MANGANESE DIOXIDE SUPPORTED ONTO HZSM-5 ZEOLITE, A VERSATILE REAGENT FOR THE AROMATIZATION OF HANTZSCH 1,4-DIHYDROPYRIDINES

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A general and practical route for the fast and high yield aromatization of 1,4-dihydropyridine using a relatively benign oxidant, manganese dioxide under classical heating and microwave irradiation is described.

Keywords: Manganese dioxide, zeolite, aromatization, Hantzsch, 1,4-dihydropyridine.

INTRODUCTION

Hantzsch 1,4-dihydropyridines (1,4-DHPs) have attracted considerable attention as calcium channel blockers for the treatment cardiavascular diseases (1). During the redox processes (2) and in the course of drug metabolism (1b) 1,4-DHP systems are oxidatively transformed into the corresponding pyridine derivatives.

Oxidation of Hantzsch pyridine usually yields the corresponding pyridine derivatives, but expulsion of the substituent in the 4 position has been for some oxidant is observed (3). A plethora of reagents has been used for this oxidation. Aromatization of 1,4 DHP has been achieved using various oxidants such as nitric acid (4), CAN (5), ferric or cupric nitrates (6), nitric oxide (7), PCC (8), clay supported cupric nitrate accomplished under ultrasound promotion (8), $TEMDO^+ BF_4^-$ (9). However many of the reported methods either suffer from the use of strong oxidant, require serve conditions or need excess of oxidant. Manganese dioxide (10) and manganese triacetate (11) have also been used for Hantzsch 1,4-DHP oxidation. However these methods also suffer from the disadvantage of prolonged reaction time, drastic reaction conditions and tedious work up procedures.

In view of the above limitations and since manganese compounds are inexpensive, available and relatively benign oxidant, we decided to develop a practical and general approach for this oxidative conversion using a mild oxidant,

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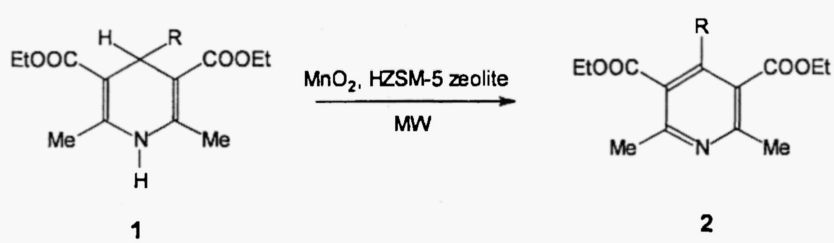
manganese dioxide.

Microwave heating in organic synthesis is now widely used. Its application in the case of organic solid-supported reactions has been recently reviewed (12). Solvent free organic reactions or dry media techniques under microwave irradiation are one of the main topics of research in our laboratory(13). We have recently supported the well known and documented chromium trioxide on HZSM-5 zeolite (14) to oxidize alcohols selectively to carbonyl compounds.

In this communication we wish to report a general and fast Hantzsch 1,4-DHPs oxidation using active manganese dioxide supported onto HZSM-5 zeolite under microwave irradiation in solvent-less system. Several 1,4-DHPs are aromatized to the corresponding pyridines in high yields and in very short time (Table). The most salient feature of this method is the stability of the substituents at 4-position which are dealkylated during aromatization with MnO_2 under classical condition (14).

We investigated the oxidizing ability of MnO_2 on various inorganic solid supports such as alumina, clay, silica, HY and NaY, HZSM-5 zeolites etc. and found that among these materials HZSM-5 zeolite (15) affords the best result for the sake of stability of substituent at 4 position. The important role of inorganic solid support is apparent from the fact that a mixture of the products and side product as well as starting 1,4-DHPs was obtained without HZSM-5 zeolite as exemplified for the product.

The reaction involves a simple mixing of 1,4-DHP with equivalent weight of active HZSM-5 zeolite in a beaker using a spatula. Exposure to microwave convert 1,4-DHP to the corresponding pyridine derivative in a short time.



SCHEME 1

Table. Oxidation of Hantzsch 1,4-dihyropyridines by MnO_2 supported onto HZSM-5 zeolite under microwave irradiation in solvent-free conditions

Entry	Substituent (R)	Reaction time (min)	Yield[a] (%)	Mp (°C)	Mp (lit.) (°C)
2a	H	7	98	68-70	70-71 (16)
2b	Me	6	92	Liquid	Liquid (16)
2c	C_2H_5	7	98	Liquid	Liquid (11)
2d	C_3H_7	7	96	61-63	-
2e	C_6H_5	7	95	61-63	62-64 (11)
2f	4-$(OCH_3)C_6H_4$	7	88	50-52	50 (11)
2g	3-$(NO_2)C_6H_4$	7	93	62-64	61-63 (17)
2h	4-Cl-C_6H_4	6	95	66-68	-
2i	2-furyl	7	85	Liquid	Liquid

[a]Yields refer to isolated products.

In conclusion, the paper describes a novel and relatively eco-friendly method for the aromatization of 1,4-DHPs using the inexpensive MnO_2 with no solvent. Due to short reaction time, easy work up procedure and stability of substituent at 4 position, we believe this procedure is highly advantageous over existing methods.

EXPERIMENTAL

All products were known and are identified by comparison of their physical and spectroscopic data (Ir and ^{1}HNMR) with those of reported in the literature. 1,4-Dihydropyridines were synthesized according to reported procedure (3). Ir spectra were recorded (KBr disc) on Philips, Ph 9800 FT-IR spectrometer. ^{1}HNMR spectra were recorded on FT-NMR-Bruker 500 MHz spectrometer in $CDCl_3$ and chemical shifts are indicated in δ ppm. Melting points are uncorrected and were measured by electrothermal 9100.

Pyridines 2a-1, Gerneral procedure.

Hantzsch 1,4-dihydropyridine (1 mmol) was thoroughly mixed with MnO_2 (0.5 g) and HZSM-5 zeolite (0.5 g) in a beaker using a spatula. The beaker was placed in a household microwave oven for indicated time (TABLE). The progress of the reaction was monitores by TLC using CH_2Cl_2:EtOAc 98:2. After the completion of the reaction CH_2Cl_2 (20 mL) was added. The mixture was filtered off, washed with CH_2Cl_2. The solvent is evaporated off to afford the corresponding pyridine (Table).

CAUTION

Although we did not have any accident using MnO_2 in microwave, it is highly recommended to use the microwave oven in an efficient hood.

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