$KBrO_3/FeCl_3$ as an efficient oxidising system for aromatisation of Hantzsch 1,4-dihydropyridines in wet acetonitrile

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$KBrO_3$ in the presence of anhydrous $FeCl_3$ efficiently aromatised Hantzsch 1,4-dihydropyridines to their corresponding pyridine derivatives in high to excellent yields. The reactions were carried out in wet CH_3CN under reflux condition.

aromatisation, hantzsch 1,4-dihydropyridines, $KBrO_3$, $FeCl_3$

Several 1,4-dihydropyridine-based drugs such as nifedipine and niguldipine are used as calcium channel blockers for the treatment of cardiovascular diseases.[1] These compounds are oxidised to their corresponding pyridine derivatives at the first-pass metabolism by the action of cytochrome P-450 in the liver.[2] This transformation, because of its importance to gain reference standards for studying *in vivo* reactions and easy access to pyridine compounds, has attracted much attention. However, the development and introduction of convenient methods for the aromatisation of 1,4-dihdropyridines is practically important and a vast variety of oxidants and reagents have been reported for this achievement.

The methods such as using CrO_3,[3] $KMnO_4$,[4] HNO_3,[5] MnO_2,[6] $BaMnO_4$,[7] $K_2S_2O_8$,[8] $Mn(OAc)_3$,[9] $H_2O_2/Co(OAc)_2$,[10] ceric ammonium nitrate,[11] pyridinium chlorochromate,[12] *t*-butylhydroperoxide,[13] $SiO_2/Fe(NO_3)_3$ or $Cu(NO_3)_2$,[14] $NaNO_2/C_2H_2O_4.2H_2O$, $NaNO_2/Mg(HSO_4)_2$, $NaNO_2$/wet SiO_2,[15] [hydroxyl(tosyloxy)iodo] benzene[16] and iodobenzene diacetate[17] are examples for this transformation. However, the requirement for severe conditions such as using strong or excess amounts of oxidants, use of expensive reagents, sometimes low yields of products and long reaction times are disadvantages of some reported methods.

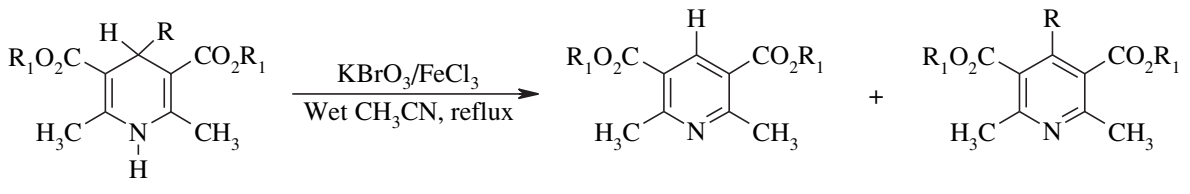
Therefore, the usefulness of this synthetic methodology and the need for introduction of a mild and convenient protocol for aromatisation of 1,4-dihydropyridines encouraged our interest in this subject. Herein, we describe a new and efficient method for aromatisation of Hantzsch 1,4-dihydropyridines by using the inexpensive and readily available reagents, $KBrO_3$ in the presence of $FeCl_3$, in refluxing wet CH_3CN (Scheme 1).

Potassium bromate ($KBrO_3$) as a mild oxidising agent has found useful applications in organic synthesis.[18] Recently, it was reported that this reagent in the presence of sodium bisulfite can aromatise 1,4-dihydropyridines to their corresponding pyridine compounds.[19] Our interest to explore the further utility of $KBrO_3$ led us to investigate the potentiality of this mild oxidising agent towards aromatisation of 1,4-dihydropyridines by increasing its activity in the presence of a Lewis acid. Anhydrous $FeCl_3$, because of its good Lewis acidity, has found numerous applications[18,20] and was selected as an activator for the aromatisation of 1,4-dihydropyridines with $KBrO_3$.

Our experiments showed that $KBrO_3$ alone cannot affect the aromatisation of 1,4-dihydropyridines under any conditions, but that this reagent in the presence of anhydrous $FeCl_3$ showed an increased activity towards aromatisation of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1,4-DHP) (**1**) to the corresponding pyridine compound (**15**) in dry CH_3CN within 1.7–4 h (Table 1, entries 4–6). By performing a set of experiments, we found that by adding a small amount of water to the reaction mixture as a co-solvent, the rate of aromatisation reaction was dramatically increased and the reaction was completed in 30 min (Table 1, entry 7). We also observed that $FeCl_3.6H_2O$, in contrast to anhydrous $FeCl_3$, showed a lower influence on this transformation (Table 1, entry 8).

