

# A simple, green and one-pot four-component synthesis of 1,4-dihydropyridines and their aromatization

Saikat Das Sharma, Parasa Hazarika, Dilip Konwar \*

*Synthetic Organic Chemistry Division, North East Institute of Science & Technology (Formerly Regional Research Laboratory, Jorhat), Jorhat 785 006, Assam, India*

Received 15 May 2007; received in revised form 8 August 2007; accepted 16 August 2007  
Available online 23 August 2007

## Abstract

A simple, green and cost-effective protocol was achieved for the solvent free synthesis of 1,4-dihydropyridines catalyzed by  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  as a mild and effective catalyst at  $60^\circ\text{C}$  in high yields. 1,4-Dihydropyridines thus formed were aromatized to pyridines by in situ generation of HOCl employing  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}/\text{H}_2\text{O}_2/\text{H}_2\text{O}/\text{EtOH}$  as an excellent reagent system under domestic microwave irradiation (MWI). Both the synthesis and oxidation steps were efficiently accomplished in one-pot four-component fashion following the same protocol.

© 2007 Elsevier B.V. All rights reserved.

**Keywords:** Hantzsch; 1,4-Dihydropyridines;  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ ; Oxidation to pyridines;  $\text{H}_2\text{O}_2$

## 1. Introduction

1,4-Dihydropyridine (DHP) [1] scaffold represents the heterocyclic unit of remarkable pharmacological efficiency. They are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, such as, nifedipine and nitrendipine are used for the treatment of hypertension and angina pectoris, nisoldipine is a potent vasodilator and nimodipine exhibits selectivity for cerebral vasculature [2]. A number of DHP derivatives are employed as potential drug candidates for the treatment of congestive heart failure [3].

Moreover DHPs also act as NADH mimics for the reduction of carbonyl compounds and their derivatives [4]. In human body the main metabolic route of dihydropyridine drugs involve their oxidation to pyridines catalyzed by cytochrome-450 in liver [5]. Additionally, the synthesis of heteroaromatics by oxidative dehydrogenation is of fundamental importance in organic chemistry. These

ubiquitous features always encourage synthetic chemist to explore improved protocols for the synthesis as well as the oxidation of 1,4-DHPs.

1,4-Dihydropyridines are generally synthesized by Hantzsch reaction which involves the condensation of aldehydes,  $\beta$ -ketoester and ammonia or ammonium acetate. A number of improved methods have been reported in the literature for this condensation which involve the use of microwave, ionic liquids, reflux at high temperature, TMSI,  $\text{I}_2$ ,  $\text{Yb}(\text{OTf})_3$ , CAN [6], silica gel/ $\text{NaHSO}_4$  [7] and  $\text{Sc}(\text{OTf})_3$  [8]. On the other hand, a plethora of reagents have been employed for the oxidation of 1,4-DHPs [9–16]. In spite of potential utility of these reagents, most of the existing methods for the synthesis of 1,4-DHPs as well as their aromatization suffer from drawbacks such as low yields, long reaction times, occurrence of several side products, use of stoichiometric amount of reagents, use of strong oxidants, high temperature and the use of expensive and toxic transition metallic reagents. Therefore, exploring the new catalytic system preferably in an environmentally benign method to overcome these drawbacks is a challenging task to the organic chemists.

\* Corresponding author. Tel.: +91 376 2370009.

E-mail address: [dkonwar@yahoo.co.uk](mailto:dkonwar@yahoo.co.uk) (D. Konwar).

The chemistry of anhydrous  $\text{AlCl}_3$  has been well explored in organic synthesis but its hydrated counter part, i.e.,  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  is not fully studied till today [17,18]. In recent years, we have used  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  as a versatile reagent for different organic transformations [19–21] because it is inexpensive, readily available, less toxic and air and moisture stable. So as a part of our ongoing research interest in green chemistry [22–26] and a continual efforts to use aluminum reagents [19–21,27,28] in various organic transformations we wish to report here a solvent free synthesis of DHPs catalyzed by 10 mol% of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  at 60 °C and their one-pot oxidation to pyridines by employing 30%  $\text{H}_2\text{O}_2$  in presence of 10 mol% of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  under microwave irradiation in hydrated media.

