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Research note

# A new method for the oxidation of 1, 4-dihydropyridine derivatives by guanidinium nitrate in the presence of silica sulfuric acid under mild, heterogeneous and metal-free conditions

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**KEYWORDS**

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1, 4-dihydropyridines;  
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**Abstract** In this paper, a new and convenient method is introduced for the oxidation of a variety of Hantzsch 1, 4-dihydropyridine derivatives to their corresponding pyridine compounds using guanidinium nitrate and silica sulfuric acid. The reactions were carried out in dichloromethane at room temperature and the products were isolated at high to excellent yields.

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Open access under [CC BY-NC-ND license](http://creativecommons.org/licenses/by-nc-nd/4.0/).**1. Introduction**

Since more than 100 years ago, when aryldihydropyridines were synthesized, great effort has been made to introduce a new reagent or reagent systems for the oxidation and synthesis of dihydropyridine derivatives. The oxidation of DHPs to the corresponding pyridine derivatives is the principal metabolic route in biological systems [1,2]. 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 [3]. Therefore, the oxidation of 1, 4-dihydropyridines has attracted considerable attention. Numerous reagents and catalysts, such as  $\text{SeO}_2$  [4], lead(IV) tetraacetate [5],  $\text{FeCl}_3/\text{KMnO}_4$  [6], ceric ammonium nitrate (CAN) [7], bentonite clay-supported manganese(IV) oxide [8], solid supported pyridinium chlorochromate (PCC) [9], silica gel supported ferric nitrate [10], nitric oxide,  $6\text{MnO}_2$  [11],  $\text{BaMnO}_4$  [12], catalytic aerobic oxidation by using  $\text{RuCl}_3$  [13], Pd/C [14], activated carbon [15],  $\text{Fe}(\text{ClO}_4)_3$  [16], iron(III) and copper(II) nitrates [17],  $\text{Zr}(\text{NO}_3)_4$  [18],  $\text{H}_2\text{O}_2/\text{Co}(\text{OAc})_2$  [19],  $\text{CrO}_3$  [20], Co(II)-catalyzed auto oxidation [21],  $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$

Table 1: Solvent screening for the oxidation of dimethyl 2, 6-dimethyl-4-phenyl-1, 4-dihydropyridine-3, 5-dicarboxylate to the corresponding pyridine using guanidinium nitrate and silica sulfuric acid at room temperature.<sup>a</sup>

Entry	Solvent	Time	Yield (%) <sup>b</sup>
1	$\text{CH}_2\text{CN}$	17.5 h	97
2	$\text{CH}_3\text{Cl}$	2 h	98
3	$n\text{-C}_6\text{H}_{14}$	3.5 h	72
4	$\text{CH}_3\text{COCH}_3$	24 h	– <sup>c</sup>
5	$\text{CH}_3\text{CH}_2\text{OH}$	24 h	– <sup>c</sup>
6	$\text{CH}_3\text{COOEt}$	24 h	– <sup>c</sup>
7	$\text{CH}_2\text{Cl}_2$	65 min	99

<sup>a</sup> Substrate/guanidinium nitrate/silica sulfuric acid: 1 mmol/3 mmol/0.45 g.

<sup>b</sup> Isolated yield.

<sup>c</sup> Reaction not completed.

and/or  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}/\text{SiO}_2\text{-OSO}_3\text{H}$  [22], supported nitric acid on silica gel and poly vinyl pyrrolidone [23] and  $\text{KBrO}_3/\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$  [24], have been used for this purpose. Even though we can find many articles regarding oxidation of these compounds, many efforts are still being made to introduce a new procedure for better oxidation of DHPs.

**2. Results and discussion**

In order to participate in these great challenges, I decided to develop a new convenient method for the oxidation of 1, 4-dihydropyridines to the corresponding pyridine derivatives

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Table 2: Oxidation of 1, 4-dihydropyridines 1 to the corresponding pyridines 2 using gunidinium nitrate I and silica sulfuric acid II in dichloromethane at room temperature.

Entry	Substrate	Product	Substrate/Reagents <sup>a</sup>		Time	Yield (%) <sup>b</sup>
			I	II		
1			3	0.45	235 min	99
2			3	0.45	15 min	90
3			3	0.45	30 min	94
4			3	0.45	90 min	98
5			3	0.45	60 min	93
6			3	0.45	55 min	99
7			3	0.45	450 min	98
8			3	0.45	445 min	97
9			3	0.45	25 min	92
10			3	0.45	440 min	96
11			3	0.45	20 min	99

(continued on next page)

Table 2 (continued)

Entry	Substrate	Product	Substrate/Reagents <sup>a</sup>		Time	Yield (%) <sup>b</sup>
			I	II		
12			3	0.45	560 min	99
13			3	0.45	65 min	99
14			3	0.45	125 min	98
15			3	0.45	20 min	96
16			3	0.45	20 min	94
17			3	–	24 h	No reaction

<sup>a</sup> I refers to mmol of guanidinium nitrate and II refers to grams of silica sulfuric acid.

