Fast microwave-assisted oxidation of 1,4-dihydropyridines with \( \text{FeCl}_3\cdot\text{SiO}_2 \)

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Pyridine derivatives are easily obtained in high yields by microwave-promoted rapid oxidation of the corresponding 1,4-dihydropyridines with ferric chloride hexahydrate and silica gel under solvent-free conditions.

Keywords: 1,4-dihydropyridines, ferric chloride, microwave, oxidation

The oxidation of Hantzsch 1,4-dihydropyridines (1,4-DHPs) to the corresponding pyridines has attracted considerable attention since they have been extensively utilised as the analogues of NAD(P)H coenzymes to study the mechanism and synthetic potential of various redox processes.\textsuperscript{1} In addition, some 1,4-DHP based antihypertensive drugs (Ca\textsuperscript{2+} channel blockers) have been used in the treatment of various cardiovascular disorders.\textsuperscript{2} Consequently, this aminosilation reaction continues to attract the attention of researchers seeking milder and general protocols applicable to a wide range of 1,4-dihydropyridines. Many of the reported reagents involve the use of oxidants including CrO\textsubscript{3},\textsuperscript{3a} HNO\textsubscript{3},\textsuperscript{3b} KMnO\textsubscript{4},\textsuperscript{3c} DDQ,\textsuperscript{3d} Bi(NO\textsubscript{3})\textsubscript{3},\textsuperscript{3e} FeCl\textsubscript{3}.6H\textsubscript{2}O,\textsuperscript{3f} PCC,\textsuperscript{3g} CAN,\textsuperscript{3h} Bentonite clay supported manganese dioxide,\textsuperscript{3i} NO,\textsuperscript{3j} RuCl\textsubscript{3}/O\textsubscript{2},\textsuperscript{3k} Mn(OAC)\textsubscript{2}\textsuperscript{3l}. All the 1,4-DHPs were consumed after 2 minutes, with the exception of 4-aryl DHPs bearing electron-withdrawing groups (entries 8 and 9) that required a somewhat longer reaction time, 3 min, for complete conversion. Inspection of the Table reveals that FeCl\textsubscript{3}.SiO\textsubscript{2} is an air-stable reagent and the reaction times have been reduced compared to the conventional method.

Complete dealkylation occurs when the 1,4-DHPs bear a secondary alkyl group or a benzyl group at the 4-position. We observed (Table) that reaction times are dependent slightly on the nature of the substituent at the 4-position in the starting 1,4-DHPs. After chromatography or crystallisation the corresponding pyridines were isolated in good yields. Longer microwave irradiation times were found to increase the formation of side products. Whilst oxidation of 4-MeDHP gave only the pyridine derivative 13, the reaction with 4-isoPrDHP produced a mixture of 12 and 14. This is attributed to increased electron releasing ability and consequent greater stability of the corresponding secondary alkyl cation. In conclusion, the use of FeCl\textsubscript{3}.SiO\textsubscript{2} reagent for the microwave-assisted oxidation of DHPs provides a technique which is very fast, simple and ecofriendly.

![Scheme 1](image_url)

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Table 1  Microwave-promoted oxidation reaction of 1, 4-DHPs\textsuperscript{a, b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time MW/min</th>
<th>Product</th>
<th>Isolated yield/%</th>
<th>M.p. /°C</th>
<th>Lit. m.p. /°C</th>
<th>Thermal heating\textsuperscript{c}</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1</td>
<td>liq</td>
<td>95</td>
<td>69–70</td>
<td>69–70\textsuperscript{(3d)}</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>CH\textsubscript{3}</td>
<td>2</td>
<td>liq</td>
<td>90</td>
<td>–</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>CH\textsubscript{3}CH\textsubscript{2}\textsubscript{c,d}</td>
<td>2</td>
<td>liq</td>
<td>75</td>
<td>liq\textsuperscript{(3d)}</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>(CH\textsubscript{3})\textsubscript{2}CH</td>
<td>2</td>
<td>liq</td>
<td>85</td>
<td>69–70</td>
<td>69–70\textsuperscript{(3d)}</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>2</td>
<td>liq</td>
<td>93</td>
<td>62–63</td>
<td>63–64\textsuperscript{(9)}</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}</td>
<td>2</td>
<td>liq</td>
<td>82</td>
<td>69–70</td>
<td>69–70\textsuperscript{(3d)}</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>3</td>
<td>liq</td>
<td>93</td>
<td>66–67</td>
<td>65–67\textsuperscript{(3d)}</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>3-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>3</td>
<td>liq</td>
<td>80</td>
<td>61–63</td>
<td>61–63\textsuperscript{(3d)}</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{4}</td>
<td>2</td>
<td>liq</td>
<td>90</td>
<td>50–52</td>
<td>51–53\textsuperscript{(30)}</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>4-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
<td>2</td>
<td>liq</td>
<td>91</td>
<td>71–72</td>
<td>72–73\textsuperscript{(30)}</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>2-Furyl</td>
<td>2</td>
<td>liq</td>
<td>88</td>
<td>liq\textsuperscript{(31)}</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All of 1, 4-DHPs were prepared according to literature procedure.\textsuperscript{9}

\textsuperscript{b}All products are known compounds and were characterised by their mps and NMR spectra.

\textsuperscript{c}Compound 12 was also detected.

Experimental
In a typical experimental procedure, FeCl\textsubscript{3}.6H\textsubscript{2}O (0.27 g, 1 mmol) was mixed with silica gel (0.54g). The 1,4-dihydropyridine (0.5mmol) was added to the above supported reagent and mixed thoroughly in an agate mortar. The reaction mixture was transferred to a beaker which was placed in a domestic microwave oven and irradiated for the required period of time to complete the reaction (as monitored by TLC). The reaction mixture was extracted with chloroform, the filtrate evaporated and the residue crystallised from aq. EtOH to afford the corresponding pyridine, (see Table).

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References: