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Poly-(4-vinylpyridinium nitrate) and silica sulfuric acid (SiO_2-OSO_3H): an efficient and metal-free oxidizing media for the oxidation of 1,4-dihydropyridine and urazole derivatives

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An efficient and metal-free oxidative aromatization of alkyl or aryl-substituted derivatives of 1,4-dihydropyridines and urazoles has been studied using poly-(4-vinylpyridinium nitrate) in the presence of silica sulfuric acid (SiO_2-OSO_3H). The reaction was carried out in dichloromethane at room temperature and the products were isolated in good to excellent yields.

Keywords*:* 1,4-Dihydropyridines, Oxidation, Urazole, Poly-(4-vinylpyridinium nitrate), Triazolinedione

INTRODUCTION

Nitrogen-heterocyclic compounds (NHCs) are produced by chemical industry for a variety of applications, including pharmaceuticals, cosmetics, pesticides, disinfectants, agrochemicals, dyestuffs, antifreeze, corrosion inhibitor, coal-tar wastes and creosote wood preservation [1].

In particular, pyridine and urazol derivatives are used as reagents in manufacture and industry [2,3].

Urazole derivatives (1,2,4-triazolidine-3,5-diones) are very interesting five-membered heterocyclic compounds, which at position 4 can provide a wide variety of aliphatic as well as aromatic constituents. Although a variety of oxidants such as iodobenzenediacetate, N_2O_4, periodic acid, *tert*-butyl hypochlorite or potassium dichromate, have been used for the oxidations of urazoles to triazolinediones, there are harsh conditions involved precluded oxidation of urazoles in the presence of other sensitive groups [4-8], because these compounds are very sensitive to the oxidizing agents and reaction conditions [9, 10]. In addition, most of the reported reagents produce by-products which are difficult to be removed from, the sensitive triazolinedione.

Also 1,4-dihydropyridines (1,4-DHPs) belong to a class of nitrogen containing heterocycles having a six-membered ring. Much attention has been devoted to explore their pharmacological activities [11]. The Oxidation (aromatization) of 1,4-dihydropyridines into the corresponding pyridines is generally the key step in their numerous biological reactions [12-14]. Therefore, oxidation of 1,4-DHPs have attracted continuing interests of organic and medicinal chemists and a plethora of protocols have been developed [15-20]. Numerous reagents or reagent systems have been recommended for this purpose, such as isoxazolones [21], $Fe(ClO_4)_3$/HOAc [22], lead (IV) tetraacetate [23], $FeCl_3$/$KMnO_4$ [24], triazolinediones [25]. This transformation has attracted a great deal of attentions for the discovery of mild and general.

However, some of these procedures, which have been used for the oxidation of 1,4-dihydropyridines and urazoles have some disadvantages such as long reaction times, low yields of products, the requirement for severe conditions and the use of strong or toxic oxidants.

The use of heterogeneous reagents in different areas of the organic synthesis has now reached significant levels, not only for the possibility to perform environmentally benign synthesis, but also for the good yields frequently, accompanied by selectivity that can be achieved.

Recently, we have reported several new synthetic methods for environmentally reactions using catalytic and metal-free media for *in situ* generation of bromonium ion (Br^+) and nitronium ion (NO_2^+) [26-28]. During these studies, it was found that nitronium ion (NO_2^+) is an excellent oxidant for the oxidation of organic compounds [29-32].

EXPERIMENTAL

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

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Oxidation of 4-cyclohexylurazole using poly-(4-vinylpyridiniumnitrate) of and silica sulfuric acid and silica sulfuric acid

In a 25 ml round bottom flask, to a solution of **2a** (0.183 g, 1.0 mmol) in CH_2Cl_2 (10 mL), silica sulfuric acid (0.1 g), wet-SiO_2 (0.2 g) and poly-(4-vinylpyridinium nitrate) (0.270 g) was added. The resulting reaction mixture was stirred magnetically at room temperature for 90 min (monitored by TLC). After completion of reaction, the solvent was filtered. Anhydrous Na_2SO_4 (1.5 g) was added to the filtrate. The residue was washed with CH_2Cl_2 (20 ml). Finally, CH_2Cl_2 was evaporated and 4-cyclohexyl-4H-1,2,4-triazole-3,5-dionewas obtained in 98% yield.

