Research Article

An Efficient Oxidation of 1,4-Dihydropyridines to Pyridines by Superoxide under Microwave Irradiation

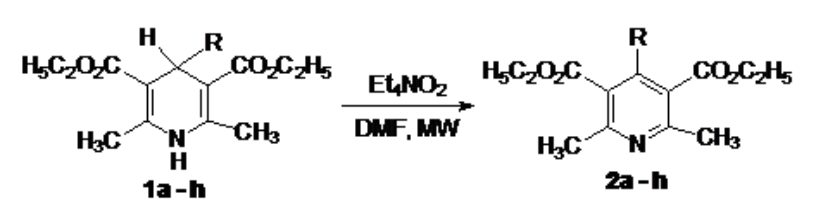
Raghvendra S. Raghuvanshi*, Virendra P. Yadav and Vinod K. Singh

Department of Chemistry, Faculty of Science, Udai Pratap (Autonomous) College, Varanasi 221002, India

Abstract

Hantzsch 1,4-dihydropyridines (1,4-DHPs) were efficiently and rapidly converted to their corresponding pyridine derivatives by tetraethylammonium superoxide under microwave irradiation in high yields.

Keywords: 1,4-Dihydropyridines, superoxide, microwave irradiation, oxidation



***Correspondence**

Raghvendra S. Raghuvanshi,
Department of Chemistry
Email: rsr_itbhu@rediffmail.com

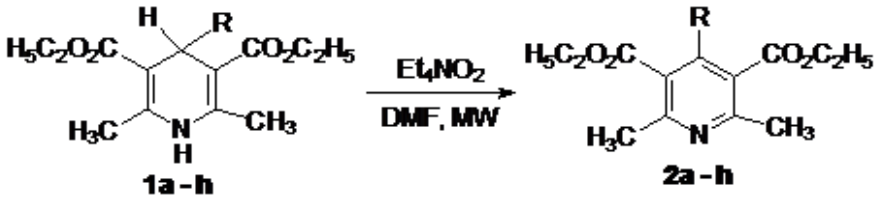
Introduction

Oxidation of Hantzsch 1,4-dihydropyridines (1,4-DHPs) to the corresponding pyridines is of interest because of its relevance to biological NADH redox processes[1], as well as to the metabolic studies pertaining to 1,4-DHPs based cardiovascular drugs[2,3]. Moreover, the oxidation of readily accessible 1,4-DHPs provides one of the shortest routes to pyridine derivatives, which show antihypoxic and antiischemic activities[4]. Consequently, this oxidative aromatization reaction continues to attract the attention of organic and medicinal chemists for the discovery of a plethora of protocols applicable to a wide range of 1,4-DHPs. Many of the reported procedure involve the use of ceric ammonium nitrate[5], clay supported cupric nitrate/ultrasound[6], potassium permanganate[7], *p*-nitrosodimethylaniline[8], diisoamyl disulfide[9], S-nitrosoglutathione[10], $CO(NH_2)_2 \cdot H_2O_2/I_2$[11], heteropolyacid/$NaNO_2$/wet SiO_2[12], microwave under solid phase condition[13], Mn(TPP)Cl[14], 4-phenyl-1,2,4-triazole-3,5-dione[15], $Zr(NO_3)_4$[16], N-nitroso-2-aryl-1,3-oxazolidines[17], *in situ* generated acetyl hypoiodide or bromide[18], silica chromate/$NaHSO_4 \cdot H_2O$/wet SiO_2[19], 9-phenyl-10-methylacridinium[20] and sodium chlorite[21]. Although, some of these reactions are carried out under mild conditions, most of these reactions require an extended period of time for completion, utilize strong oxidants and tedious work-up.

The use of microwave irradiation to simplify and improve classic organic reactions has become very popular technique because of its cleaner reactions, decreased reaction time and easier work-up[22,23]. Superoxide ion ($O_2^{\cdot-}$) is a reactive oxygen species (ROS) and play a key role in various life processes[24]. From chemical view point, it is multipotent reagent[25-27] and is achieved using chemical or electrochemical method[28,29]. Recent studies have shown that superoxide under microwave irradiation is an effective reagent for organic synthesis [30,31].

In the view of the above and as a part of the ongoing research on superoxide chemistry[32], herein is reported a rapid and efficient method to effect 1,4-DHP to pyridine conversion. Tetraethylammonium superoxide (Et_4NO_2), generated *in situ* by the phase transfer reaction of potassium superoxide and tetraethylammonium bromide, serves as

an excellent oxidant under microwave irradiation in DMF for oxidative aromatization of 1,4-dihydropyridines to pyridines (**Scheme 1**).



Scheme 1

Experimental Procedure

Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a JASCO FT/IR–5300 spectrophotometer. ^{1}H NMR spectra were run on a JEOL AL300 FT-NMR and the chemical shift are expressed as (ppm), using TMS as internal reference. Potassium superoxide and tetraethylammonium bromide were procured from E. Merck, and were used as received. Dry DMF of Aldrich, was stored over molecular sieves (4Å) prior to use. Hantzsch 1,4-dihydropyridines were prepared according to a literature procedure[33]. A Kenstar digital microwave oven at full power (800 W) was used.

