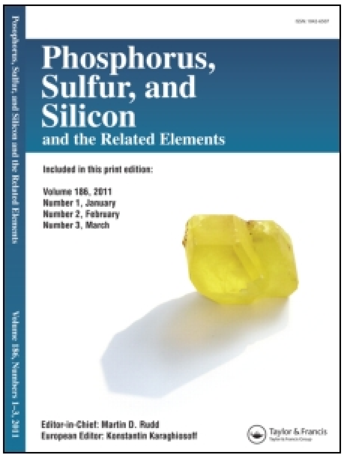

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Hantzsch 1,4-dihydropyridines (1,4 DHPs) can be aromatized to pyridines by bismuth(III) chloride supported onto wet HZSM-5 zeolite under microwave irradiation in high yields and in a short time.

Keywords Aromatization; bismuth(III) chloride; hantzsch 1,4-dihydropyridines; microwave irradiation; pyridines; solventless system

INTRODUCTION

Aromatization of Hantzsch 1,4-dihydropyridines has attracted much attention due to the fact that some of them are hypertensive drugs (Ca^{2+} channel blockers)[1] and they can be oxidatively converted to pyridine derivatives by the action of cytochrome P-450 in the liver. The reaction has also been used to investigate the NADH redox processes.[2] Furthermore, the oxidation of Hantzsch 1,4-DHPs is a common and easy way to pyridine derivatives.

Consequently, this oxidation reaction continues to attract the attention of synthetic organic chemists for the introduction of milder, faster, and eco-friendly protocols applicable to a wide range of 1,4-dihydropyridines.

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Several oxidizing agents and a variety of methods have been reported in the literature.[3] Each method has its merits and drawbacks. However the aromatization reaction with most of these methods lead to dealkylation at the 4-position or formation of side products.[4]

Bismuth compounds are environmentally friendly reagents for organic synthesis.[5] They are relatively nontoxic, readily available, inexpensive, and fairly insensitive to small amounts of water.[6] The biochemistry,[7] toxicology,[8] and environmental effects of bismuth compounds have been well documented and show that they are attractive candidates for use in green chemistry.

Prompted by stringent environment protection laws in recent years there has been increasing emphases on the use and design of eco-friendly reagents and solid and solvent free reactions.[9] Application of microwave heating technique is currently under intensive examination.[10] Dry technique has attracted much attention recently since organic solvents are expensive and hazardous and open vessels can be used.[11] Due to the importance of Hantzsch 1,4 dihydropyridines, advantages of bismuth compounds, and merits of coupling of microwave irradiation with dry technique, in this communication we wish to report our results on an expeditious supported $BiCl_3$ mediated oxidation of 1,4-dihydropyridine.

RESULTS AND DISCUSSION

The reagent impregnated on solid supports, especially that are efficient in dry media, have gained popularity in organic synthesis because of their selectivity and ease of manipulation. During the course of the study of organic reaction in solvent-free conditions, we have observed the usefulness of HZSM-5 zeolite* and microwave irradiation in enhancing of the reaction.[12] In connection with these observations, we became interested in developing a rapid and eco-friendly condition to effect conversion of 1,4-dihydropyridines to pyridines under microwave irradiation in solventless system. Our initial attempts to induce oxidation of the simple Hantzsch 1,4-dihydropyridine as a test case with (R—H) and bismuth chloride under microwave irradiation and without solvent was not very promising as considerable amounts of inchanged starting material was recovered after a relatively long reaction period of up to 10 min. However, when $BiCl_3$ was supported onto equal amounts of HZSM-5 zeolite and the mixture was made wet by addition of a few

*HZSM-5 zeolite was prepared by calcination of NH_4ZSM-5 zeolite at 500°C for 8 hrs. Si:Al = 40:1 and pore diameters are 5.1×5.5 Å. We are grateful to Dr. A. R. Garakani for a gift of zeolite.

drops of water, under microwave irradiation, the oxidation was performed rapidly in (12 min) in the case of the oxidation of **1** (R=H). It is noteworthy to mention that in the absence of water the reaction is sluggish. To establish the generality of the method a variety of 1,4-dihydropyridines **1–10** were oxidized under similar conditions (Table I).

