OXIDATIVE-AROMATIZATION OF HANTZSCH ESTER 1,4-DIHYDROPYRIDINES BY $KBRO_3/COCL_2.6H_2O$ UNDER MILD CONDITION

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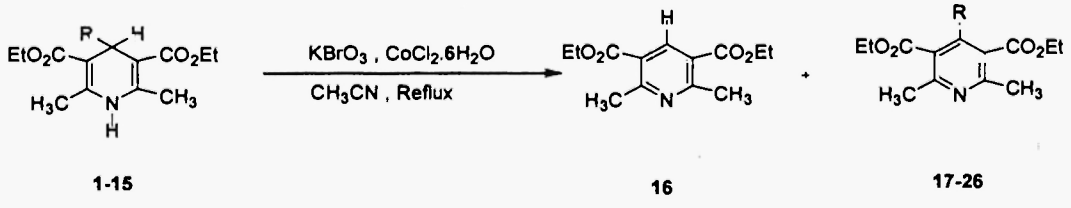
Abstract : $KBrO_3/CoCl_2.6H_2O$ system was used as an effective oxidizing agent for the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives in refluxing CH_3CN. The products were obtained in high to excellent yields.
Key Words: Oxidation, 1,4-dihydropyridines, $KBrO_3$, $CoCl_2.6H_2O$

The oxidation of hantzsch 1,4-dihydropyrines (1, 4-DHPs) and analogs to the corresponding pyridines is of interest because it is relevance to the biological NADH redox processes[1] as well as to the metabolic studies pertaining to 1,4-DHP based cardiovascular drug such as nifedipine and niguldipine.[2] Furthermore the oxidation of readily accessible Hantzsch ester 1, 4-dihydropyrines constitutes by for the easiest method to obtain pyridine derivatives.

A vast variety of oxidants and reagents were reported for this oxidative reaction e.g., HNO_3,[2b,3] $KMnO_4$,[4] CrO_3,[5] MnO_2,[6] pyridinium chlorochromate,[7] ceric ammonium nitrate,[8] $BaMnO_4$,[9] $K_2S_2O_8$,[10] phenyliodine(III) bis(trifluoroacetate) and elemental sulfur,[11] $SiO_2/Fe(NO_3)_3$ or $Cu(NO_3)_2$,[12] *ter*-butylhydroperoxide,[13] $Mn(OAc)_3$,[14] $NaNO_2$ in the presence of oxalic acid, sodium hydrogen sulfate, magnesium hydrogen sulfate and wet SiO_2,[15] [hydroxyl(tosyloxy)iodo]benzene,[16] $H_2O_2/Co(OAc)_2$,[17] iodobenzene diacetate,[18] $FeCl_3.6H_2O$[19] and $[NO^+.Crown.H(NO_3)_2^-]$.[20]

However, some of these methods suffer from disadvantages such as using strong or excess amounts of oxidants, low yield of products, long reaction times and the requirement for severe conditions. The importance of this synthetic methodology in organic reactions and developing a mild and high yielding protocol for the transformation of 1,4-dihydropyridines to pyridines compounds encouraged us to become interest in this subject.

Herein, we report a mild and efficient method for the oxidative-aromatization of 1, 4-dihydropyridines to the corresponding pyridine derivatives with $KBrO_3$/ $CoCl_2.6H_2O$ system in refluxing CH_3CN. (Scheme-1).



1-15 16 17-26

Scheme-1

Literature review showed that, recently, use of potassium bromate in the presence of sodium bisulfite[21], and $SnCl_4.5H_2O$[22] has been reported for the aromatization of 1,4-DHPs. Our experiments

led us to this fact the solely $KBrO_3$ in a variety of solvents could not affect the transformation of 1,4-dihydropyridines to pyridine compounds. To explore the further utility of this mild oxidizing agent, we decided to increase the potentiality of $KBrO_3$ towards aromatization of 1, 4-dihydropyridines in the presence of additives such as Co (II) halide as an activator. For optimization of the reaction conditions, we accomplished a set of experiments with diethyl 2,6-dimethyl-4-pheny-1,4-dihydropyridine-3,5-dicarboxylate (4-substituted-1,4-DHP) (**1**) as a model compound in aprotic solvents such as CH_2Cl_2, CH_3CN, THF, C_6H_6 and different amounts of potassium bromate in the presence of $CoCl_2.6H_2O$. The obtained results showed that the molar ratio of substrate/$KBrO_3$/ Co (II) (1:1:0.5) in refluxing CH_3CN is the best optimal for this achievement.