## 2. Experimental

Melting points were measured using Buchi B-540 apparatus and are uncorrected.  $^1\text{H}$  NMR spectra were recorded on Avance DPX 300 MHz FT NMR spectrometer. Chemical shifts are expressed in  $\delta$  units relative to tetramethylsilane (TMS) signal as internal reference. IR spectra were recorded on FT-IR-system-2000 Perkin Elmer spectrometer on KBr pellets or in  $\text{CHCl}_3$ . Mass spectra were recorded on ESQUIRE 3000 Mass Spectrometer. Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane as eluent.

Physical and spectroscopic data of all the known compounds are in agreement with those of authentic samples [6–16].

### 2.1. Typical experimental procedure for the synthesis of 1,4-dihydropyridines

In a 50 ml round-bottom flask, aldehyde (2 mmol), ethyl acetoacetate (4 mmol) and ammonium acetate (2 mmol) were stirred in presence of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  (10 mol%) in solvent free condition at 60 °C for 1.0–2.2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with ethyl acetate (2 × 25 ml), washed with 10%  $\text{NaHCO}_3$  solution and then organic layer with brine (2 × 15 ml), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The products were separated and purified by column chromatography on silica gel (60–120 mesh) using ethyl acetate/hexane mixture as eluent to afford pure 1,4-dihydropyridines.

#### 2.1.1. Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a)

M.P. 157–158 °C; Pale yellow crystals;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.20 (t, 6H), 2.26 (s, 6H), 4.06 (q, 4H), 4.98 (s, 1H), 5.62 (s, 1H), 7.09–7.26 (m, 5H); FT-IR ( $\text{CHCl}_3$ ,  $\text{cm}^{-1}$ ): 1697.7, 3337.9; MS ( $m/z$ ): 352 [ $\text{M}+\text{Na}$ ] $^+$ . Anal. Calcd. for  $\text{C}_{19}\text{H}_{23}\text{O}_4\text{N}$ : C, 69.28; H, 7.04; N, 4.25. Found: C, 69.24; H, 7.09; N, 4.21.

### 2.2. Typical experimental procedure for the oxidation of 1,4-dihydropyridines to pyridines

In a 50 ml beaker, DHP (2 mmol) was mixed with 10 mol%  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  and 2 equiv of 30%  $\text{H}_2\text{O}_2$  in a 2 ml mixture of  $\text{H}_2\text{O}$  and of EtOH (5:1). The reaction mixture was then irradiated in a domestic microwave oven for 4–8 min employing 180 W at 35 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with ethyl acetate (2 × 25 ml), washed with 10%  $\text{NaHCO}_3$  solution and then organic layer with brine (2 × 15 ml), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum to give the crude product which was reasonably pure (TLC and  $^1\text{H}$  NMR). However, analytically pure product can be obtained by recrystallisation of the crude product from ethanol or in case of liquid, the product may be purified by column chromatography on silica gel (60–120 mesh) using ethyl acetate/hexane mixture as eluent.

#### 2.1.2. Diethyl-2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate (5a)

M.P. 61–62 °C; Colorless crystals.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  0.92 (t, 6H), 2.60 (s, 6H), 4.01 (q, 4H), 7.19–7.35 (m, 5H); FT-IR ( $\text{CHCl}_3$ ,  $\text{cm}^{-1}$ ): 1727.6; MS ( $m/z$ ): 328 [ $\text{M}^++1$ ]. Anal. Calcd. for  $\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}$ : C, 69.71; H, 6.47; N, 4.28. Found: C, 69.76; H, 6.43; N, 4.25.

