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# Oxidative-Aromatization of Hantzsch Ester 1,4-Dihydropyridines by $KBrO_3/SnCI_4 \cdot 5H_2O$ Under Mild Condition

Behzad Zeynizadeh<sup>a</sup>, Karim Akbari Dilmaghani<sup>a</sup> & Asli Roozijoy<sup>a</sup> <sup>a</sup> Department of Chemistry, Faculty of Sciences, Urmia University, Urmia, Iran

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## Oxidative-Aromatization of Hantzsch Ester 1,4-Dihydropyridines by KBrO<sub>3</sub>/ SnCl<sub>4</sub>·5H<sub>2</sub>O Under Mild Condition

Behzad Zeynizadeh, Karim Akbari Dilmaghani, and Asli Roozijoy

Department of Chemistry, Faculty of Sciences, Urmia University, Urmia, Iran

**Abstract:** Different kinds of Hantzsch ester 1,4-dihydropyridines were oxidatively aromatized to their corresponding pyridine derivatives by  $KBrO_3/SnCl_4 \cdot 5H_2O$  system in refluxing CH<sub>3</sub>CN. The products were obtained in high to excellent yields.

Keywords: Aromatization, Hantzsch 1,4-dihydropyridines, KBrO<sub>3</sub>, SnCl<sub>4</sub> · 5H<sub>2</sub>O

Aromatization of Hantzsch ester 1,4-dihydropyrines (1,4-DHPs) into the corresponding pyridine derivatives occurred in the first-pass metabolism by the action of cytochrome P-450 in the liver.<sup>[1]</sup> These compounds have been known as calcium channel blockers for the treatment of cardiovascular diseases.<sup>[2a,2b]</sup> So, this transformation in the aspect of gaining reference standards for the studying in vivo reactions and easy access to pyridine derivatives has attracted a great deal of attentions.

A vast variety of oxidants and reagents were reported for this oxidative reaction e.g.,  $HNO_3$ ,<sup>[2b,3]</sup>  $KMnO_4$ ,<sup>[4]</sup>  $CrO_3$ ,<sup>[5]</sup>  $MnO_2$ ,<sup>[6]</sup> pyridinium chlorochromate,<sup>[7]</sup> ceric ammonium nitrate,<sup>[8]</sup>  $BaMnO_4$ ,<sup>[9]</sup>  $K_2S_2O_8$ ,<sup>[10]</sup> phenyliodine(III) bis(trifluoroacetate) and elemental sulfur,<sup>[11]</sup>  $SiO_2/Fe(NO_3)_3$  or  $Cu(NO_3)_2$ ,<sup>[12]</sup>

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Address correspondence to Behzad Zeynizadeh, Department of Chemistry, Faculty of Sciences, Urmia University, Urmia 57159-165, Iran. E-mail: b.zeynizadeh@mail. urmia.ac.ir

*ter*-butylhydroperoxide,<sup>[13]</sup> Mn(OAc)<sub>3</sub>,<sup>[14]</sup> NaNO<sub>2</sub> in the presence of oxalic acid, sodium hydrogen sulfate, magnesium hydrogen sulfate and wet SiO<sub>2</sub>,<sup>[15]</sup> [hydroxyl(tosyloxy)iodo]benzene,<sup>[16]</sup> H<sub>2</sub>O<sub>2</sub>/Co(OAc)<sub>2</sub>,<sup>[17]</sup> iodobenzene diacetate,<sup>[18]</sup> FeCl<sub>3</sub>.6H<sub>2</sub>O<sup>[19]</sup> and [NO<sup>+</sup> · Crown · H(NO<sub>3</sub>)<sub>2</sub>].<sup>[20]</sup>

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 oxidativearomatization of 1,4-dihydropyridines to the corresponding pyridine derivatives with  $KBrO_3/SnCl_4 \cdot 5H_2O$  system in refluxing  $CH_3CN$  (Scheme 1).

Literature review showed that, recently, use of potassium bromate in the presence of sodium bisulfite has been reported for the aromatization of 1,4-DHPs.<sup>[21]</sup> Our experiments led us to the fact that solely KBrO<sub>3</sub> 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 KBrO3 toward aromatization of 1,4-dihydropyridines in the presence of additives such as Sn(II) or Sn(IV) halides as an activator. For optimization of the reaction conditions, we accomplished a set of experiments with diethyl 2,6-dimethyl-4-phenyl-1,4dihydropyridine-3,5-dicarboxylate (4-substituted-1,4-DHP) (1) as a model compound in aprotic solvents such as CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>CN, THF, C<sub>6</sub>H<sub>6</sub>, and different amounts of potassium bromate in the presence of SnCl<sub>2</sub> · H<sub>2</sub>O or  $SnCl_4 \cdot 5H_2O$ . The obtained results showed that the molar ratio of substrate/  $KBrO_3/Sn(II \text{ or } IV)$  (1:1:0.5) in refluxing CH<sub>3</sub>CN is the best optimal for this achievement. KBrO<sub>3</sub>/SnCl<sub>2</sub>·H<sub>2</sub>O system in refluxing acetonitrile showed a faster reaction rate relative to  $KBrO_3/SnCl_4 \cdot 5H_2O$  but the yield of aromatized products were low (30-40%).

