TUNGSTATE SULFURIC ACID/ $KMnO_4$ AS A NOVEL HETEROGENEOUS SYSTEM FOR THE RAPID AROMATIZATION OF HANTZSCH 1, 4-DIHYDROPYRIDINES UNDER MILD CONDITIONS

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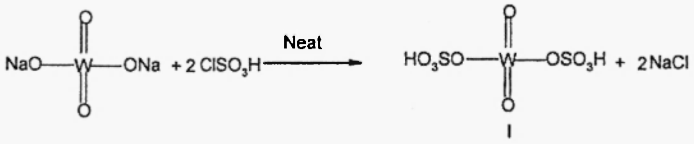
Abstract: Neat chlorosulfonic acid reacts with anhydrous sodium tungstate to give tungstate sulfuric acid (TSA) as a new two basic inorganic solid acid in which two sulfuric acid connect to tungstate moiety via covalent bond. Hantzsch 1, 4-dihydro pyridines (1, 4-DHP) were aromatized efficiently to their corresponding pyridine derivatives by heterogeneous (wet TSA)/$KMnO_4$ system in dichloromethane under mild conditions in excellent yields.

Introduction

Today, heterogenation of chemical systems is active field in industrial and laboratorial chemistry because of simplification in handling procedures, reduction of corrosion, green chemistry point of view, avoidance of by-products, easy and clean reaction and simple work-up. Based on wide application of acids as reagent or catalyst in organic chemistry (for producing more than 1×10^8 mt/year of products) introduction of new inorganic solid acids is required in this direction. Recently silica sulfuric acid (1) and Nafion-H® (2) have been used for a wide variety of reactions such as production of disulfides from thiols, oxidation of 1, 4-dihydropyridines (3), N-nitrosation of secondary amines (2), deprotection of acetals (4), oxidation of alcohols (5) and rearrangement chemistry (2). In continuation of above and our studies (6) on the application of inorganic solid acid, *we were interested to design a new inorganic solid acid that combine both protic and Lewis acid moieties.* Therefore, we synthesized TSA **I** by reaction of anhydrous sodium tungstate with chlorosulfonic acid (1:2 mole ratios). The reaction is performed easy, clean and without any work-up (Scheme-1).



Scheme-1

It has been recognized Hantzsch 1, 4-DHP act as vital drugs in the treatment of angina and hypertension. Some of these compounds such as Amlodipine, Felodipine, Isradipine, Lacidipine, Nicardipine and Nimodipine are commercially available. Therapeutic success of these compounds is related to their efficiency to bind to calcium channels and consequently to decrease the passage of the transmembrance calcium current for the treatment of cardiovascular diseases (7-8). In addition to biological application of 1, 4-DHP, in organic synthesis these compounds are used for preparation of pyridine derivatives. Various reagents and methods have been introduced for this purpose, such as ferric or cupric nitrates on a solid support (clayfen or claycop), ceric ammonium nitrate, clay-supported cupric nitrate accompanied by ultrasound-promotion, manganese dioxide or DDQ, nitric oxide, bismuth nitrate pentahydrate, PCC, tetrakis-pyridine cobalt(II) dichromate (TPCD), nicotinium dichromate, S-nitrosoglutathion, N_2O_4 complex of 18-crown-6, diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidizing agents, $KMnO_4$, CrO_3, HNO_3, HNO_2, *tert*-butylhydroperoxide, silica gel supported ferric nitrate (silfen), N_2O_3, photochemical oxidation, inorganic acidic salts and sodium nitrite or nitrate (3).

In this work we wish to report simple, clean and convenient method for the effective oxidation of 1,4-DHP(**1**) with TSA (**I**) to pyridine derivatives (**2,3**) under mild and heterogeneous conditions via complexation between nitrogen moiety of 1,4-DHP (**1**) and MnO_4^-.

Experimental

General: Chemicals were purchased from Merck, Fluka, and Aldrich chemical companies. The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with those in literature (3). All 1, 4-DHP (**1**) were synthesized by the reported procedure (3-10). IR spectra were recorded on FT-IR Jasco- 680 and the 1H- NMR spectra were obtained on a Brucker-instrument 300 MHz model.

Preparation of Tungstate Sulfuric Acid (I)

To a 0.2 mol chlorosulfonic acid (23.304 g, 13.31 mL) in 250 mL round button flask equipped with ice-bath 0.1mol (29.38 g) anhydrous sodium tungstate was added gradually. After the completion of addition, the mixture was shaken for 1 h. A yellowish-with solid (TSA) of 40 g was obtained.