General procedure for the preparation of 2a-h

A mixture of potassium superoxide (0.43 g; 0.006 mole) and tetraethylammonium bromide (0.63 g; 0.003 mole) were weighted under nitrogen atmosphere using an atmosbag and were transferred into the two-necked round bottom flask equipped with a magnetic stirrer, nitrogen inlet and a Liebig condenser protected by calcium chloride drying tube. Dry dimethylformamide (15 mL) was added to it and the mixture was agitated magnetically for 15 min to facilitate the formation of tetraethylammonium superoxide. The Hantzsch 1,4-dihydropyridine **1** (0.003 mole) was finally introduced and the contents of vessel were subjected to microwave irradiation for the specified time (Table 1).

The reaction-mixture was poured into a beaker containing brine solution (15 mL) and cold water (15 mL) and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was dried over Na_2SO_4 (anhyd.), filtered and evaporated to give the product **2**, which was purified by column chromatography and identified by ^{1}H NMR and IR spectroscopy.

2a: ^{1}H NMR ($CDCl_3$), δ : 1.4 (t, 6H), 2.9 (s, 6H), 4.4 (q, 4H), 8.7 (s, 1H).
2b: ^{1}H NMR ($CDCl_3$), δ : 1.4 (t, 6H), 2.3 (s, 3H), 2.5 (s, 6H), 4.4 (q, 4H).
2c: ^{1}H NMR ($CDCl_3$), δ : 0.9 (t, 6H), 2.6 (s, 6H), 4.0 (q, 4H), 7.1-7.3 (m, 5H).
2d: ^{1}H NMR ($CDCl_3$), δ : 1.2 (t, 6H), 2.4 (s, 6H), 2.6 (s, 3H), 4.1 (q, 4H), 7.2-7.3 (m, 4H).
2e: ^{1}H NMR ($CDCl_3$), δ : 1.0 (t, 6H), 2.6 (s, 6H), 4.0 (q, 4H), 7.3-7.4 (m, 2H), 8.1-8.2 (m, 2H).
2f: ^{1}H NMR ($CDCl_3$), δ : 1.2 (t, 6H), 2.3 (s, 6H), 4.1 (q, 4H), 7.1-7.2 (m, 4H).
2g: ^{1}H NMR ($CDCl_3$), δ : 0.9 (t, 6H), 2.5 (s, 6H), 3.7 (s, 3H), 4.0 (q, 4H), 6.8 (d, 2H), 7.1 (d, 2H).
2i: ^{1}H NMR ($CDCl_3$), δ : 1.1 (t, 6H), 2.5 (s, 6H), 4.2 (q, 4H), 6.4 (d, 1H), 6.5(d, 1H), 7.4 (s, 1H).

Results and Discussion

A number of Hantzsch 1,4-DHPs viz., diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**1a**), diethyl 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate (**1b**), diethyl 1,4-dihydro-4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate (**1c**), diethyl 1,4-dihydro-4-(4-methylphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**1d**), diethyl 1,4-dihydro-4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**1e**), diethyl 1,4-dihydro-4-(4-

chlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**1f**), diethyl 1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**1g**), diethyl 1,4-dihydro-4-(2-furyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**1h**) were reacted with KO_2 in the presence of Et_4NBr in dry DMF under microwave irradiation. As an outcome, under the mild reaction conditions of Et_4NO_2, the Hantzsch 1,4-DHPs **1a-h** are oxidized to their corresponding pyridine derivatives **2a-h** in high yield. The results are summarized in **Table 1**.

A molar ratio of 2 : 1 : 1 for KO_2 : Et_4NBr : Substrate **1** was employed for achieving reaction. Each reaction was monitored by TLC for its completion. The products were fully identified by their physical and spectral data, which are in full agreement with the values described in literature[33-36].

The general applicability, versatility and scope of this reaction is defined by using various substrates which illustrate the tolerance of several substituents namely alkyl, aryl and heterocycle at the 4-position. The salient features of this reaction are mild reaction conditions, short time and excellent yields.

Table 1 Oxidation of 1,4-dihydropyridines to pyridines with tetraethylammonium superoxide/microwave

Entry	R	Product	Time MW/min	Yield (%)	Mp (^oC)	Lit. mp (^oC)
a	H	2a	4.0	82	70	69-70[34]
b	CH_3	2b	4.0	84	oil	oil[34]
c	C_6H_5	2c	4.5	80	64	63-64.5[33]
d	4-$CH_3C_6H_4$	2d	4.5	85	73	73-74[34]
e	4-$NO_2C_6H_4$	2e	5.0	80	116	115[35]
f	4-ClC_6H_4	2f	5.0	84	67	66-67[36]
g	4-$CH_3OC_6H_4$	2g	4.5	79	52	51-52[36]
h	2-Furyl	2h	4.0	85	oil	oil[34]

It is important to mention that tetraethylammonium superoxide alone in the absence of microwave was able to achieve the same transformation in considerably longer reaction time (4 hours) with **1c**[37]. To observe the sole role of microwave on the above reactions, some blank experiments under microwave irradiation in absence of tetraethylammonium superoxide were also carried out resulting no net reactions. However when microwave is coupled with superoxide, the rate of reaction is dramatically enhance, thereby highlighting the significance of microwave-superoxide combination.

Conclusion

In conclusion, we have developed a mild and rapid method for the oxidation of 1,4-dihydropyridines to pyridines in high yield.

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