Oxidation dimethyl 4-(phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

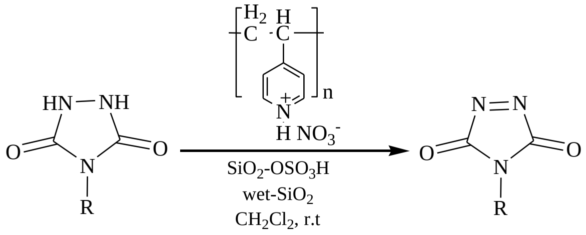
In a typical procedure, to a mixture **4a** (0.329 g, 1.0 mmol) in CH_2Cl_2 (10 mL), silica sulfuric acid (0.2 g) and poly-(4-vinylpyridinium nitrate) (0.608 g) was added. The resulting reaction mixture was stirred magnetically at room temperature for 100 min (monitored by TLC). After completion of reaction, the solvent was filtered. Anhydrous Na_2SO_4 (1.5 g) was added to the filtrate. The residue was washed with CH_2Cl_2 (20 ml). Finally, CH_2Cl_2 was evaporated and pale yellow solid, diethyl 2,6-dimethy-l-4-phenylpyridine-3,5-dicarboxylate was obtained in 94% yield.

RESULTS AND DISCUSSION

Consequently, we were interested to apply poly-(4-vinylpyridinium nitrate) in the presence of silica sulfuric acid (SiO_2-OSO_3H) as a new source of nitronioum ion (NO_2^+) for the oxidation of urazole and 1,4-dihydropyridines. A white powder of poly-(4-vinylpyridinium nitrate) reagent is obtained by the reaction of poly-(4-vinylpyridine) with nitric acid. This reagent is ideal for 'green chemistry', because is not toxic and doesn't make environmental pollution.

Initially, oxidation of different types of 4-substituted urazole **1** with poly (4-vinylpyridinium nitrate), silica sulfuric acid and wet SiO_2 in dichloromethane at room temperature have been examined. This reaction gave the corresponding 4-substituted-1,2,4-triazolidine-3,5-diones **2** with excellent yields. General form of this approach has been demonstrated by the oxidation of a wide variety of 4- alkyl or aryl -1,2,4-triazolidine-3,5-diones shown in Table 1 and Scheme 1.

As mentioned above, the oxidation reactions are heterogeneous because urazoles are insoluble in dichloromethane. Therefore, the oxidation reaction has been performed at the surface of wet SiO_2 and appropriate amount of poly-(4-vinylpyridinium nitrate) in the presence of silica sulfuric acid (SiO_2-OSO_3H). Then, the oxidation products migrate to the liquid phase (CH_2Cl_2) immediately. Pure product can be extracted by simple filtration and dichloromethane was removed by evaporation.



1

2

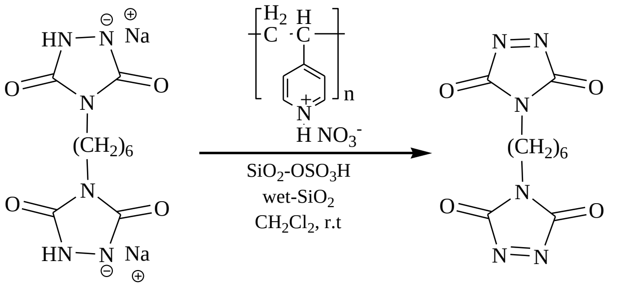
Scheme 1

Also the oxidation reaction has been performed for bis-triazolinedione **3** under mild and completely heterogeneous conditions at room temperature with excellent yield (91%), (Scheme 2). The reaction was readily promoted by stirring starting materials in CH_2Cl_2 at room temperature for 6 hours, and the bis-triazolinedione **4** was isolated by simple filtration and evaporation of the solvent.

