Oxidation of Hantzsch 1,4-Dihydropyridines Using Supported Nitric Acid on Silica Gel and Poly Vinyl Pyrrolidone (PVP) under Mild and Heterogeneous Conditions

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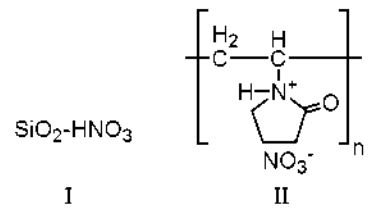
Nitric acid is an important constituent of acid precipitation.[1] It is an extremely important chemical used in the manufacture of fertilizers, explosives and widely used in the functional group transformations in organic reactions.[2-4]

In the last few years, supported reagents [5-8] have become increasingly used in organic synthesis, mainly because the reactions are carried out under mild conditions and the organic products are easily isolated.

1,4-Dihydropyridine (DHP) scaffold represents the heterocyclic unit of remarkable pharmacological efficiency.[9] Hantzsch 1,4-dihydropyridines are an important class of drugs for the treatment of cardiovascular diseases such as hypertension and angina pectoris.[10-12] They process neuroprotective, platet anti-aggregration, and antidiabetic activities.[13] The oxidation of Hantzsch 1,4-dihydropyridines, a class of model compounds of NADH coenzyme,[14,15] has attracted continuing interest of organic chemists over the years.[16] In recent years, it was found that drugs such as nifedipine and niguldipine undergo redox processes due to the catalysis of cytochrome P-450 in the liver during their metabolism.[17] Although the several reports on the oxidation of this compounds has been reported in the recent years,[18-28] most of the reported oxidation procedures require use of strong and toxic oxidants, harsh conditions, long reaction times, necessity of excess reagent, formation of by-products, laborious work-up, and poor yields of the target products. Also there are some reports on the aromatization of 1,4-dihydropyridines by dilute nitric acid[29,30] and metal nitrates,[31-33] which produce *in situ* HNO_3, but unfortunately these procedures suffer from some drawbacks, too.

Recently we have reported[34] a convenient procedure for the oxidation of sulfides to sulfoxides using supported nitric acid on silica gel and poly vinyl pyrrolidone (PVP), (Figure 1) in the presence of bromide ion as a catalyst. To investigate the scope and limitation of these new supported reagents we decided to study oxidizing ability of these reagents for the aromatization of Hantzsch 1,4-dihydropyridine derivatives.



I II

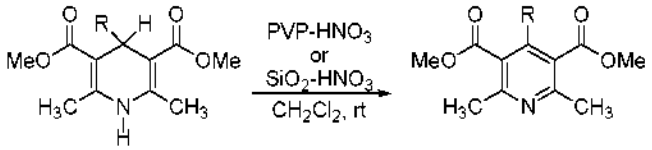
Figure 1. Supported nitric acid on silica gel **I**; supported nitric acid on poly vinyl pyrrolidone **II**.

Initially a series of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates were prepared *via* one-pot three-component condensation of an aliphatic or aromatic aldehyde, methyl acetoacetate, and NH_4OAc under neat conditions according to our recently reported work,[35] and they were used to investigate their conversion to pyridines.

Herein, we report a simple, efficient and heterogeneous procedure for the aromatization of 1,4-dihydropyridine derivatives using SiO_2-HNO_3 or PVP-HNO_3 in short reaction time at room temperature.

Therefore a variety of dimethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives were subjected to aromatization *via* combination of SiO_2-HNO_3 or PVP-HNO_3 in dichloromethane at room temperature with good to excellent yields (Scheme 1 and Table 1).