### 2.3. Typical experimental procedure for the synthesis of 1,4-dihydropyridines and their subsequent oxidation to pyridines in one-pot

In a 50 ml round-bottom flask, aldehyde (2 mmol), ethyl acetoacetate (4 mmol) and ammonium acetate (2 mmol) were stirred in presence of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  (10 mol%) in solvent free condition at 60 °C for 1.0–2.2 h. After complete formation of 1,4-dihydropyridines (monitored by TLC), the reaction mixture was treated with 2 equiv of 30%  $\text{H}_2\text{O}_2$  in 2 ml mixture of  $\text{H}_2\text{O}$  and EtOH (5:1). The reaction mixture was then irradiated in a domestic microwave oven for 4–8 min employing 180 W at 35 °C. After completion of the reaction, the product was extracted with ethyl acetate (2 × 25 ml), washed with 10%  $\text{NaHCO}_3$  solution, and then organic layer with brine (2 × 15 ml), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum to give the crude product which was purified by column chromatography on silica gel (60–120 mesh) using ethyl acetate/hexane mixture as eluent to afford pure pyridine derivatives.

## 3. Results and discussion

In the efforts to develop an efficient and environmentally benign methodology for the synthesis of DHPs we initiated our studies by subjecting catalytic amount of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  to the mixture of benzaldehyde, ethyl acetoacetate and ammonium acetate in solvent free condition at room temperature. Unfortunately, the resulted yield was very poor

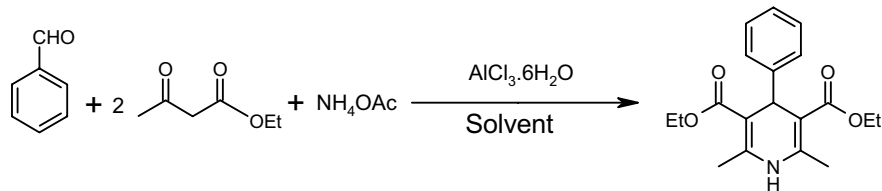
even after 24 h of stirring. To effect the reaction, various solvent systems were screened at different temperatures. We were pleased to see that the synthesis of DHP was efficiently catalyzed by  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  in solvent free condition at elevated temperature leading to high yield of product. The reaction condition was then optimized by conducting the reaction in different temperatures and employing different catalyst loadings. The results are summarized in Table 1. It is evident that the best result was obtained by the application of 10 mol% of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  in solvent free condition at 60 °C (Table 1, entry 7). Higher amount of the catalyst substantially reduce the amount of yield as side products formed, out of which the major one was found to be 2,6-diphenyl-3-ethoxycarbonyl-4-piperidone (m.p. 112–114 °C) [29]. Although, the role of higher amounts of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  for its formation is not clear. Other side products were present in less amounts and not identified.

The optimized reaction conditions were subsequently applied to the reaction between various aldehydes and  $\beta$ -ketoesters in presence of ammonium acetate in solvent free condition at 60 °C. In most cases, the desired DHP derivatives were obtained in high yields. Both electron rich and electron deficient aromatic aldehydes as well as heterocyclic ones worked well. Aliphatic aldehydes afforded equally good results. Many of the pharmacologically significant substitution patterns can be introduced with efficiency (Table 2). In a typical procedure, 2 mmol of aldehyde, 4 mmol of  $\beta$ -ketoester and 2 mmol of ammonium acetate were mixed in solvent free condition in presence of 10 mol% of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  and the reaction mixture was stirred for 1.0–2.2 h at 60 °C, after work-up, it produced the corresponding DHPs with good yields.

