Aromatization of 1,4-Dihydropyridines in the Presence of Methanesulfonic Acid/$NaNO_2$/Wet SiO_2 under Both Heterogeneous and Solvent Free Conditions

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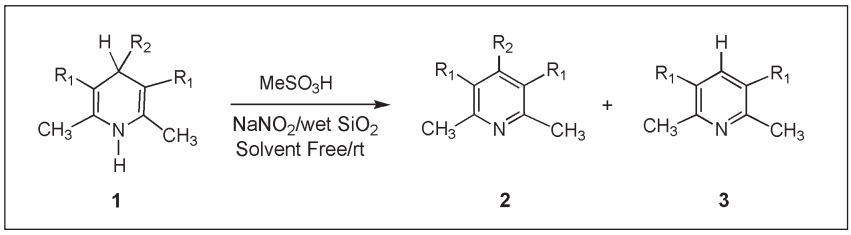

A combination of methanesulfonic acid and sodium nitrite in the presence of wet SiO_2 was used as an effective oxidizing agent for the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives under mild and heterogeneous conditions in excellent yields.

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Introduction.

4-Substituted Hantsch dihydropyridines (**1**) are analogues of NADH coenzymes and an important class of drugs [1]. The oxidation of dihydropyridines is an old reaction in general organic chemistry. 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 [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 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], $H_2O_2/Co(OAc)_2$ [23], peroxydisulfate-cobalt(II) [24], $Zr(NO_3)_4$ [25], hypervalent iodine reagents [26], Co(II) catalyzed auto oxidation [27], anodic oxidation [28], I_2-MeOH [29], inorganic acidic salts or heteroply acid and sodium nitrite or nitrate [30-38], selenium dioxide [39].

Results and Discussion.

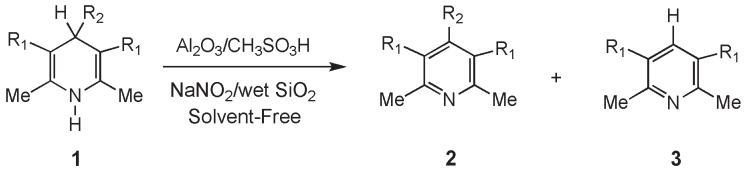
Recently, Hayashi *et al* reported an excellent procedure for this transformation. They have demonstrated the remarkably practical use of O_2 gas as a clean and efficient oxidant for this purpose [1]. Also, Ohsawa *et al* reported a remarkably practical use of NO gas as a clean and efficient oxidant for this conversion [2].

Although a variety of reagents are capable of affecting these oxidations [1-39], 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 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 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.

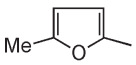
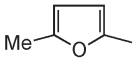
In this article, we would like to report a simple, cheap and convenient method for effective conversion of 1,4-dihydropyridine (**1**) with $CH_3SO_3H/NaNO_2$ into their corresponding pyridine derivatives (**2** or **3**) under mild, heterogeneous and solvent free conditions *via in situ* generation of NOX (X= $CH_3SO_3^-$), (Scheme 1).

Different type of dihydropyridines (**1**) were subjected to oxidation in the presence of CH_3SO_3H (**I**), $NaNO_2$ (**II**), and wet SiO_2 (50% w/w) under solvent free conditions or in dichloromethane (Table 1). It was also observed that the oxidation of 1,4-dihydropyridines

Scheme 1



1 **2** **3**

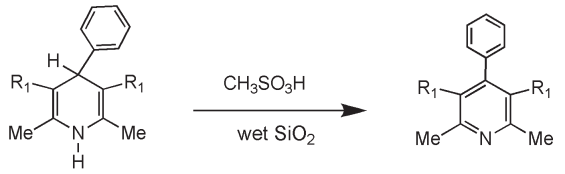
1,2	R_1	R_2	**1,2**	R_1	R_2	**1,2**	R_1	R_2
a	COOEt	H	**i**	COOEt	2,5-$(MeO)_2$-C_6H_3-	**q**	COMe	Me
b	COOEt	Me	**j**	COOEt		**r**	COMe	Ph
c	COOEt	Et	**k**	COOEt		**s**	COMe	4-MeO-C_6H_4-
d	COOEt	Ph	**l**	COOEt		**t**	COMe	2-MeO-C_6H_4-
e	COOEt	4-Br-C_6H_4-	**m**	COOEt	i-Pr	**u**	COMe	2,5-$(MeO)_2$-C_6H_3-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

(Table 1, entry 13) bearing alkyl substituent (alkyl moieties may be responsible for generating stable carbocations) at the 4-position gave only the dealkylated pyridine derivative (**3**). This is in agreement with the observation made by other employing different oxidative conditions [2]. However, aryl substituted 1,4-dihydropyridines (Table 1, entries 4-12, 14, 15, 18-24) furnished the corresponding pyridine derivatives.

It is worth mentioning, that these reactions were accomplished faster and with higher yields under solvent free conditions (Table 1). For example, for pyridine substituted in the 4-position (entries 14, 15, Table 1) the oxidation complete after 15 min at room temperature. However, these reactions did not occur with the same molar ratio of oxidizing agent in dichloromethane solution at room temperature (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 NOX [36]. It also eases the reaction work-up. Oxidation reaction by using $MeSO_3H$ and without applying $NaNO_2$ preceded very slowly for example; conversion of $\mathbf{1_d}$ was about 40% after 72 h. (Scheme 2). In this reaction the molar ratio of acid was the same with that used in Tables 1.

