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Manganese Triacetate Mediated Oxidation of Hantzsch 1,4-Dihydropyridines to Pyridines

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Abstract: A general and practical route for the high yield oxidative conversion of readily accessible 1,4-dihydropyridines to the corresponding pyridines is described using a relatively benign oxidant, manganese triacetate.

The oxidation of Hantzsch 1,4-dihydropyridines to the corresponding pyridines has been extensively studied in view of the pertinence of this reaction to the metabolism of Hantzsch esters and the calcium channel blocking drugs used in the treatment of various cardiovascular disorders.[1] The reaction has also been used to study the biologically significant NADH redox processes.[2] Consequently, this aromatization reaction continues to attract the attention of researchers for the discovery of milder and general protocols applicable to a wide range of 1,4-dihydropyridines. Many of the reported reagents[3] involve the use of strong oxidants such as $KMnO_4$,[3b] CrO_3,[3c] HNO_3,[3d] pyridinium chlorochromate (PCC),[3e] ceric ammonium nitrate (CAN),[3f] bentonite clay-supported manganese dioxide[3g] and more recently, bismuth nitrate $Bi(NO_3)_3$.[3h] However, this aromatization reaction with most of these reagents leads to dealkylation at the 4-position or formation of side products.[3b,g] In some other instances only moderate to poor yields are obtained.[3b,e,g]

In view of the above limitations, we decided to develop a practical and general approach for this oxidative conversion using a mild oxidant, manganese triacetate, which has been increasingly utilized in a wide variety of organic reactions[4] namely lactonization of olefins,[5] oxidative cycloadditions,[6] deoximation of carbonyl compounds[7] and oxidative cyclization of phenolic Schiff's bases.[8] Herein, we report our results on an expeditious manganese triacetate-mediated oxidation of 1,4-dihydropyridines to pyridines. Acetic acid is the solvent of choice in this conversion for the optimum yield of products; the reaction in various other solvents such as dichloromethane, methanol and acetonitrile is very slow and does not lead to completion even after 24 h. Manganese triacetate being a one-electron oxidant, two equivalents of manganese

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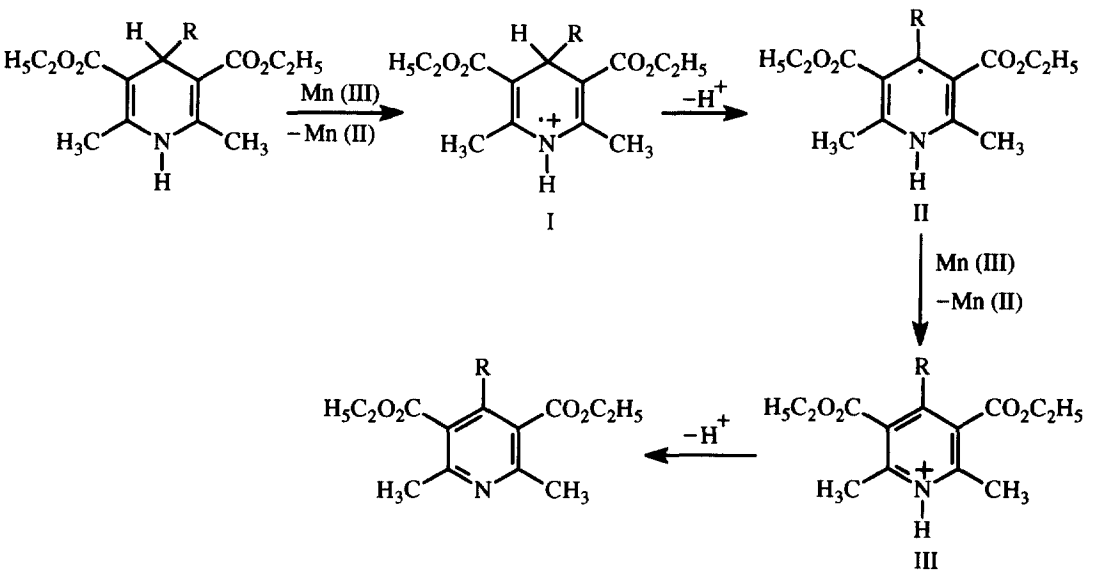
triacetate are required for the completion of the reaction that generates pyridine derivatives in excellent yields within 15-90 minutes (**Table**).