After the successful preparation of DHPs we next wished to aromatize them by an eco-friendly method. In this regard we envisioned that if we treat hydrogen peroxide to  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  it will generate HOCl because  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  is in reality [19–21,30],  $[\text{Al}(\text{H}_2\text{O})_6]\text{Cl}_3$ , and can exist as  $[\text{Al}(\text{H}_2\text{O})_5(\text{OH})]^{2+}\text{H}^+3\text{Cl}^-$  or  $[\text{Al}(\text{H}_2\text{O})_4(\text{OH})_2]^{2+}\text{H}^+3\text{Cl}^-$  etc. in solution and accordingly the oxidation of 1,4-DHP could be accomplished by HOCl. In an initial endeavor, diethyl-4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate were stirred in water and few drops of ethanol in presence of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  and  $\text{H}_2\text{O}_2$  at ambient temperature. But the resulted yield was very poor even after 12 h of stirring. The yield was not satisfactory even after 2 h reflux. In recent years, microwave assisted organic reactions has received much attention from chemists, because of the reduction of reaction time, formation of high yield of products and suppression of side products relative to conventional thermal heating. So we have decided to study the oxidation of 1,4-DHPs under microwave irradiation condition for the efficient synthesis of pyridines. To our delight, 1,4-DHP furnished the corresponding pyridine derivative in excellent yield under domestic microwave irradiation by  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}/30\% \text{H}_2\text{O}_2/\text{H}_2\text{O}/\text{EtOH}$  system. We then screened the reaction condition by taking different oxidants in presence of 10 mol% of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ . The results are documented in Table 3. Interestingly, almost quantitative yields were achieved when  $\text{H}_2\text{O}_2$  and  $\text{NaNO}_2$  were used as oxidants (Table 3, entries 1 and 2). Whereas, yields gradually decreased as we moved along  $\text{KClO}_3$ ,  $\text{KBrO}_3$  to  $\text{KIO}_3$  (Table 3, entries 3,4,5). These results are quite expected as the oxidizing strength of the corresponding acids which

Table 1

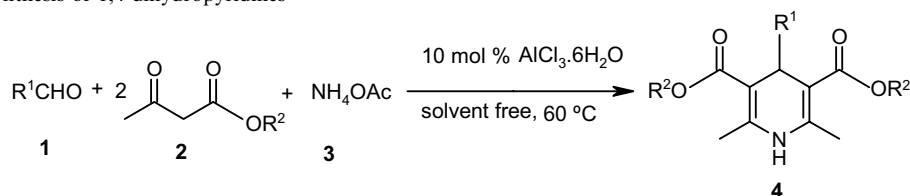
Condensation of benzaldehyde, ethyl acetoacetate and ammonium acetate catalyzed by  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  under different catalyst loadings, temperature and solvent systems



Entry	Catalyst load (mol%)	Solvents	Temperature (°C)	Time (h)	Conversion (%)	Yield (%)
1	10	Neat	rt	24	43	41
2	10	EtOH	rt	24	40	34
3	10	EtOH	60	3	71	67
4	10	MeOH	60	3	68	62
5	10	MeCN	60	3	57	53
6	10	Neat	65	1	83	80
7	10	Neat	60	1	83	80
8	10	Neat	50	1.3	77	75
9	5	Neat	50	1.3	80	77
10	5	Neat	60	1.3	80	77
11	15	Neat	50	1.3	79	76
12	15	Neat	60	1.3	75	74
13	30	Neat	50	1.3	74	74
14	30	Neat	60	1.3	71	70

Yield refers to isolated yield. Conversions determined by <sup>1</sup>H NMR spectroscopy.

Table 2  
AlCl<sub>3</sub> · 6H<sub>2</sub>O catalyzed synthesis of 1,4-dihydropyridines