To explore the further utility of this protocol, we examined the aromatisation of different kinds of 1,4-dihydropyridines by $KBrO_3$ in the presence of anhydrous ferric chloride with molar ratio of 1,4-DHP/$KBrO_3$/$FeCl_3$ (1:2:2) and simply refluxing in wet acetonitrile, CH_3CN/H_2O (3:0.05 ml). Table 2 shows the results of this transformation and indicates the scope of procedure with respect to various 1,4-dihydropyridines. The results show that the present method is clean and efficient. The aromatisation reactions were completed within 8–45 min with high to excellent yields of the corresponding pyridine compounds (75–98%). The method is mild and tolerates several substituted aryl groups at the 4-position of 1,4-dihydropyridines. 4-Substituted secondary alkyl groups, such as isopropyl, showed a complete dealkylation reaction with 98% yield of the corresponding pyridine compound (**14**) (Table 2, entry 7). This result is in agreement with the results which have been reported by various oxidants. 1,4-Dihydropyridines with heterocyclic group such as the 2-furyl moiety at the 4-position also showed an aromatisation reaction with tolerance of a heterocyclic group in 75% yield (Table 2, entries 5,6).

In conclusion, we have shown that $KBrO_3$ in the presence of anhydrous $FeCl_3$ efficiently aromatised the various kinds of 1,4-dihydropyridines to their corresponding pyridine derivatives by simply refluxing in wet CH_3CN. The reactions were completed within 8–45 min. The mildness, high efficiency and readily availability of the reagents, as well as the easy work-up procedure, are the advantages which could make this procedure a useful addition to the present methodologies.



1–13 **14** **15–26**

Scheme 1

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Table 1 Aromatisation of 1,4-dihydropyridine (**1**) with $KBrO_3/FeCl_3$ system under different conditions

Entry	Reaction components (molar ratio)	Solvent	Condition	Product	Time/h	Conversion/%
1	DHP/$KBrO_3$ (1:2)	CH_3CN	Reflux	-	4	0
2	DHP/$FeCl_3$ (1:2)	CH_3CN	Reflux	15	12	5
3	DHP/$FeCl_3$ (1:2)	CH_3CN/H_2O (3:0.05 ml)	Reflux	15	4	10
4	DHP/$KBrO_3/FeCl_3$ (1:1:1)	CH_3CN	Reflux	15	4	100
5	DHP/$KBrO_3/FeCl_3$ (1:2:2)	CH_3CN	RT	15	3.5	100
6	DHP/$KBrO_3/FeCl_3$ (1:2:2)	CH_3CN	Reflux	15	1.7	100
7	DHP/$KBrO_3/FeCl_3$ (1:2:2)	CH_3CN/H_2O (3:0.05 ml)	Reflux	15	0.5	100
8	DHP/$KBrO_3/FeCl_3{\cdot}6H_2O$ (1:2:2)	CH_3CN/H_2O (3:0.05 ml)	Reflux	15	2	70

Table 2 Aromatisation of 1,4-dihydropyridines with $KBrO_3/FeCl_3$ system[a]

Compound	R	R_1	Product	Time/min	Yield/%[b]	M.p./°C	Lit. M.p./°C
1	C_6H_5	C_2H_5	**15**	30	97	63–64	62–63 [6a]
2	C_6H_5	CH_3	**16**	40	95	135–136	135–136 [22]
3	3-$NO_2C_6H_4$	C_2H_5	**17**	45	93	59–62	61–63 [6a]
4	2-$NO_2C_6H_4$	CH_3	**18**	35	95	103–104	104–105 [22]
5	2-Furyl	C_2H_5	**19+14**	15	75+25	40–42	Oil [9]
6	2-Furyl	CH_3	**20+14**	10	75+25	Oil	Oil [9]
7	$(CH_3)_2CH$	CH_3	**14**	8	98	69–70	69–70 [6a]
8	4-(MeO)C_6H_4	C_2H_5	**21**	20	96	49–50	50 [23]
9	4-(MeO)C_6H_4	CH_3	**22**	20	97	114–115	115 [22]
10	4-MeC_6H_4	C_2H_5	**23**	45	98	71–72	72–73 [9]
11	4-ClC_6H_4	CH_3	**24**	20	94	137–138	137–139 [22]
12	4-ClC_6H_4	CH_3	**25**	30	95	70–71	69–70 [22]
13	4-Hydroxy-3-methoxyphenyl	C_2H_5	**26**	40	93	–	–

[a]All reactions were carried out in refluxing CH_3CN/H_2O (3:0.05 ml) with molar ratio of Subs./$KBrO_3/FeCl_3$ (1:2:2); [b] yields refer to isolated pure products.

Experimental

All Hantzsch 1,4-dihydropyridines were synthesised by the reported methods.[21] The products were characterised by a comparison with authentic samples (melting or boiling points) and their ^1H NMR or IR spectra. All yields refer to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F_{254} aluminum sheets. Products were purified by column chromatography with silica gel 60 (70–230 mesh ASTM).

Aromatisation of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1**) with $KBrO_3/FeCl_3$ system: a typical procedure.

To a round-bottomed flask (10 ml) charged with a solution of 1,4-DHP (**1**) (0.329 g, 1 mmol) in CH_3CN/H_2O (3:0.05 ml), $KBrO_3$ (0.334 g, 2 mmol) and $FeCl_3$ (0.324 g, 2 mmol) were added. The resulting mixture was then stirred under reflux for 30 min. TLC monitored the progress of the reaction (eluent; CCl_4/Et_2O (5:3)). At the end of the reaction, distilled water (5 ml) was added and the reaction mixture was 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 [eluent; CCl_4/Et_2O (5:3)] afforded the pure corresponding pyridine compound (**15**) (0.317 g, 97% yield, Table 2).

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