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, styryl and heterocycles at the 4-position. The salient features of this reaction are milder reaction conditions, excellent yields of the products and the stability of the substituents at 4-position which are normally dealkylated during aromatization by existing methods e.g. oxidants such as $KMnO_4$,[3b] and clay-MnO_2.[3g] The general exception, typical of all known oxidants described in the modern literature, is the case of secondary alkyl (isopropyl) and benzyl groups. In view of their electron releasing ability and the stability of the corresponding radicals these substituents are expelled with the formation of dealkylated products.[3g] In the case of reaction with diethyl 4-(4-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, **1f**, desired pyridine, **2f** is readily obtained; nitrated side products are normally formed in reaction with bismuth nitrate.[3h] Our results on nearly quantitative conversion of various substrates to the corresponding pyridine derivatives are summarized in the Table.

Presumably, the oxidation of 1,4-dihydropyridine is initiated by a single electron transfer to Mn (III) that produces Mn (II) and a radical cation I which subsequently loses a proton to generate a radical II. The second mole of Mn (III) then oxidizes radical II to the protonated pyridine III. Finally, the pyridinium species III loses a proton to deliver the desired pyridine derivative (**Scheme 1**).

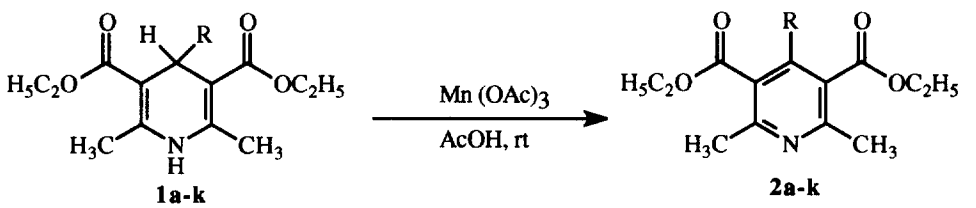


Scheme 1

Experimental

Manganese triacetate was obtained from Aldrich Chemical Co. and the 1,4-dihydropyridines were prepared according to the literature procedure.[9]

General Procedure: The preparation of diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate, **2a**, is representative of the general procedure employed. To a solution of manganese triacetate (0.536 g, 2 mmol) in acetic acid (5 mL) was added diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate **1a**, (0.253 g, 1 mmol). The reaction mixture was stirred at room temperature for 20 min. After completion of the reaction, as indicated by TLC examination, manganese diacetate was filtered off and the reaction mixture poured into water. The contents were then neutralized by $NaHCO_3$, extracted with dichloromethane (2 x 10 mL) and dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the resulting crude product obtained was crystallized from ethanol to afford pure **2a** in 98 % yield (0.248 g); m.p. 71 °C (lit.[10] m.p. 70-71 °C).



1a-k **2a-k**

Table: Oxidation of 1,4-dihydropyridines to pyridine derivatives using manganese triacetate

Entry	R	Time (min)	Yield (%)[b]	m. p. (°C)[a] Observed	Reported
2a	H	20	98	71	70-71[10]
2b	CH_3	20	97	liq	liq[11]
2c	CH_3CH_2	20	97	liq	liq[10]
2d	C_6H_5	35	98	63-64	62-64[11]
2e	C_6H_5-CH=CH	60	92	162-63	162-65[11]
2f	4-HOC_6H_4	30	90	171	171-73[12]
2g	4-$CH_3C_6H_4$	35	98	72-73	72-73[11]
2h	4-$CH_3OC_6H_4$	40	94	51-53	51-53[12]
2i	4-$NO_2C_6H_4$	60	91	114-15	115[13]
2j	2-Furyl	90	94	liq	liq[14]
2k	2-Thienyl	90	96	liq	liq[15]

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

In conclusion, we have developed a general and practical route for the oxidative conversion of 1,4-dihydropyridines to the corresponding pyridine derivatives in excellent yields using a relatively benign oxidant, manganese triacetate.

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