Entry	R <sup>1</sup>	R <sup>2</sup>	Products	Time (h)	Conversion (%)	Yield (%)
a	C <sub>6</sub> H <sub>5</sub>	Et	<b>4a</b>	1.0	83	80
b	4-MeOC <sub>6</sub> H <sub>4</sub>	Et	<b>4b</b>	1.2	81	77
c	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Et	<b>4c</b>	2.2	77	75
d	4-ClC <sub>6</sub> H <sub>4</sub>	Et	<b>4d</b>	2.1	79	76
e	CH <sub>3</sub>	Et	<b>4e</b>	2.0	76	74
f	CH <sub>3</sub> CH <sub>2</sub>	Et	<b>4f</b>	2.0	77	76
g	(CH <sub>3</sub> ) <sub>2</sub> CH	Et	<b>4g</b>	1.5	81	78
h	2-Furyl	Et	<b>4h</b>	2.0	75	73
i	C <sub>6</sub> H <sub>5</sub>	Me	<b>4i</b>	1.0	82	78
j	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>4j</b>	1.2	77	75

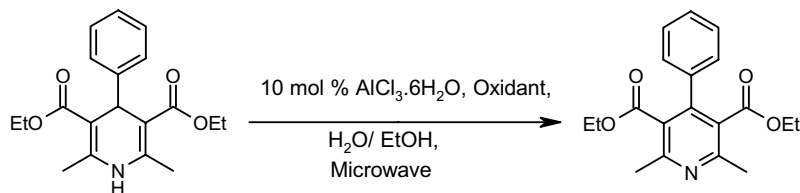
Yield refers to isolated yield. Conversions determined by <sup>1</sup>H NMR spectroscopy.

were generated in situ by the reaction of hydrogen peroxide or metal oxidants with HCl (source is AlCl<sub>3</sub> · 6H<sub>2</sub>O) follow the order HOCl > HClO<sub>3</sub> > HBrO<sub>3</sub> > HIO<sub>3</sub> [31]. On the other hand, in situ generation of nitrous acid from sodium nitrite and HCl in aqueous medium might have acted as a source of NO<sup>+</sup> [32], which seems to be responsible for the excellent yield of pyridine. The best result was achieved by carrying out the reaction with 2 equiv of 30% H<sub>2</sub>O<sub>2</sub> in presence of 10 mol% of AlCl<sub>3</sub> · 6H<sub>2</sub>O in H<sub>2</sub>O/EtOH as solvent system.

In light of these findings, we proceeded to investigate the substrate generality of AlCl<sub>3</sub> · 6H<sub>2</sub>O/H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O/EtOH mediated oxidation of DHPs under microwave irradiation. A wide variety of 1,4-DHPs having alkyl, aryl and heterocyclic

substituents were successfully oxidized to corresponding pyridines in excellent yield (Table 4). It was observed that the oxidation of DHP with secondary alkyl group at four-position was accompanied by expulsion of this (Table 4, entry g) substituent resulting dealkylated pyridines. This probably due to the electron releasing ability as well as stability of the corresponding radical. In a representative experiment, 2 mmol of DHP was treated with 10 mol% of AlCl<sub>3</sub> · 6H<sub>2</sub>O and 2 equiv of 30% H<sub>2</sub>O<sub>2</sub> in 2 ml mixture of H<sub>2</sub>O and EtOH (5:1) under microwave irradiation for 3–8 min, after work-up, it furnished the corresponding pyridine in excellent yields. The reaction was very clean and no side product was obtained in any run. Additionally,

Table 3  
Oxidation of 1,4-dihydropyridines to pyridines under different oxidants in the presence of 10 mol% AlCl<sub>3</sub> · 6H<sub>2</sub>O in H<sub>2</sub>O/EtOH under microwave irradiation



Entry	Oxidant	Time (m)	Conversion (%)	Yield (%)
1	30% H <sub>2</sub> O <sub>2</sub>	4	100	99
2	NaNO <sub>2</sub>	6	100	99
3	KClO <sub>3</sub>	10	77	72
4	KBrO <sub>3</sub>	10	54	51
5	KIO <sub>3</sub>	10	43	39
6	No oxidant	30	0	No reaction

Yield refers to isolated yield. Conversions determined by <sup>1</sup>H NMR spectroscopy.  
Reaction conditions: 2 equiv oxidants were used, MWI 180 W (35 °C).

