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Room Temperature Catalytic Aromatization of *Hantzsch* 1,4-Dihydropyridines by Sodium Nitrite in the Presence of Acidic Silica Gel

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Summary. Various alkyl, aryl, and heterocyclic *Hantzsch* 1,4-dihydropyridines were converted to the corresponding pyridines in excellent yields and short times using sodium nitrite in the presence of a catalytic amount of acidic silica gel at room temperature.

Keywords. *Hantzsch* 1,4-dihydropyridines; Aromatization; Sodium nitrite; Silica gel.

Introduction

Hantzsch 1,4-dihydropyridines (*DHP*s) and their derivatives are an important class of bioactive molecules in the field of drugs and pharmaceuticals, and have been extensively studied in view of the biological pertinence of these compounds to the *NAD*H redox process [1]. Aromatization of *Hantzsch DHP*s has attracted considerable attention due to the fact that *DHP*s based antihypertensive drugs (Ca^{2+} channel blockers) are oxidatively converted to pyridine derivatives by cytochrome P-450 in the liver [2]. Furthermore, the oxidation of *DHP*s provides an easy access to pyridine derivatives. Therefore, oxidative aromatization of *DHP*s has attracted continuing interest of organic and medicinal chemists and a plethora of protocols has been developed [2–11]. Early works mostly used strong oxidants, such as HNO_3 [2], $KMnO_4$ [3], or *CAN* [4]. Recently, attention has been paid to more efficient and environmentally benign methods, such as electrochemical oxidation [5] and catalytic aerobic oxidation using $RuCl_3$ [6], Pd/C [7], activated carbon [8], $Fe(ClO_4)_3$ [9], or *N*-hydroxyphthalimide [10] as the catalyst. We have also reported aromatization of *DHP*s with hydrogen peroxide in the presence of cobalt(II) acetate [11].

Recently, the use of solid supported reagents has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction

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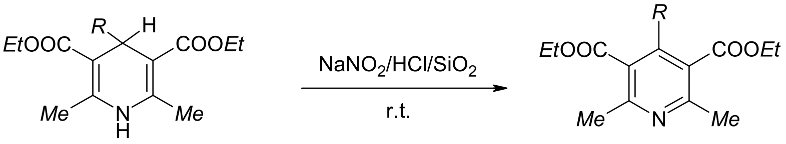

Scheme 1

times, greater selectivity, simple workup, and recoverability of catalysts [12]. Among the various heterogeneous catalysts silica gel, particularly, impregnated with hydrochloric acid has advantages of low cost and ease of preparation.

Sodium nitrite generates HNO_2 when used under acidic condition and is been known as oxidant [13]. Recently, sodium nitrite in the presence of silica sulfuric acid [14] and trifluoroacetic acid [15] has been reported for the oxidation of alcohols.

Results and Discussions

As part of our studies on the development of supported reagents and catalysts for the oxidation of organic compounds [11, 16], we describe here a simple, cheap, and convenient method for the effective aromatization of *DHP*s with $NaNO_2$ under mild and heterogeneous condition using acidic silica gel (HCl/SiO_2) at room temperature (Scheme 1).

The catalyst (acidic silica gel) is stable and can be easily prepared by addition of silica gel to aqueous hydrochloric acid, followed by evaporation of the solvent. Different types of *DHP*s were subjected to the aromatization at room temperature with sodium nitrite using acidic silica gel as catalyst. The aromatization of *DHP*s is carried out in dichloromethane as solvent and workup is a simple extraction and separation of the heterogeneous catalyst by filtration. Removal of solvent followed by purification of products gives pyridines in high yields.

Table 1. Aromatization of *Hantzsch* 1,4-dihydropyridines by sodium nitrite in the presence of acidic silica gel

Entry	*R*	Time/min	Yield/%
1	H	5	95
2	CH_3	10	90
3	CH_3CH_2	10	91
4	$CH_3CH_2CH_2$	10	92
5	C_6H_5	10	92
6	3-$NO_2C_6H_4$	40	85
7	2-thienyl	30	90
8	C_6H_5–CH=CH	30	75
9	4-ClC_6H_4	15	92
10	2-ClC_6H_4	15	85
11	2-$NO_2C_6H_4$	50	84
12	2-OHC_6H_4	35	90
13	4-BrC_6H_4	10	92
14	4-MeC_6H_4	10	91

To establish the generality of this catalytic method, various alkyl, aryl, and heterocyclic *DHP*s were converted to the corresponding pyridines. Representative reaction times and yields are given in Table 1.

Some experiments were performed in order to show the utility of the methodology. When this reaction was done without catalyst after 10 h only starting materials were observed on the TLC plate.

In conclusion, we have extended successfully the application of sodium nitrite and acidic silica gel for the aromatization of *DHP*s at room temperature. This method offers advantages in terms of simplicity of performance, room temperature condition, no side product formation, very low reaction times, and a wide range of *DHP*s can be converted to their corresponding pyridines. In addition, the silica gel can be recycled after activation.

Experimental

Products were characterized by comparison of their physical and spectral data with those of authentic samples. All yields refer to isolated products. IR and NMR spectra were recorded on Perkin Elmer 781 and Bruker DPX500. The progress of reactions was monitored by TLC. *DHP*s were synthesized according to the *Hantzsch* procedure [17].

Preparation of the Catalyst: Acidic Silica Gel

Silica gel (1 g) was added to 1 cm^3 conc HCL and stirred at room temperature for 10 min. The mixture was evaporated and dried in vacuum.

Typical Experimental Procedure

To a solution of 1 mmol *DHP* in 2 cm^3 CH_2Cl_2, 2 mmol $NaNO_2$ and 0.1 g acidic silica gel were added. The resulting mixture was stirred at room temperature for the time indicated in Table 1. After completion of the reaction (TLC), the heterogeneous mixture was filtered and thoroughly washed with the solvent. Rotatory evaporation of the combined filtrate gave the corresponding pyridines. The crude product was pure based on ^1H NMR analysis and could be further purified by crystallization.

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