Aromatization of 1,4-dihydropyridines to the corresponding pyridines was carried out under completely heterogeneous conditions in dichloromethane at room temperature. The aromatization procedure is very simple and the products are easily isolated from the reaction media by simple filtration and evaporation of CH_2Cl_2. As is evident from Table 1, oxidation reaction proceeds more rapidly with SiO_2-HNO_3 than PVP-HNO_3. It is interesting to note that no side reaction such as nitration of 1,4-dihydropyridines including activate



1 **2**

1, 2	R	1, 2	R
a	CH_3-	**f**	4-F-C_6H_4-
b	$CH_3(CH_2)_5$-	**g**	4-NO_2-C_6H_4-
c	C_6H_5-	**h**	4-OMe-C_6H_4-
d	4-Br-C_6H_4-	**i**	3,4-OMe-C_6H_3-
e	4-Cl-C_6H_4-		

Scheme 1

Table 1. Oxidation of 1,4-dihydropyridines **1** to the corresponding pyridines **2** with SiO_2-HNO_3 **I** or PVP-HNO_3 **II** in dichloromethane at room temperature

Entry	Substrate	Product	Substrate/Reagents[a]		Time (Min)	Yield (%)[b]
			I	II		
1	**1a**	**2a**	0.15	---	34	99
2	**1a**	**2a**	---	0.15	42	99
3	**1b**	**2b**	0.2	---	11	95
4	**1b**	**2b**	---	0.15	33	99
5	**1c**	**2c**	0.15	---	44	99
6	**1c**	**2c**	---	0.15	47	97
7	**1d**	**2d**	0.15	---	4	96
8	**1d**	**2d**	---	0.15	9	94
9	**1e**	**2e**	0.15	---	6	98
10	**1e**	**2e**	---	0.15	14	96
11	**1f**	**2f**	0.15	---	3	93
12	**1f**	**2f**	---	0.15	15	95
13	**1g**	**2g**	0.25	---	45	92
14	**1g**	**2g**	---	0.15	21	98
15	**1h**	**2h**	0.15	---	4	99
16	**1h**	**2h**	---	0.15	3	97
17	**1i**	**2i**	0.15	---	10	97
18	**1i**	**2i**	---	0.15	9	96

[a]I and II refer to grams of used SiO_2-HNO_3 and PVP-HNO_3, respectively, per 1 mmol of substrates; [b]Isolated yield; All products were identified by comparison with authentic samples (mp, IR, ^1H or ^{13}C NMR).

aromatic moiety was observed in this investigation (entries 15-18, Table 1, Scheme 2).

In order to show the efficiency of the described system we compared our obtained results for the aromatization of 2,6-dimethyl-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate with the best of the well-known data from the literature as shown in the Table 2.

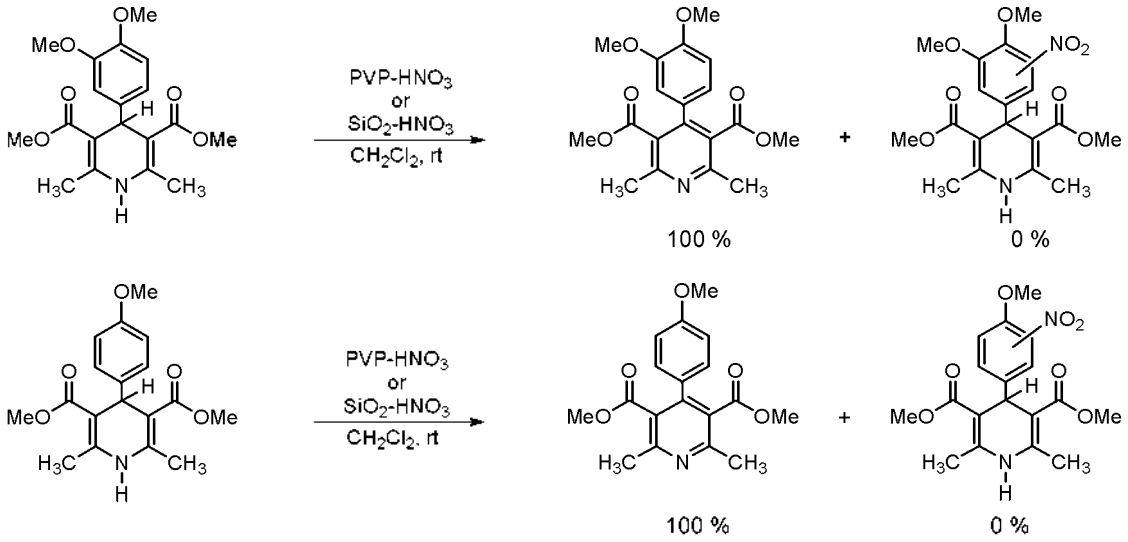
In summary in this communication we have introduced another ability of SiO_2-HNO_3 and PVP-HNO_3 as efficient oxidizing agents for the oxidation of 1,4-dihydropyridines under mild and heterogeneous conditions. Also the cheapness and availability of the reagents, easy and clean work-up and high yields make this method attractive for chemists.

