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AROMATIZATION OF 1,4-DIHYDROPYRIDINES UNDER MILD AND HETEROGENEOUS CONDITIONS

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Abstract: A combination of $Mg(HSO_4)_2$ and $NaNO_2$ in the presence of wet SiO_2 was used as an effective oxidizing agent for the oxidation of dihydropyridines to their corresponding pyridine derivatives at room temperature with moderate to excellent yields.

The 4-substituted-2,6-dimethyl-3,5-pyridine dicarboxylic acid diethyl esters have anti-hypoxic and anti-ischemic activity, some of the representatives of this class have acaricidal, insecticidal, bacterial and herbicidal activity.¹ There are several method are reported for the aromatization of 1,4-dihydropyridines,¹⁻⁴ but most of them required vigorous conditions.⁴ Literature showed that nitrosonium cation releasing reagents (e. g. clayfen and silfen) are efficient for aromatization

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of 1,4-dihydropyridines.^{1,2} Therefore, we decided to develop a heterogeneous system and we have investigated a number of different reaction conditions based upon the *in situ* generation of HNO_2^5 and NO^+ by relatively strong *solid inorganic acidic salt* [Mg(HSO₄)₂, Pk_a~2] and sodium nitrite for the oxidation of 1,4-dihydropyridines. Consequently, in this article we would like to report a simple, cheap and convenient method for the effective conversion of 1,4-dihydropyridines (1) to their corresponding pyridine derivatives (2 or 3) under mild and heterogeneous conditions.

Different kinds of dihydropyridines (1) were subjected to oxidation reaction in the presence of NaNO₂, wet SiO₂ (50% w/w) and inorganic acidic salt e. g. Mg(HSO₄)₂ in dichloromethane (Scheme). The oxidation reactions were performed under mild and completely heterogeneous conditions at room temperature with moderate to excellent yields (Table).



1, 2	R	1, 2	R	1, 2 R		
a	Н	đ	2-Thienyl-	g	2-CH ₃ O-C ₆ H ₄ -	
b	Me	e	2-NO ₂ -C ₆ H ₄ -	h	2, 5-(CH ₃ O) ₂ -C ₆ H ₄ -	
c	Ph	f	3-NO ₂ -C ₆ H ₄ -	i	CH ₃ -CH-C ₆ H ₅	

It was also observed that the oxidation of 1,4-dihydropyridines (Entry 9) bearing alkyl substituents (alkyl moiety which are susceptible for generating stable carbocation) at 4-position give only dealkylated pyridine derivative (**3**). This is in agreement with the observation made by others employing different oxidative conditions.³ However aryl substituted 1,4-dihydropyridines (Entries 3-8) furnished corresponding pyridine derivatives (Table).

The present oxidation reaction can be readily carried out only by placing NaNO₂, Mg(HSO₄)₂, 1, wet SiO₂ (50% w/w) and CH₂Cl₂ as the solvent in a reaction vessel and efficiently stirring the resulting heterogeneous mixture at room temperature for 15-120 minutes and the pyridine derivatives (2 or 3) can be obtained by simple filtration and evaporation of the solvent. The results and reaction conditions are tabulated in Table.

In conclusion, practical and efficient oxidations of 1,4-dihydropyridines have been achieved by the new methodology described. The heterogeneous

Table. Oxidation of 1,4-Dihydropyridines (1) to Their Corresponding Pyridine Derivatives with a Combination of NaNO₂ (I), Mg(HSO₄)₂ (II) and Wet SiO₂ (50% w/w) in Dichloromethane at Room Temperature.

Entry	Substrate		(Reagent/Substrate) ^a I II		Time (Min)	Yield ^b (%)
1	1a	3	2	1	10	75
2	1b	2b	2	1	25	72
3	1c	2c	2	1	25	90
4	1d	2d	3	1.5	120	97
5	le	2e	4	2	15	86
6	lf	2f	4	2	15	80
7	1g	2g	2	1	15	76
8	1h	2h	. 2	1	15	81
9	1i	3	2	1	15	95

* Wet SiO,: substrate (0.2 g : 1 mmol). ^b Isolated yields.

nature, cheapness and the availability of the reagents, easy procedure and work-up make this method attractive for the large-scale operations. We believe that the present methodology would be an important addition to existing methodologies.

EXPERIMENTAL SECTION

General: Chemicals were purchased from Fluka, Merck, Riedel-dehaen AG and Aldrich chemicals companies. Yields refer to isolated products. The oxidation products were characterized by comparison of their spectral (IR, ¹H-NMR, ¹³C-NMR and TLC) and physical data with the authentic samples. All Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures.^{4b}

Oxidation of Dihydropyridine (1a) to Substituted Pyridine (2a). A Typical Procedure.

A suspension of compound **1a** (0.331 g, 1 mmol), Mg(HSO₄)₂ (0.22 g, 1 mmol), wet SiO₂ (50% w/w) (0.2 g) and NaNO₂ (0.138 g, 2 mmol) in dichloromethane (4 ml) was stirred at room temperature for 10 minutes (the progress of the reaction was monitored by TLC) and then filtered. Anhydrous Na₂SO₄ (5 g) was added to the filtrate. After 15 minutes dichloromethane (20 ml) was added to the resulting mixture and filtered. Dichloromethane was removed by water bath (40-50 °C) and simple distillation. The yield was . 0.247 g, (75%) of crystalline pale yellow solid (**2a**), mp 69-72 °C [Lit.² mp 72-73 °C]. ¹H-NMR (CDCl₃)/TMS): 1.42 (t, 6 H), 2.86 (s, 6 H), 4.36 (q, 4 H), 8.69 (s, 1 H) [Lit.^{4c}].

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