The usefulness of this procedure was examined by subjecting different kinds of 4-substituted-1, 4-dihydropyridines towards $KBrO_3$/ $CoCl_2.6H_2O$ system. The results summarized in Table 1 indicate the scope of the reaction with respect to various 1, 4-DHPs (**1-15**).

Table (**1**) shown that the percent method is clean and efficient. The aromatization reactions were completed within (15-120) minute in high to excellent yielding of the corresponding pyridine compounds. The method is the mild and tolerates several substituted such as aryl and alkyl groups of on 4-posion of dihydropyridines. 4-Substitued alkyl group such as isopropyl (**15**), methyl (**10**), propyl (**5**) and 4-hydroxyphenyl (**7**) showed a complete dealkilation reaction of the corresponding pyridine compounds. For 3-Hydroxy-4-methoxyphenyl (**9**) mixture of products, 4-hydroxi-3-methoxyphenyl (**8**), 90% dealkylated pyridine compounds were observed.

Experimental

General

All Hantzsch ester 1,4-dihydropyridines were synthesized by the reported procedures[23]. The products were characterized by a comparison with authentic samples (melting or boiling points) and their ^{1}H-NMR or IR spectra. All yields referred to isolated pure products. TLC was used for the purity determination of substrates, products and reaction monitoring 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 -dicarboxylate (1) by $KBrO_3$/ $CoCl_2.6H_2O$ System. A Typical Procedure

In a round-bottomed flask (10 mL) equipped with magnetic stirrer and condenser, to a solution of 1,4-DHP (1) (0.329 g, 1 mmol) in CH_3CN (3 mL), $KBrO_3$ (0.167 g, 1 mmol) and $CoCl_2.6H_2O$ (0.175 g, 0.5 mmol) were added. The resulting mixture was stirred under reflux condition for 15 min. TLC monitored the progress of reaction (eluent; CCl_4/Et_2O: 2/5). At the end of reaction, dis- tilled water (4 mL) was added to the reaction mixture and stirred for an additional 5 min. The mixture was extracted with CH_2Cl_2 (3-8 mL) 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 affords the pure corresponding pyridine (**17**) (0.293 g, 95% yield, mp. 63–64°C, Lit.[14] 62–63 °C) (Table-1).

Table 1. Aromatization of hantzsch 1, 4-DHPs to the corresponding pyridine with $KBrO_3$/ $CoCl_2.6H_2O$[a]

Compound	R	Refluxing condition			Mp (°C)	Lit.Mp(°C)
		Product	Time (min)	Yield (%)[b]		
1	C_6H_5	17	15	95	63-64	62-63[14]
2	H	16	12	92	68.5-69.5	69-70[14]
3	3-$NO_2C_6H_4$	18	30	89	59-62	61-63[16]
4	2-Furyl	19	25	82	40-42	Oil[14]
5	$CH_3CH_2CH_2$	16	15	90	Oil	Oi[16]
6	2-ClC_6H_4	20	10	89	61-62	62[16]
7	4-OHC_6H_4	16	75	90	169-170	171[24]
8	4-OH-3-MeO-C_6H_3	16+21	120	88+10	-	-
9	4-MeO-3-OH-C_6H_3	22+Other product	60	-	-	-
10	CH_3	16	25	90	Oil	Oil[14]
11	4-$(MeO)C_6H_4$	23	25	91	49-50	50[14]
12	4-$N(Me)_2C_6H_4$	24	110	90	-	-
13	$C_6H_4CH=CH_2$	25	25	93	162-163	162-163[14]
14	4-MeC_6H_4	26	70	92	71-72	72-73[14]
15	$(CH_3)_2CH$	16	15	93	69-70	69-70[16]

[a]All reactions have a molar ratio as substrate$KBrO_3$/ $CoCl_2.6H_2O$ (1 : 1 : 0.5).
[b]Yields refer to isolated pure products.

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