<sup>b</sup> Isolated yield; all products were identified by comparison with authentic samples (mp, IR, <sup>1</sup>H and <sup>13</sup>C NMR).



Scheme 1: Aromatization of 1,4-dihydropyridines.

using guanidinium nitrate and silica sulfuric acid in a proper solvent under mild and heterogeneous conditions.

The reaction was initially tested in different solvents. From the solvent screening (Table 1), dichloromethane emerged as the most convenient (Entry 7), due to the fact that the product was isolated in an almost quantitative yield in the shortest reaction time. The other tested solvents required prolonged stirring to reach satisfactory conversion (Entries 1–3), or reaction was not completed until after 24 h (Entries 4–6).

Eventually, with optimal conditions at hand, a variety of 1,4-dihydropyridines (Scheme 1) were transformed into corresponding pyridines smoothly *via* reaction with a combination of guanidinium nitrate in the presence of silica sulfuric acid in dichloromethane at room temperature (Scheme 1). The results of this transformation are summarized in Table 2.

All oxidation reactions have been performed heterogeneously. The pure product was easily obtained by simple fil-

tration, washing by dichloromethane and evaporation of the solvent. In order to approve the role of acid in the described transformation, the effect of silica sulfuric acid on the oxidation process was investigated. It was found that the reaction did not proceed after 24 h without silica sulfuric acid (Table 2, Entry 17). Also, it is interesting to note that due to mild reaction conditions, no side reaction, such as nitration, was observed, even for activated aromatic rings, such as Entries 4, 5, 14 and 15 from Table 2.

A suggested mechanism for this transformation has been outlined in Scheme 2.

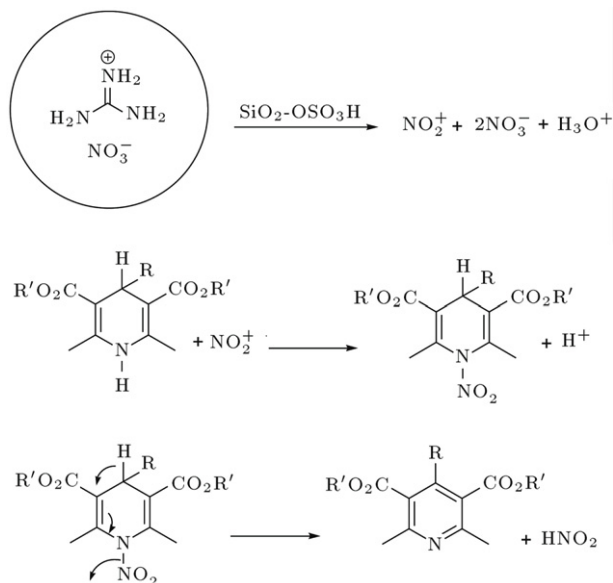
### 3. Conclusion

This procedure has the following advantages:

- Short reaction time.
- High selectivity.
- Non-toxic conditions.
- Cost effective reagents.
- Clean and easy work up of products.
- Metal free conditions.

### 4. Experimental

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The oxidation products were characterized by comparison of their spectral (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR)



Scheme 2: Mechanism of aromatization of 1, 4-dihydropyridines into pyridines.

and physical data with authentic samples. Silica sulfuric acid was prepared via the reported procedure by Zolfigol [25].

#### 4.1. General procedure for the oxidation of 1, 4-dihydropyridine to pyridine with guanidinium nitrate and silica sulfuric acid

The reaction was carried out at room temperature in a 25 mL flask equipped with a magnetic stirring bar. Guanidinium nitrate (0.367 g, 1 mmol) and silica sulfuric acid (0.45 g) were added to the 1, 4-dihydropyridine (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The progress of the reactions was monitored by TLC on silica gel GF254 plates with *n*-hexane and acetone (8:2 v/v) as eluent. After the reaction was completed, the residue was washed with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). Anhydrous Na<sub>2</sub>SO<sub>4</sub> (1 g) was added to the filtrate and filtered off after 20 min. Finally, CH<sub>2</sub>Cl<sub>2</sub> was removed and the corresponding pure pyridine was obtained.

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