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Efficient Oxidation Of 1,4-Dihydropyridines To Pyridines By $KBrO_3$ In The Presence Of $MnCl_2$

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ABSTRACT

4-Alkyl or aryl substituted derivatives of Hantzsch 1,4-dihydropyridine were readily oxidized by $KBrO_3$ in the presence of $MnCl_2$ under refluxing conditions to the corresponding pyridine derivatives in excellent yields. The catalysts used in the reaction are inexpensive and provide high yields and short time reactions.

KEYWORDS

Oxidation;
1,4-Dihydropyridines;
$KBrO_3$;
$MnCl_2$.

INTRODUCTION

1,4-Dihydropyridine derivatives(1,4-DHPs) of the nifedipine compound type, are potential antihypertensive drugs based on their Ca^{+2} channel antagonistic activity. Hantzsch 1,4-dihydropyridines are widely used as calcium channel blockers for the treatment of cardiovascular ailments including angina, hypertension and cardiac arehythmic[1]. These compounds are oxidized to their pyridine derivatives by the action of cytochrome P-450 in the liver[2].

The oxidation of Hantzsch 1,4-dihydropyridines is one of the ubiquitous issues in organic chemistry and even in recent years several groups have reported various new methods for aromatization including oxidation with ferric nitrate on a solid support[3], ceric ammonium nitrate[4], clay-supported cupric nitrate (Claycop)[5], pyridinium chloro-chromate[6], bromotrichloromethane[7], nitric acid[8], nitric oxide and N-methyl-N-nitrosotoluene-p-sulfonamide[9,10].

The above mentioned reagents are not efficient for the aromatization of Hantzsch 1,4-dihydropyridines bearing an alkyl group in the 4-position even under sonication conditions. However most of these reactions require an extended period of time for completion, utilize strong oxidants in large excess and afford only modest yields of the products. Recently, use of potassium bromate in the presence of sodium

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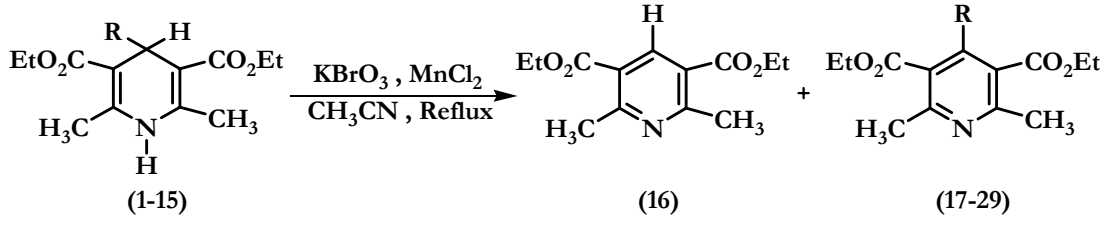
bisulfite[11], and $SnCl_4 \cdot 5H_2O$[12] have been reported for the aromatization of 1,4-DHPs. Herein we report the development of a new, simple and milder method for the oxidation of Hantzsch 1,4-dihydropyridines to the corresponding pyridines by $KBrO_3$ in the presence of $MnCl_2$ or $MnCl_2 \cdot 4H_2O$ in acetonitrile under refluxing conditions with high yields and short reaction times(SCHEME 1).

As a test case, the oxidation of the Hantzsch 1,4-DHP(1, R =C_6H_5) using $KBrO_3$ in the presence of $MnCl_2$ or $MnCl_2.4H_2O$ was investigated in different solvents under aerobic condition. The oxidation proceeded very slowly in toluene, THF and methanol(ca. 40-50% conversion with mixture of products) after 120 minutes, but faster in CH_3CN(ca. 100% conversion) after 25 minutes under reflux conditions. The obtained results showed that the molar ratio of substrate/$KBrO_3$/$MnCl_2$ (1:2:0.5) in refluxing CH_3CN is the best optimal for this achievement. Also we found that $KBrO_3$ alone or in the presence of several Lewis acids such as $Ni(OAc)_2 \cdot 4H_2O$, $ZnCl_2$, $ZnUO_4(Ac)_2$, $CaCl_2 \cdot 6H_2O$ and $MgCl_2 \cdot 6H_2O$ couldn't oxidize these compounds, another systems such as, $KBrO_3$ in the presence of the CuCl, $CaCl_2$ and $BaCl_2 \cdot 6H_2O$ have a low conversion(5-20%) after 120-180 minutes and the systems such as, $KBrO_3$ in the presence of $ZrCl_4$, $NiCl_2 \cdot 6H_2O$, $NiCl_2$, $TeCl_3$, SbF_3, $LnCl_3$, $AlCl_3$, $FeCl_2 \cdot 4H_2O$, $CeCl_3 \cdot 7H_2O$, $CuCl_2 \cdot 2H_2O$, $UO_2(OAc)_2 \cdot 2H_2O$, $U(NO_2)_3$ gave a mixture of products.