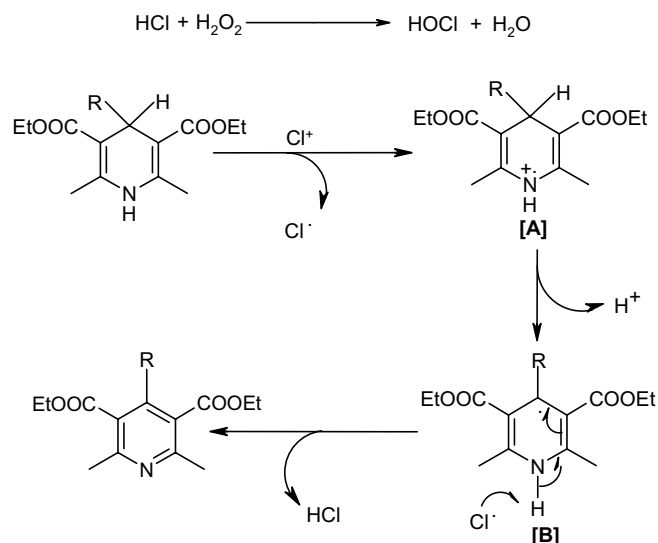
the crude products obtained were of high purity and in most of the cases no chromatographic separation were required.

Regarding the mechanism of the reaction, it may be proposed that the liberated HCl from  $[\text{Al}(\text{H}_2\text{O})_5(\text{OH})]^{2+} \text{H}^+ 3\text{Cl}^-$  or  $[\text{Al}(\text{H}_2\text{O})_4(\text{OH})_2]^+ 2\text{H}^+ 3\text{Cl}^-$  reacts with  $\text{H}_2\text{O}_2$  to generate HOCl. Then the oxidation may be initiated by a single electron transfer to  $\text{Cl}^+$  ion to produce chlorine free radical and a radical cation [A] that subsequently loses a proton to generate a radical [B] which in turn is attacked by chlorine free radical to produce pyridine in the reaction mixture (Scheme 1).

After carrying out the synthesis of 1,4-DHPs and their oxidation separately, we decided to accomplish both the reaction in one-pot four-component fashion. So, 1,4-DHPs were synthesized by employing 10 mol%  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  under solvent free condition at 60 °C and thus formed 1,4-DHPs were subsequently oxidized by adding 2 equiv of 30%  $\text{H}_2\text{O}_2$  in 2 ml mixture of  $\text{H}_2\text{O}$  and EtOH (5:1) in the same pot under microwave irradiation (Table 5). The product was not separated or purified after the first step and no additional amount of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  was added in the oxidation step.

#### 4. Conclusions

In conclusion, we have developed a simple and efficient synthetic protocol for the synthesis of 1,4-dihydropyridines under solvent free condition catalyzed by 10 mol% of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  at 60 °C and their aromatization with in situ generation of HOCl by the reaction of 30%  $\text{H}_2\text{O}_2$  and 10 mol%  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  in hydrated media under microwave irradiation in excellent yields. In addition to that both the synthesis and aromatization were achieved successfully in one-pot four-component fashion starting from alde-



Scheme 1. Plausible mechanism for the oxidation of 1,4-DHP to pyridine.

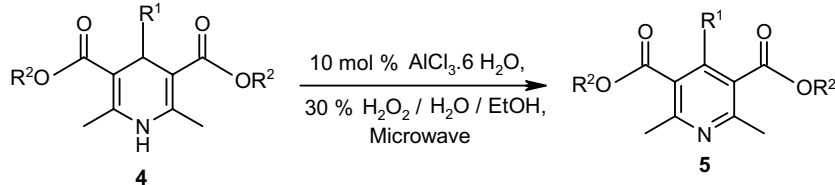
hydes,  $\beta$ -ketoesters and ammonium acetate following the same protocols. Mild reaction condition, cost efficiency, simplicity in operation, lower catalyst loading, reduction of reaction steps constitute significant features of this protocol.

#### Acknowledgements

The authors acknowledge the Director, and the Analytical Division of NEIST, Jorhat, for their helps. Also, SDS and PH thank CSIR, New Delhi for the grant of fellowships.

Table 4

Oxidation of 1,4-dihydropyridines to pyridines

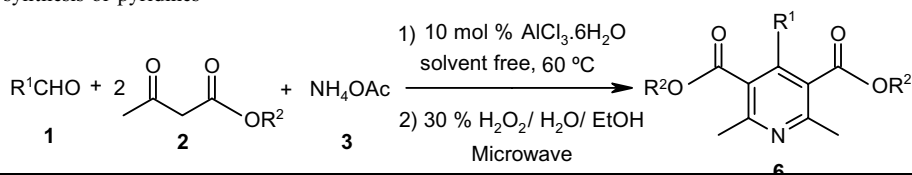


Entry	R <sup>1</sup>	R <sup>2</sup>	Products	Time (m)	Conversion (%)	Yield (%)
a	C <sub>6</sub> H <sub>5</sub>	Et	<b>5a</b>	4	100	99
b	4-MeOC <sub>6</sub> H <sub>4</sub>	Et	<b>5b</b>	5	98	97
c	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Et	<b>5c</b>	6	96	96
d	4-ClC <sub>6</sub> H <sub>4</sub>	Et	<b>5d</b>	6	97	97
e	CH <sub>3</sub>	Et	<b>5e</b>	5	97	96
f	CH <sub>3</sub> CH <sub>2</sub>	Et	<b>5f</b>	5	95	95
g	(CH <sub>3</sub> ) <sub>2</sub> CH	Et	<b>5g</b>	3	100	100
h	2-Furyl	Et	<b>5h</b>	8	94	94
i	C <sub>6</sub> H <sub>5</sub>	Me	<b>5i</b>	4	99	98
j	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>5j</b>	5	98	97

Yield refers to isolated yield. Conversions determined by <sup>1</sup>H NMR spectroscopy.

Reaction conditions: 2 equiv  $\text{H}_2\text{O}_2$  were used, MWI 180 W (35 °C).

Table 5  
One-pot four-component synthesis of pyridines



Entry	R <sub>1</sub>	R <sub>2</sub>	Products	Time (t <sub>1</sub> ) <sup>A</sup> (h)	Time (t <sub>2</sub> ) <sup>B</sup> (m)	Conversion (%)	Yield (%)
a	C <sub>6</sub> H <sub>5</sub>	Et	<b>6a</b>	1.0	4	58	55
b	4-MeOC <sub>6</sub> H <sub>4</sub>	Et	<b>6b</b>	1.2	5	54	52
c	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Et	<b>6c</b>	2.2	6	52	51
d	(CH <sub>3</sub> ) <sub>2</sub> CH	Et	<b>6d</b>	1.5	3	60	57
e	C <sub>6</sub> H <sub>5</sub>	Me	<b>6e</b>	1.0	4	57	54

Yield refers to isolated yield. Conversions determined by <sup>1</sup>H NMR spectroscopy.

Reaction conditions: 2 equiv oxidants were used, MWI 180 W (35 °C).

<sup>A</sup> t<sub>1</sub>: Reaction time for the synthesis of 1,4-DHPs.

<sup>B</sup> t<sub>2</sub>: Reaction time for the aromatization of 1,4-DHPs.

