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Aromatization of 1,4-Dihydropyridines Under Mild and Heterogeneous Conditions

Mohammad Ali Zolfigol [a], Maryam Kiany-Borazjani [a], Majid M. Sadeghi [b], Iraj Mohammadpoor-Baltork [b] & Hamid Reza Memarian [b]

[a] Chemistry Department, College of Science, Bu-Ali Sina University, Hamadan, 65174, I R, Iran E-mail:

[b] Chemistry Department, College of Science, Isfahan University, Isfahan, I R, Iran

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

Mohammad Ali Zolfigol [*a], **Maryam Kiany-Borazjani**[a]
[a] Chemistry Department, College of Science, Bu-Ali Sina University, Hamadan, zip code 65174, I. R. Iran. E-Mail: Zolfi@basu.ac.ir

Majid M. Sadeghi[b], **Iraj Mohammadpoor-Baltork**[b], **Hamid Reza Memarian**[b]
[b] Chemistry Department, College of Science, Isfahan University, Isfahan, I. R. Iran.

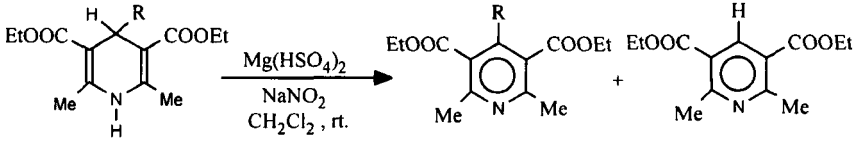
Abstract: A combination of $Mg(HSO_4)_2$ and $NaNO_2$ in the presence of wet SiO_2 was used as an effective oxidizing agent for the oxidation of dihydropyridines to their corresponding pyridine derivatives at room temperature with moderate to excellent yields.

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

* To whom correspondence should be addressed.

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* [$Mg(HSO_4)_2$, 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 $NaNO_2$, wet SiO_2 (50% *w/w*) and inorganic acidic salt e. g. $Mg(HSO_4)_2$ 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** **3**

1, 2	R	**1, 2**	R	**1, 2**	R
a	H	**d**	2-Thienyl-	**g**	2-CH_3O-C_6H_4-
b	Me	**e**	2-NO_2-C_6H_4-	**h**	2, 5-$(CH_3O)_2$-C_6H_4-
c	Ph	**f**	3-NO_2-C_6H_4-	**i**	CH_3-CH-C_6H_5

Scheme

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 $NaNO_2$, $Mg(HSO_4)_2$, **1**, wet SiO_2 (50% *w/w*) and CH_2Cl_2 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 $NaNO_2$ (I), $Mg(HSO_4)_2$ (II) and Wet SiO_2 (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	**1e**	**2e**	4	2	15	86
6	**1f**	**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

[a] Wet SiO_2: 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, ^{1}H-NMR, ^{13}C-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** (o.331 g, 1 mmol), $Mg(HSO_4)_2$ (0.22 g, 1 mmol), wet SiO_2 (50% *w/w)* (0.2 g) and $NaNO_2$ (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 Na_2SO_4 (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]. ^{1}H-NMR ($CDCl_3$)/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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