Experimental Section

General. Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The oxidation products were characterized by comparison of their spectral (IR, ^1H NMR, or ^{13}C NMR) and physical data with authentic samples.

Preparation of SiO_2-HNO_3. In a 50-mL round-bottomed flask, 4.5 g of HNO_3 (65%, 3.2 mL) and 2.0 g of silica gel was stirred for 10 min, and a white solid (SiO_2-HNO_3) was obtained.

Preparation of PVP-HNO_3. In a 50-mL round-bottomed flask, 4.5 g of HNO_3 (65%, 3.2 mL) and 4.8 g of poly vinyl



Scheme 2

Table 2. Efficiency comparison of various oxidizing systems for the oxidation of 2,6-dimethyl-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Entry	Conditions	Time (Min)	Yield (%)[a]	Reference
1	SiO_2-HNO_3 (rt)	6	98	This work
2	PVP-HNO_3 (rt)	14	96	This work
3	UHP/I_2 (rt)	90	96	22
4	DMSO/O_2 (70 °C)	270	91	36
5	*t*-BuOOH/Fe (III) phthalocyanine chloride (rt)	20	99	37
6	$VOCl_3$ (rt)	60	92	38

[a]Isolated yield.

pyrrolidone (PVP), (4 g, 3.24 mmol) was stirred for 10 min, and a white solid (PVP- HNO_3) was obtained.

Aromatization of dimethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate with PVP-HNO_3 as a typical procedure. To a solution of compound **1e** (0.335 g, 1.0 mmol) in CH_2Cl_2 (5 mL), PVP-HNO_3 (0.15 g) was added. Reaction mixture was stirred at room temperature for 14 min (the reaction progress was monitored by TLC) and then filtered. Anhydrous Na_2SO_4 (1.5 g) was added to the filtrate and filtered off after 20 min. The residue was washed with CH_2Cl_2 (4×5 mL). Finally solvent was removed and product **2e** was obtained in 96% yield (0.320 g). Pale yellow solid; mp 140-142 °C; ^{1}H NMR (400 MHz, DMSO): δ 7.51-7.54 (d, 2H, J = 11.30 Hz), 7.20-7.17 (d, 2H, J = 11.29 Hz), 3.55 (s, 6H), 2.49 (s, 6H); ^{13}C NMR (100 MHz, DMSO): δ 167.8, 155.6, 144.6, 135.0, 134.2, 129.8, 129.1, 126.6, 52.9, 23.0; IR (KBr): $\bar{\nu}$ 1731, 1597, 1573, 1557, 1492, 1434, 1374, 1240, 1211, 113, 1097, 968, 856, 832, 804, 761 cm^{-1}.

Spectral data for selected products. 2a) Pale yellow solid; mp 78-80 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.93 (s, 6H), 2.51 (s, 6H), 2.25 (s, 3H); IR (KBr): $\bar{\nu}$ 2853, 1731, 1569, 1457, 1377, 1222, 1103 cm^{-1}.

2c) Pale yellow solid; mp 123-126 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.37 (m, 5H), 3.52 (s, 2OCH_3), 2.59 (s, 2CH_3); IR (KBr): 2854, 1733, 1590, 1456, 1377, 1243, 1213, 1037 cm^{-1}.

2d) Pale yellow solid; mp 136-140 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.47 (d, 2H), 7.16 (d, 2H), 3.57 (s, 2OCH_3), 2.59 (s, 2CH_3); IR (KBr): $\bar{\nu}$ 2917, 1732, 1595, 1462, 1377, 1242, 1212, 1038 cm^{-1}.

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