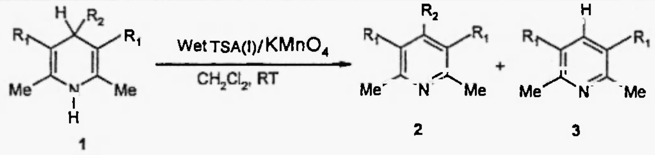
Aromatization of 1, 4-DHP (1h) to Corresponding Pyridine Derivative (2h): A Typical Procedure

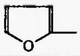
To a solution of 1mmol 1, 4-DHP **1h** (0.359 g) in 8 mL dichloromethane, 4 mmol wet (50 %) TSA **I** (0.42 g), 2 mmol $KMnO_4$ (0.316 g) were added. The heterogeneous reaction mixture was stirred at room temperature. The reaction completed after 10 minutes as monitored by TLC (n-hexane: ethylacetate 7:3). The reaction mixture was filtered and washed with 4 mL dichloromethane. Then anhydrous Na_2SO_4 was added to the filtrate and was filtered after 10 min. Dichloromethane removed by water bath (40-50°C) and simple distillation. The yield was 0.336 g, (94%) of pyridines derivative **2h** (3).

Results and Discussions

A variety of 1, 4-DHP **1** were subjected to the oxidation reaction in the presence of wet TSA I/$KMnO_4$ in dichloromethane (Table 1). The oxidation reactions were done under mild and heterogeneous conditions at room temperature with excellent yields (Table 2).

Table-1: 1, 4-DHP **1** and their corresponding pyridine derivatives **2** or **3**.



1,2, 3	R_1	R_2	1,2,3	R_1	R_2
a	COOEt	H	i	COOEt	4-CH_3O-C_6H_4-
b	COOEt	Me	j	COOEt	4-Cl-C_6H_4-
c	COOEt	Et	k	COOEt	
d	COOEt	Ph	l	COOEt	2-Br-C_6H_4-
e	COOEt	CH_3-CH-CH_3	m	$COCH_3$	H
f	COOEt	t-Bu	n	$COCH_3$	Me
g	COOEt	3-NO_2-C_6H_4-	o	$COCH_3$	Ph
h	COOEt	2-CH_3O-C_6H_4-			

It was observed that the oxidation of 1, 4-DHP **1** (Entry 5, 6) bearing alkyl substituent (alkyl moieties may be responsible for generating stable carbocations) at the 4-position gives only dealkylated pyridine derivative **3**. This is in agreement with the observation made by others employing different oxidative conditions (3, 8, 10). However, aryl substituted 1, 4-DHP **1** (Entries 4, 7-12 and 15) furnished the corresponding pyridine derivatives **2** (Table 2).

Table-2 : Oxidation of 1, 4-dihydropyridines (**1**) to their corresponding pyridine derivatives (**2** or **3**) with a combination of wet TSA (**I**) and $KMnO_4$ in dichloromethane at room temperature.

	Substrate	Product[a]	Time (Min)	Yield [b,c] (%)
1	1a	3a	7	97
2	1b	2b	40	94
3	1c	2c	25	95
4	1d	2d	25	93
5	1e	3e	15	94
6	If	3f	10	95
7	1g	2g	10	92
8	1h	2h	10	94
9	1i	2i	30	92
10	1j	2j	15	94
11	1k	2k	10	92
12	11	21	7	94
13	1m	2m	15	90
14	1n	2n	15	92
15	1o	2o	20	90

[a] Identified by comparison of physical and spectral data with authentic samples.[3]
[b] Isolated yields. [c] 4mmol wet TSA**I**: 2mmol $KMnO_4$: 1mmol substrate

It was interesting in the case of 1, 4-DHP (**1**) (Entries 1-12) bearing susceptible substituent (CO_2Et) to acidic media, hydrolysis of this functional group did not occurred. Therefore, this system behaves chemoselectively and only the nitrogen site is subjected to the oxidant.

This present oxidative aromatization reaction can be readily performed by placing of wet TSA (**I**), $KMnO_4$, 1, 4-DHP (**1**) and CH_2Cl_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 2.

In comparison to previous recently reports (3), our reaction system have some advantages. For example in those reports, wet SiO_2 is necessary but in our condition existence of wet SiO_2 is not need and a little H_2O is enough for effective progress of reaction while addition of wet SiO_2 led to longer reaction times. This reduces variety of reagents that is one of the advantages. Also in those reports, oxidant/ inorganic acid ratios were reported 5-10/1 but this ratio in our work is 1/2 that means cheapness and mild conditions. On the other hand, yield/time ratios in our report are higher than them.

In conclusion, we think TSA (**I**) is a good solid acid in the reaction in which proton is need as catalyst or reagent due to efficiency, easy production, insolubility to all organic solvents, simple for handling , convenient work–up of products, cheap and available , clean reactions , short times and high yields of reactions. In this paper we reported a convenient, efficient and practical method for oxidative aromatization of 1, 4-DHP (**1**) to pyridine derivatives (**2, 3**). Structural investigation of TSA (**I**) and similar solid acids, other application of them in various organic reactions are current researches in our laboratory.

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