Table 1. Oxidation of 4-substituted urazole 1a-k to 4-substituted-1,2,4-triazolidine-3,5-diones 2a-k with poly(4-vinylpyridinium nitrate), silica sulfuric acid and wet SiO_2 (50 %, *w/w*)[a]

Entry	1	R	2	Time (min)	Yield (%)[b]
1	a	C_6H_5	a	90	98
2	b	C_6H_{11}	b	90	98
3	c	$(CH_3)_3C$	d	104	91
4	d	$CH_3(CH_2)_3$	e	100	98
5	e	4-$NH_2C_6H_4$	f	5h	-
6	f	3,4-$(Cl)_2C_6H_3$	g	120	90
7	g	CH_3CH_2	h	90	47
8	h	4-$NO_2C_6H_4$	i	118	98
9	i	4-ClC_6H_4	j	98	87
10	j	$CH_3CH_2CH_2$	k	75	90
11	k	1-naphtyl	l	3h	91

[a] Molar ratio of the reagents: urazole / poly-(4-vinylpyridinium nitrate) / silica sulfuric acid / wet SiO_2 for entries 1-12 (1 mmol / 2 mmol / 0.1 g/ 0.2 g); [b] Isolated yield.



3 4

Scheme 2

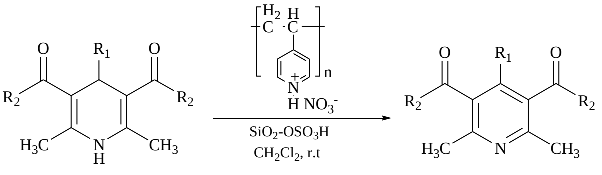
In order to investigate and develop the scope and limitation of this oxidizing media we decided to examine the oxidation of 1,4-dihydropyrines by described procedure (Scheme 3, Table 2).

Several 1,4-dihydropyridines are oxidized to corresponding pyridines by poly-(4-vinylpyridinium nitrate) in the presence of silica sulfuric acid (SiO_2-OSO_3H). Oxidation reactions were performed under mild and completely heterogeneous conditions at room temperature. After reaction completion, product is extracted by simple filtration and dichloromethane was removed by evaporation.

As shown in Table 2, both electron donating and electron withdrawing substituents on the precursors are afforded the corresponding pyridines from good to excellent yields.

To show the efficiency of the described system in comparison with previously reported procedures in the literature, we compared our obtained results for the oxidation of4-phenyl-1,2,4-triazolidine-3,5-dione to corresponding triazolinedione with the best of the well-known data from the literature as shown in (Table 3).

Also, we compared our method for the oxidation of diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (as a typical example) to corresponding pyridine with different catalyst (Table 4).



4 5

Scheme 3

Table 2. Fxidation of 1,4-dihydropyridines 4a–p to pyridines 5a–p using poly(4-vinylpyridinium nitrate) in the presence of silica sulfuric acid (SiO_2-OSO_3H)[a]

Entry	4	R1	R2	5	Time (min)	Yield (%)[b]	mp(°C)
1	a	C_6H_5	OC_2H_5	a	100	94	83
2	b	CH_3	OC_2H_5	b	30	90	79-80
3	c	4-OMeC_6H_4	OC_2H_5	c	140	90	68-72
4	d	3,4-$(OMe)_2C_6H_3$	OC_2H_5	d	103	93	72-80
5	e	4-FC_6H_4	OC_2H_5	e	195	90	98-101
6	f	4-ClC_6H_4	OC_2H_5	f	7:35 h	95	68-82
7	g	4-BrC_6H_4	OC_2H_5	g	8:15 h	90	95-98
8	h	C6H5	OCH3	h	40	98	137-145
9	i	(CH2)5CH3	OCH3	i	90	79	68
10	j	CH3	OCH3	j	135	97	108-110
11	k	4-OMeC6H4	OCH3	k	155	98	110
12	l	3,4-$(OMe)_2C_6H_3$	OCH_3	l	155	98	140-144
13	m	4-FC_6H_4	OCH_3	m	5:50 h	94	145-149
14	n	4-ClC_6H_4	OCH_3	n	8:10 h	95	146-149
15	o	4-BrC_6H_4	OCH_3	o	9:10 h	87	141-144
16	p	3-$NO_2C_6H_4$	OCH_3	p	35	95	-

[a] Molar ratio of the reagents: 1,4-dihydropyridines/ poly-(4-vinylpyridinium nitrate)/ silica sulfuric acid for entries 1-14 (1 mmol/ 0.608 g/ 0.2 g); and for entries 7,15 and 16 (1 mmol/ 0.676 g/ 0.2 g).[b] Isolated yield.