Following the success of oxidation of **(1)** with $KBrO_3$/$MnCl_2$ or $MnCl_2 \cdot 4H_2O$ systems, we extended this method to several 4-alkyl or aryl substituted Hantzsch 1,4-DHP's of the catalyst in CH_3CN. The purified substituted and unsubstituted pyridines were formed in different yields (TABLE 1). The 4-iso-



(1-15) (16) (17-29)

SCHEME 1

TABLE 1: Aromatization on of Hantzsch 1,4-DHPs to the corresponding pyridines with $KBrO_3$/$MnCl_2$ system[a]

Compound	R	Refluxing CH_3CN			Mp (°C)	Lit.Mp (°C)
		Product	Time/min	Yield (%)[b]		
1	C_6H_5	17	25	96	63-64	62-63[14]
2	H	16	15	92	68.5-69.5	69-70[14]
3	3-$NO_2C_6H_4$	18	15	94	59-62	61-63[14]
4	2-Furyl	19+16	35	5+95	40-42	Oil[14]
5	$CH_3CH_2CH_2$	20+16	15	10+90	Oil	Oil[16]
6	2-ClC_6H_4	21	20	92	61-62	62[16]
7	4-OHC_6H_4	22	25	90	169-170	171[16]
8	4-OH-3-MeO-C_6H_3	23+16	30	95+5	-	-
9	4-MeO-3-OH-C_6H_3	24+16	40	95+5	-	-
10	CH_3	25	12	92	Oil	Oil[15]
11	4-(MeO)C_6H_4	26+16	15	80+20	49-50	50[14]
12	4-$N(Me)_2C_6H_4$	27	15	94	-	-
13	$C_6H_4CH=CH_2$	28	25	93	162-163	162-163[16]
14	4-MeC_6H_4	29+16	20	80+20	71-72	72-73[17]
15	$(CH_3)_2CH$	16	13	93	69-70	69-70[14]

[a]All reaction have a molar ratio as substrate/$KBrO_3$/$MnCl_2$ (1:2:0.5).
[b]Yields refer to isolated pure products.

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propyl Hantzsch analogous[15] (R=i Pr) was oxidized to pyridine[16] completely that shows the dealkylated derivative is the sole product. This procedure was examined by subjecting different kinds of 4-substituted-1,4-dihydropyridines towards $KBrO_3/MnCl_2$ system. The results summarized in TABLE 1 indicate the scope of the reaction with respect to various 1,4-DHPs**(1-15)**. Compounds 2-furyl**(4)**, $CH_3CH_2CH_2$**(5)**, 4-OH-3-MeO-C_6H_3**(8)**, 4-MeO-3-OH-C_6H_3**(9)**, 4-(MeO)C_6H_4**(11)** and 4-Me-C_6H_4(**14**) at 4-position were converted to pyridine**(16)** in 95% yield, 90% yield, 5% yield, 5% yield, 20% yield and 20% yield respectively.

EXPERIMENTAL

General

All Hantzsch ester, 1,4-dihydropyridines, were synthesized by the reported procedures[13]. The products were characterized by a comparison with authentic samples(Melting or boiling points) and their ^{1}H-NMR and IR spectra. All yields referred to isolated pure products. TLC was used for the purity determination of substrates, products and reactions monitored over silica gel Polygram SILG/UV 254 plates. Products were purified by a column chromatography packed with silica gel.

Aromatization of Diethyl 2,6-Dimethyl-4-pheny-1,4-dihydropyridine-3,5–dicarboxy- late(1) by $KBrO_3/MnCl_2$ system. A typical procedure

In a round-bottomed flask(10ml) equipped with magnetic stirrer and condenser, to a solution of 1,4-DHP **(1)** (329mg, 1mmol) in CH_3CN(3ml), $KBrO_3$ (167mg, 1mmol) and $MnCl_2$ (175mg, 0.5mmol) were added. The resulting mixture was stirred under reflux for 25min. TLC monitored the progress of reaction(eluent; CCl_4/Et_2O:2/5). At the end of reaction, distilled water(4ml) was added to the reaction mixture and stirred for an additional 5 min. The mixture was extracted with CH_2Cl_2 (3-8ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel by eluent of CCl_4/Et_2O:2/5 afforded the pure corresponding pyridine[17] (293mg, 96% yield, mp. 63-64°C, Lit.[14] 62-63°C) (TABLE 1).

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