The usefulness of this procedure was examined by subjecting different kinds of 4-substituted-1,4-dihydropyridines toward  $\text{KBrO}_3/\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$  system. The results summarized in Table 1 indicate the scope of the reaction with respect to various 1,4-DHPs (1–13). As shown in Table 1, generally, the reactions are clean, efficient, and completed within 30–100 min. The method is mild and tolerates several substituted aryl groups on 4-position. It was observed that oxidation of 1,4-dihydropyrine with secondary alkyl group proceeds rapidly and gave dealkylated pyridine compound (14) in 96% yield. This is in agreement with the observation made by other employed oxidative conditions. 4-(2-Furyl) substituted 1,4-dihydropyridines (5,6) showed 40% aromatization with tolerance of the heterocyclic group.

In conclusion we have introduced a convenient and efficient procedure for the transformation of 1,4-dihydropyridines to their corresponding pyridine derivatives. In addition, availability of the reagents, high-yielding protocol





			Refluxing CH <sub>3</sub> CN				
Compound	R	$R_1$	Product	Time (min)	Yield $(\%)^b$	Mp. (°C)	Lit. Mp. (°C)
1	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	15	40	90	63-64	62-63 <sup>[6a]</sup>
2	$C_6H_5$	CH <sub>3</sub>	16	100	92	135-136	135-136 <sup>[23]</sup>
3	$3-NO_2C_6H_4$	$C_2H_5$	17	80	95	59-62	61-63 <sup>[6a]</sup>
4	$2-NO_2C_6H_4$	CH <sub>3</sub>	18	100	92	103-104	$104 - 105^{[23]}$
5	2-Furyl	$C_2H_5$	19 + 14	35	40 + 60	40-42	Oil <sup>[14]</sup>
6	2-Furyl	CH <sub>3</sub>	20 + 14	40	40 + 60	Oil	Oil <sup>[14]</sup>
7	(CH <sub>3</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	14	30	96	69-70	69-70 <sup>[6a]</sup>
8	$4-(MeO)C_6H_4$	$C_2H_5$	21	60	98	49-50	50 <sup>[19]</sup>
9	$4-(MeO)C_6H_4$	CH <sub>3</sub>	22	40	97	114-115	115 <sup>[23]</sup>
10	$4-\text{MeC}_6\text{H}_4$	$C_2H_5$	23	35	97	71-72	72-73 <sup>[14]</sup>
11	$4-ClC_6H_4$	CH <sub>3</sub>	24	42	96	137-138	137-139 <sup>[23]</sup>
12	$2-ClC_6H_4$	CH <sub>3</sub>	25	45	98	70-71	69-70 <sup>[23]</sup>
13	4-Hydroxyl-3-methoxyphenyl	$C_2H_5$	26	45	94	—	

Table 1. Aromatization of 1,4-dihydropyridines with KBrO<sub>3</sub>/SnCl<sub>4</sub> · 5H<sub>2</sub>O system<sup>a</sup>

<sup>*a*</sup>All reactions have a molar ratio as substrate KBrO<sub>3</sub>/SnCl<sub>4</sub> · 5H<sub>2</sub>O (1:1:0.5).

<sup>b</sup>Yields refer to isolated pure products.

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and easy work-up procedure make this method an important addition to the present methodologies.

#### **EXPERIMENTAL**

#### General

All Hantzsch ester 1,4-dihydropyridines were synthesized by the reported procedures.<sup>[22]</sup> The products were characterized by a comparison with authentic samples (melting or boiling points) and their <sup>1</sup>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-phenyl-1,4dihydropyridine-3,5-dicarboxylate (1) with KBrO<sub>3</sub>/SnCl<sub>4</sub>·5H<sub>2</sub>O 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<sub>3</sub>CN (3 mL), KBrO<sub>3</sub> (0.167 g, 1 mmol) and SnCl<sub>4</sub> · 5H<sub>2</sub>O (0.175 g, 0.5 mmol) were added. The resulting mixture was stirred under reflux condition for 40 min. TLC monitored the progress of reaction (eluent; CCl<sub>4</sub>/Et<sub>2</sub>O: 5/3). At the end of reaction, distilled water (4 mL) was added to the reaction mixture and stirred for an additional 5 min. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub>/Et<sub>2</sub>O: 5/3 affords the pure corresponding pyridine (15) (0.295 g, 90% yield, mp. 63–64°C, Lit.<sup>[6a]</sup> 62–63°C) (Table 1).

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