reaction was followed by TLC. The residue was washed with CH_2Cl_2 (2 × 10 mL) and filtrated neutralized with saturated sodium bicarbonate (10%). The resulting dichloromethane solution was separated and dried over anhydrous Na_2SO_4. The crude products were obtained after evaporation in vacuo and purified by recrystallization from petroleum ether except for **2b-c**, which were oils and were purified by column chromatography.

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