Scheme 2



Acid	Time(h)	Conversion%
CH_3SO_3H	72	40

1,4-Dihydropyridines (Table 1, 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 (**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 [30].

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.

Table 1

Oxidation of 1,4-dihydropyridines (**1**) to their corresponding pyridine derivatives (**2** or **3**) with a combination of $MeSO_3H$ (**I**), $NaNO_2$ (**II**) and wet SiO_2 (50% *w/w*) under solvent free conditions or in dichloromethane at room temperature

Entry	Substrate	Product	Reagent/Substrate (mmol)[a]		Solvent Free Conditions		CH_2Cl_2 Solution	
			I	**II**	Time (Min)	Yield[b]	Time (Min)	Yeild[b]
1	1a	3a	2	1.5	3	92	5	92
2	1b	2b	3	3	6	90	10	87
3	1c	2c	3	3	10	89	15	85
4	1d	2d	4.5	4.5	5	90	8	87
5	1e	2e	4.5	4.5	10	85	17	83
6	1f	2f	5.5	5.5	5	89	10	84
7	1g	2g	5.5	5.5	5	90	10	88
8	1h	2h	3	3	3	91	5	90
9	1i	2i	3	3	10	91	15	90
10	1j	2j	4	4	15	89	25	88
11	1k	2k	5.5	5.5	14	87	25	86
12	1l	2l	5.5	5.5	7	88	13	86
13	1m	3m	3	3	13	83	25	83
14	1n	2n	17	17	15	89	-	-[c]
15	1o	2o	17	17	15	88	-	-[c]
16	1p	3p	2	2	3	92	25	90
17	1q	2q	3	3	4	90	10	89
18	1r	2r	4.5	4.5	8	90	12	88
19	1s	2s	3	3	15	89	25	87
20	1t	2t	3	3	12	89	20	89
21	1u	2u	3	3	10	90	20	90
22	1v	2v	4.5	4.5	12	88	20	88
23	1w	2w	5.5	5.5	5	87	25	85
24	1x	2x	5.5	5.5	10	86	15	85

[a] Wet SiO_2: substrate (0.2 g : 1 mmol); [b] Isolated yields. [c] Reaction did not occur.

EXPERIMENTAL

General.

Methanesulfonic acid and other chemicals were purchased from Fluka, Merck and Aldrich chemicals companies. The products were characterized by comparing of their spectral (IR, ^1H NMR), TLC and physical data with authentic samples.

General Procedure for the Oxidation of 1,4-Dihydropyridines (**1**) to the Corresponding Pyridine Derivatives (**2** or **3**) under Solvent Free conditions.

A suspension of compound **1** (1 mmol), CH_3SO_3H (**I**), sodium nitrite (**II**), [the molar ratio of CH_3SO_3H and sodium nitrite to the substrate **1** was optimized, Table 1], and wet SiO_2 (0.2 g, 50% w/w) was stirred magnetically at room temperature. The progress of the reaction was followed by TLC. After completion of the reaction, the residue was washed with dichloromethane (2x20 mL), then a solution of sodium bicarbonate 10% (20 mL) was added and extracted. To the organic layer anhydrous Na_2SO_4 (10 g) was added and filtered after 20 min. The solvent was evaporated and pyridine derivatives (**2**) obtained. If further purification is needed, flash chromatography on silica gel [eluent: acetone/petroleum ether (10:90)] provides pure (**2**) derivatives.

Typical Procedure.

Diethyl-2,6-dimethylpyridine-3,5-dicarboxylate (**3a**).

A suspension of diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **(1)** (1 mmol, 0.253 g), CH_3SO_3H (2 mmol, 0.192 g), sodium nitrite (1.5 mmol, 0.104 g), and wet SiO_2 (0.2 g, 50% w/w) was stirred magnetically at room temperature. The progress of the reaction was followed by TLC. After 3 minutes the reaction was completed. The residue was washed with dichloromethane (2x20 mL), then a solution of sodium bicarbonate 10% (20 mL) was added and extracted. To the organic layer anhydrous Na_2SO_4 (10 g) was added and filtered after 20 min. The solvent was evaporated and a crystalline pale yellow solid of diethyl-2,6-dimethyl pyridine-3,5-dicarboxylate (**3a**) 0.233 g (92%) obtained, mp 68-69 °C (Lit. [6] mp 69-70 °C). ^1H NMR: δ 1.2 (t, 6H), 3.0 (s, 6H), 4.36 (q, 4H), 8.69 (s, 1H) (Lit. [6]).

General Procedure for the Oxidation of 1,4-Dihydropyridines (**1**) to the Corresponding Pyridine Derivatives (**2** or **3**) in Dichloromethane**.**

A suspension of compound **1** (1 mmol), CH_3SO_3H (**I**), sodium nitrite (**II**), [the molar ratio of CH_3SO_3H and sodium nitrite to the substrate **1** was optimized, Table 1], and wet SiO_2 (0.2 g, 50% w/w) in dichloromethane (8 mL) was stirred magnetically at room temperature. The progress of the reaction was followed by TLC. The reaction mixture was filtered after completion of the reaction. The residue was washed with CH_2Cl_2 (20 mL), then a solution of sodium bicarbonate 10% (20 mL) was added and extracted. To the organic layer anhydrous Na_2SO_4 (10 g) was added and filtered after 20 min. The solvent was evaporated and pyridine derivatives (**2**) obtained. If further purification is needed, flash chromatography on silica gel [eluent: acetone/petroleum ether (10:90)] provides pure (**2**) derivatives.

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