The salient features of this reaction are mild reaction conditions, short time, eco-friendly conditions, excellent yields, and the stability of the substituents at the 4-position, which are normally dealkylated during aromatization by existing methods. i.e., oxidant such as $KMnO_4$[13] and MnO_{14} in addition, $BiCl_3$ does not show the disadvantage of giving nitrated side products, was observed in the reaction with bismuth(III) nitrate.[15]

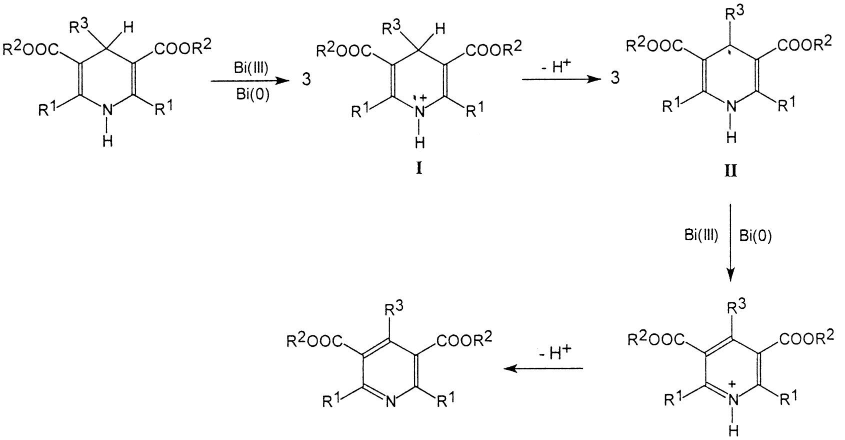
The oxidation of 1,4-dihydropyridine was initated by a three electron transfer to Bi(III) to produce Bi^0. A radical cation subsequently looses a proton to afford a radical II. The second mole of Bi(III) then oxidizes radical II to the protonated pyridine III. At the end, the pyridinium species III loses a proton to give the corresponding pyridine derivative (Scheme 1).

In summary, we have found $BiCl_3$ supported onto HZSM-5 zeolite can serve as a mild and clean oxidant under microwave irradiation in solvent free conditions for aromatization of 1,4-dihydropyridines to pyridines in high yield, giving the additional benift of easy work up and eco-friendly conditions.

TABLE I Aromatization of Hantzsch 1,4-Dihydropyridines with $BiCl_3$ Supported onto HZSM-5 Zeolite Under Microwave Irradiation in Solventless System

				Mp (°C)	
Entry	R	Reaction time (s)	Yield[a] (%)	Observed	Reported
1	H	180	92	68–9	70–1[17]
2	CH_3	120	90	Oil	Oil[18]
3	$CH_3CH_2CH_3$	120	65	Oil	Oil[18]
4	$(CH_3)_2CH$	120	77	69–70	69–70[17]
5	4-Cl-C_5H_4	180	82	65–6	66–7[17]
6	2-NO_2-C_6H_4	180	80	75–6	75[19]
7	3-NO_2-C_6H_4	270	81	62–3	61-3[17]
8	4-NO_2-C_6H_4	210	80	114–5	114–6[17]
9	4-CH_3O-C_8H_4	120	78	49–50	50[20]
10	2-furyl	120	85	Oil	Oil[19]

[a] Yields refer to isolated pure product. Products exhibited physical and spectral properties in accordance with the assigned structure.



SCHEME 1

EXPERIMENTAL

All dihydropyridines were prepared in the same manner, using the appropriate aldehyde, ammonia, and ethyl acetoacetate. All compounds were known and identified by comparison of their spectral data with those of authentic samples.

Oxidation of Dihydropyridines. General Procedure

Bismuth(III) chloride (1 mmol) was mixed thoroughly with HZSM-5 zeolite (0.5 g). The appropriate Hantzsch 1,4-dihydropyridine was added to the above reagent in a beaker and mixed thoroughly using a spatula. The beaker was placed in a microwave oven and irradiated for the specified time (Table I). After completion of the reaction (monitored by TLC) chloroform was added and the solid filtered off. The filtrate was evaporated to dryness and the residue was crystallized from ethanol to afford the corresponding pyridine (Table I).

CAUTION

Although we did not have any accident during this work, use of the microwave oven in an efficient hood is highly recommended.

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