Table 3. Comparison of the different methods used for the oxidation of 4-phenyl-1,2,4-triazolidine-3,5-dione to corresponding triazolinedione with different catalyst

Entry	Catalyst	Time (Min)	Yield (%)[a]	Reference
1	Poly-(4-vinylpyridinium nitrate)	90	98	This work
2	H_5IO_6, $NaNO_2$ and Wet SiO_2 (50% w/w)	60	80	6
3	$K_2Cr_2O_7/AlCl_3$	3	95	8
4	*N,N,N',N'*-Tetrabromobenzene-1,3-disulfonylamide	120	83	10
5	$NaNO_2$, $C_2H_2O_4 .2H_2O$	60	80	33

[a]Isolated yield.

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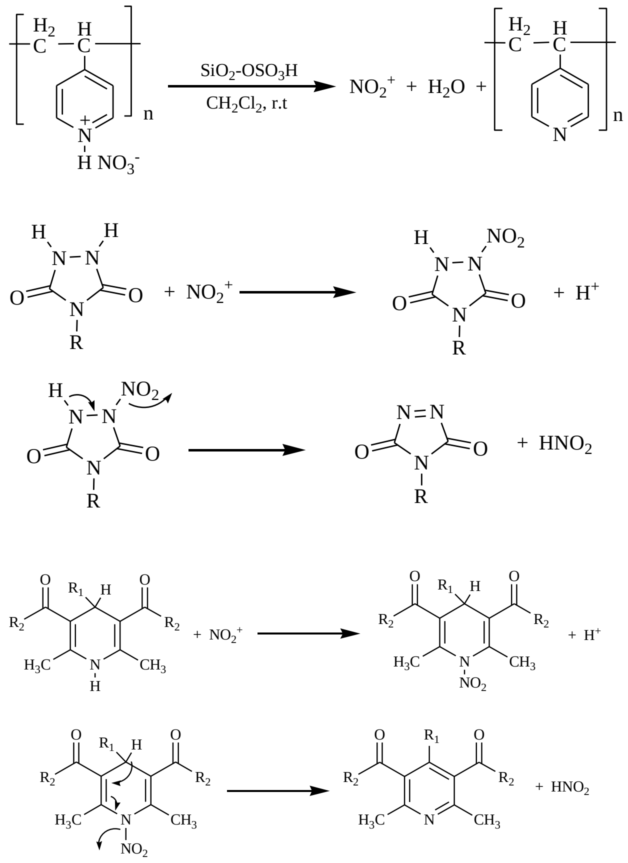
phenylpyridine-3,5-dicarboxylate to corresponding pyridine with different catalyst

Entry	Catalyst	Time (Min)	Yield (%)[a]	Reference
1	Poly-(4-vinylpyridinium nitrate)	100	94	This work
2	$CO(NH_2)_2$ / H_2O_2	12h	89	11
3	$PhCH_2Ph_3PHSO_5$ / $BiCl_3$	120	89	15
4	*N*-hydroxyphthalimide, O_2	4h	99	21(a)
5	$Rucl_3$ / O_2	53h	55	20(a)

[a]Isolated yield.

A plausible mechanism for the transformation is shown in Scheme 4.



Scheme 4

In summary, we describe an efficient and mild protocol for the oxidation of urazoles and 1,4-dihydropyridines using poly-(4-vinylpyridinium nitrate) as new oxidizing polymer. Advantages of this method for the oxidation of organic compounds over conventional homogeneous reactions enhanced reaction rates, cleaner products, simple experimental procedures, mild reaction conditions and minimization of chemical wastes as compared to the solution phase counterparts.

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ПОЛИ-(4-ВИНИЛПИРИДИНИЕВ НИТРАТ) И СИЛИЦИЕВ ДИОКСИД-СЯРНА КИСЕЛИНА (SiO_2-OSO_3H): ЕФЕКТИВНА И БЕЗМЕТАЛНА СРЕДА ЗА ОКИСЛЕНИЕ НА 1,4-ДИХИДРОПИРИДИН И ПРОИЗВОДНИ НА УРАЗОЛА

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(Резюме)

Изследвана е ефективна и безметална окислителна ароматизация на алкил- или арил-заместени производни на 1,4-дихидропиридини и уразоли чрез използване на поли-(4-винилпиридиниев нитрат) в присъствие на силициев диоксид - сярна киселина (SiO_2-OSO_3H). Реакцията протича в дихлорометан при стайна температура и продуктите са изолирани с добри до отлични добиви.