## References

- [1] D.M. Stout, A.I. Meyers, *Chem. Rev.* 82 (1982) 223.
- [2] R.H. Boecker, F.P. Guengerich, *J. Med. Chem.* 29 (1986) 1596.
- [3] D. Vo, W.C. Matowe, M. Ramesh, N. Iqbal, M.W. Wolowyk, S.E. Howlett, E.E. Knaus, *J. Med. Chem.* 38 (1995) 2851.
- [4] M. Rueping, A.P. Antonchick, T. Theissmann, *Angew. Chem., Int. Ed.* 45 (2006) 3683, and references cited therein.
- [5] F.P. Guengerich, M.V. Martin, P.H. Beaune, P. Kremers, T. Wolff, D.J. Waxman, *J. Biol. Chem.* 261 (1986) 5051.
- [6] S. Ko, C.-F. Yao, *Tetrahedron* 62 (2006) 7293, and references cited therein.
- [7] M.A. Chari, K. Syamasundar, *Catal. Commun.* 6 (2005) 624.
- [8] J.L. Donelson, R.A. Gibbs, S.K. De, *J. Mol. Catal. A: Chem.* 256 (2006) 309.
- [9] S.H. Mashraqui, M.A. Karnik, *Tetrahedron Lett.* 39 (1998) 4895.
- [10] R.S. Varma, D. Kumar, *Tetrahedron Lett.* 40 (1999) 21.
- [11] Y.-Z. Mao, M.-Z. Jin, Z.-L. Liu, L.-M. Wu, *Org. Lett.* 2 (2000) 741.
- [12] N. Nakamichi, Y. Kawashita, M. Hayashi, *Org. Lett.* 4 (2002) 3955.
- [13] M.M. Heravi, F.K. Behbahani, H.A. Oskooie, R.H. Shoar, *Tetrahedron Lett.* 46 (2005) 2775.
- [14] M. Nasr-Esfahani, M. Moghadam, S. Tangestaninejad, V. Mirkhani, A.R. Momeni, *Bioorg. Med. Chem.* 14 (2006) 2720.
- [15] J.J. Xia, G.W. Wang, *Synthesis* (2005) 2379.
- [16] J.S. Yadav, B.V.S. Reddy, A.K. Basak, G. Baishya, A.V. Narsaiah, *Synthesis* (2006) 451.
- [17] D.K. Dutta, D. Konwar, *J. Chem. Res.* (1998) 266.
- [18] D.K. Dutta, D. Konwar, J.S. Sandhu, *Indian J. Chem.* 34B (1995) 725.
- [19] M. Boruah, D. Konwar, *Synlett* (2001) 795.
- [20] M. Boruah, D. Konwar, *J. Org. Chem.* 67 (2002) 7138.
- [21] P. Gogoi, D. Konwar, S. Das Sharma, P.K. Gogoi, *Synth. Commun.* 36 (2006) 1259.
- [22] P. Gogoi, G.K. Sarmah, D. Konwar, *J. Org. Chem.* 69 (2004) 5153.
- [23] P. Gogoi, P. Hazarika, D. Konwar, *J. Org. Chem.* 70 (2005) 1934.
- [24] P. Gogoi, D. Konwar, *Org. Biomol. Chem.* 3 (2005) 3473.
- [25] P. Gogoi, D. Konwar, *Tetrahedron Lett.* 47 (2006) 79.
- [26] S. Das Sharma, P. Gogoi, D. Konwar, *Green Chem.* 9 (2007) 153.
- [27] D.K. Dutta, D. Konwar, *Tetrahedron Lett.* 41 (2000) 6227.
- [28] D. Konwar, R.C. Boruah, J.S. Sandhu, *Synthesis* (1990) 337.
- [29] V. Baliah, V. Gopalakrishnan, T.S. Govindarajan, *J. Indian Chem. Soc.* 31 (1954) 832.
- [30] N.N. Greenwood, A. Enandshow, *Chemistry of Elements*, Pergamon Press, 1984, p. 254.
- [31] J.D. Lee, *Concise Inorganic Chemistry*, Blackwell Science Ltd., Oxford, 1996, p. 613.
- [32] M.A. Zolfigol, M.H. Zebarjadian, G. Chehardoli, H. Keypour, S. Salehzadeh, M. Shamsipur, *J. Org. Chem.* 66 (2001) 3619.