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MOLYBDATOPHOSPHORIC ACID/ NaNO_2 /WET SiO_2 AS AN EFFICIENT SYSTEM FOR OXIDATION OF 1,4-DIHYDRO-PYRIDINES UNDER MILD AND HETEROGENEOUS CONDITIONS

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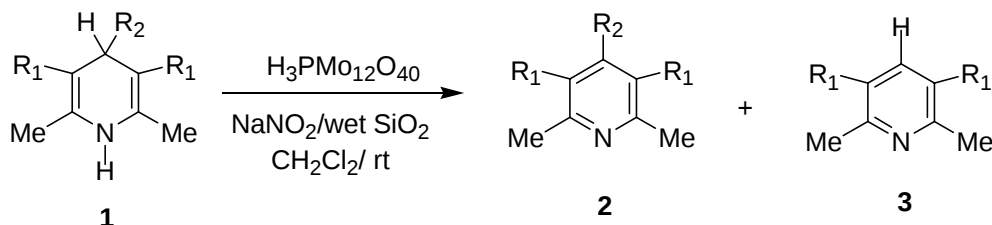
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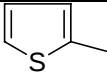
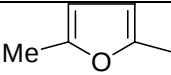
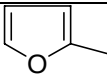
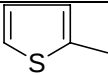
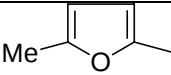
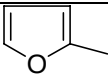
Abstract-A combination of molybdatophosphoric acid ($\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$) and sodium nitrite in the presence of wet SiO_2 was used as an effective oxidizing agent for the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives under mild and heterogeneous conditions in excellent yields.

Acids are widely used as catalysts in industry for producing more than 1×10^8 mt/year of products. In recent years, the use of solid acids as a catalyst have received considerable attention in organic reactions for following advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal. Also, wastes and by-products can be minimized or avoided by developing cleaner synthesis routes. On the other hand, any reduction in the amount of liquid acid needed and/ or any simplification in handling procedures is required for risk reduction, economic advantage and environment protection.¹

4-Substituted Hantzsch dihydropyridines (**1**) are analogues of NADH coenzymes and an important class of drugs.² Although a variety of reagents is capable of effecting these oxidations,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 caution.³

In this article, we would like to report a simple, cheap and convenient method for effective conversion of 1,4-dihydropyridine (**1**) with molybdatophosphoric acid ($\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$) into their corresponding pyridine derivatives (**2** or **3**) under mild and heterogeneous conditions *via in situ* generation of HNO_3 (Scheme 1).



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 ₆ H ₃ -	q	COOEt	Me
b	COOEt	Me	j	COOEt		r	COOEt	Ph
c	COOEt	Et	k	COOEt		s	COOEt	4-MeO-C ₆ H ₄ -
d	COOEt	Ph	l	COOEt		t	COMe	2-MeO-C ₆ H ₄ -
e	COOEt	4-Br-C ₆ H ₄ -	m	COOEt	i-Pr	u	COMe	2,5-(MeO) ₂ -C ₆ H ₃ -
f	COOEt	2-NO ₂ -C ₆ H ₄ -	n	COOEt	2-Py	v	COMe	
g	COOEt	3-NO ₂ -C ₆ H ₄ -	o	COOEt	4-Py	w	COMe	
h	COOEt	2-MeO-C ₆ H ₄ -	p	COMe	H	x	COMe	

Scheme 1

Different type of dihydropyridines (**1**) were subjected to oxidation in the presence of molybdatophosphoric acid (**I**), NaNO_2 (**II**), and wet SiO_2 (50% w/w) in dichloromethane (Scheme 1). The oxidation reactions were performed under mild and heterogeneous conditions at room temperature 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.^{3,8-10} However, aryl substituted 1,4-dihydropyridines (Table 1, Entries 4-12, 14, 15, 18-24) furnished the corresponding pyridine derivatives. The oxidation reactions proceed very slowly 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 HNO_3 .⁹ It also eases the reaction work-up.

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 amino group in 1,4-dihydropyridines.⁹

Table 1. Oxidation of 1,4-dihydropyridines (**1**) to their corresponding pyridine derivatives (**2** or **3**) with a combination of $\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$ (**I**), NaNO_2 (**II**) and wet SiO_2 (50% w/w) in dichloromethane at room temperature.

Entry	Substrate	Product	Reagent/Substrate (mmol) ^A		Time (min)	Yield ^B %
			I	II		
1	1a	3a	0.3	1.5	7	96
2	1b	2b	0.6	3	10	94
3	1c	2c	0.6	3	7	93
4	1d	2d	0.9	4.5	8	91
5	1e	2e	0.8	4	50	90
6	1f	2f	1.1	5.5	20	91
7	1g	2g	1.1	5.5	17	92
8	1h	2h	0.6	3	20	95
9	1i	2i	0.6	3	40	94
10	1j	2j	0.9	4.5	25	94
11	1k	2k	1.1	5.5	40	90
12	1l	2l	1.1	5.5	25	91
13	1m	3m	0.6	3	10	90
14	1n	2n	3.4	17	40	93
15	1o	2o	3.4	17	50	92
16	1p	2p	0.3	1.5	12	95
17	1q	2q	0.6	3	10	95
18	1r	2r	0.9	4.5	10	94
19	1s	2s	0.6	3	20	93
20	1t	2t	0.6	3	20	94
21	1u	2u	0.6	3	20	94
22	1v	2v	0.9	4.5	20	90
23	1w	2w	1.1	5.5	45	90
24	1x	2x	1.1	5.5	15	91

^AWet SiO_2 : substrate (0.5 g : 1 mmol), **II** refer to mmol of NaNO_2 and **I** refer to gram of $\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$. ^BIsolated yields.

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.

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, ^1H NMR), TLC and physical data with those reported in the literature.

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

A suspension of sodium nitrite, molybdatophosphoric acid [the gram ratio of $\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$ (**I**) and the molar ratio of sodium nitrite to the substrate **1** was optimized, Table 1], compound (**1**) (1 mmol) and wet SiO_2 (0.5 g, 50% w/w) in dichloromethane (8 mL) was stirred vigorously at rt. 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) and saturated sodium bicarbonate (20 mL). The resulting dichloromethane solution was separated and dried over anhydrous Na_2SO_4 . Evaporation of the solvent resulted in a highly pure product.

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