CHAPTER III

Catalytic Oxidative Conversion of Alcohols, Aldehydes and Amines into Nitriles using KI/I₂–TBHP system
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Introduction:

The need for simple and efficient strategies to obtain complex molecules and their analogues is a driving force for the development of new methodologies. Nitriles are useful functional groups in synthetic organic chemistry as they are the most important precursors for esters, amides, carboxylic acids, amines, and nitrogen-containing heterocycles like oxazoles and imidazoles. It is useful for the introduction of nitrogen into organic molecules for the activation of adjacent -CH bonds. Moreover, nitriles can be transformed into heterocyclic compounds of significant biological importance.¹

The organic nitrile group has quite different properties associated with lethal inorganic cyanide. Laetrile, for example, is extracted from apricot kernels, and used earlier as an anticancer drug.

![Laetrile](image)

Figure 1: Laetrile

Another notable example is an insecticide decamethrin which is having nitrile functional group and has a safety factor of >10,000 for mustard beetles over mammals, and leaves no significant environmental residue.
State of the art

The most common and well-known procedure for the preparation of nitriles is the nucleophilic displacement of substrates with suitable leaving groups such as halogen compounds, aryl sulfonates, alcohols, esters, ethers, nitro or amino compounds and diazonium salts with inorganic cyanide ions. The other alternative procedures are dehydration of amides and aldoximes, conversion of alcohols, aldehydes and carboxylic acids to nitriles using various reagents and direct conversion of amines. Some of the recent reports are discussed.

From amides:

Shia and co-workers have developed an operationally simple and high-yielding procedure for the conversion of primary amides to the corresponding nitriles, using ethyl dichlorophosphate (EtOPCl₂) / DBU as the mild dehydrating agent (Scheme 1).3a

\[
\text{Scheme 1}
\]

Bergman and Ruck have developed a new method for the dimethylzirconocene-mediated conversion of primary amides to the corresponding nitriles in excellent yields (Scheme 2).3b
From aldoximes:

Chang and Yang carried out catalytic dehydration of aldoximes with a catalyst system of [RuCl₂(p-cymene)]₂/molecular sieves under essentially neutral and mild conditions, and various types of cyano compounds are produced in good to excellent yields (Scheme 3).

\[
\text{RCHO-NH}_2 + \text{[RuCl}_2(p\text{-cymene})]_2 \xrightarrow{\text{MS 4A}} \text{RCN} + \text{H}_2\text{O}
\]

Scheme 3

From alcohols:

Chen et al. presented the synthesis of nitriles from the corresponding primary alcohols by nickel catalyzed oxidation with tetrabutylammonium peroxydisulfate in the presence of NH₄HCO₃ under basic conditions (Scheme 4).

\[
\text{RCH}_2\text{OH} \xrightarrow{\text{Cu(HCO}_3}_2\text{Ni(HCO}_3}_2, \text{aq KOH, } \text{t}-\text{PrOH}} \text{RCN}
\]

Scheme 4

Iranpoor et al. showed that triphenylphosphine and 2,3-dichloro-5,6-dicyanobenzoquinone affords an adduct, which in the presence of n-Bu₄NCN converts alcohols, thiols, and trimethylsilyl ethers into their corresponding alkyl cyanides in good to excellent yields at room temperature (Scheme 5).
Togo and Mori carried out the direct oxidative conversion of alcohols to nitriles in the presence of excess iodine and aqueous ammonia (Scheme 6). 5c

\[
\text{RCH}_2\text{OH} \xrightarrow{\text{I}_2 \text{(3equiv), aq.NH}_3} \text{RCN} \quad 60^\circ\text{C} \quad 66\text{-}99\%
\]

**Scheme 6**

*From aldehydes:*

As far as conversion of aldehydes to nitriles is concerned, several methods are reported and some of them are listed below (Table 1).

\[
\text{RCHO} \xrightarrow{\text{Methods a-i}} \text{RCN}
\]

**Table 1. Conversion of aldehydes to nitriles under different conditions:**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents (or) catalytic system</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH\textsubscript{2}OH.HCl, NaHSO\textsubscript{4}.SiO\textsubscript{2}, M.W.\textsuperscript{6c}</td>
<td>86 - 93</td>
</tr>
<tr>
<td>2</td>
<td>IBX/ aq. NH\textsubscript{3}.\textsuperscript{6g}</td>
<td>88 - 95</td>
</tr>
<tr>
<td>3</td>
<td>Dry- Al\textsubscript{2}O\textsubscript{3}, NH\textsubscript{2}OH.HCl, MeSO\textsubscript{2}Cl, 100°C.\textsuperscript{6h}</td>
<td>85 - 98</td>
</tr>
<tr>
<td>4</td>
<td>HOF. CH\textsubscript{3}CN.\textsuperscript{6i}</td>
<td>80 - 98</td>
</tr>
<tr>
<td>5</td>
<td>NH\textsubscript{2}OH.HCl, KF/ Al\textsubscript{2}O\textsubscript{3}, DMF, 100°C.\textsuperscript{6j}</td>
<td>73 - 91</td>
</tr>
<tr>
<td>6</td>
<td>NH\textsubscript{2}OH.HCl/ Et\textsubscript{3}N, Phthalic anhydride.\textsuperscript{6k}</td>
<td>80 - 95</td>
</tr>
<tr>
<td>7</td>
<td>NaI, NH\textsubscript{2}OH.HCl, CH\textsubscript{3}CN, reflux.\textsuperscript{6l}</td>
<td>75 - 98</td>
</tr>
<tr>
<td>8</td>
<td>CAN, liq. NH\textsubscript{3}, H\textsubscript{2}O, 0°C.\textsuperscript{6m}</td>
<td>69 - 94</td>
</tr>
<tr>
<td>9</td>
<td>NaN(SiMe\textsubscript{3})\textsubscript{2}, DMEU, THF, sealed tube,185°C, H\textsubscript{3}O.\textsuperscript{6n}</td>
<td>81 - 98</td>
</tr>
</tbody>
</table>

73
From acids:

Kangani et al. carried out the one step synthesis of acyl nitriles from carboxylic acids using bis(2-methoxyethyl)aminosulfur trifluoride (Scheme 7).\textsuperscript{7c}

\[
\text{RCOOH} + \text{NaN}_3 \xrightarrow{\text{TEA, PPh}_3, \text{CH}_2\text{Cl}_2, \text{Deoxo-fluor, 0°C - rt}} \text{RCN} \quad 83 - 96\%
\]

Scheme 7

Telvekar and Rane carried out the conversion of various carboxylic acids to nitriles using diphosphorus tetraiodide in combination with ammonium carbonate at room temperature (Scheme 8).\textsuperscript{7d}

\[
\text{RCOOH} \xrightarrow{\text{Diphosphorus tetraiodide, NH}_4\text{CO}_3, \text{CS}_2, \text{rt}} \text{RCN} \quad 80 - 92\%
\]

Scheme 8

From amines:

In case of oxidative transformation of primary amines to nitriles,\textsuperscript{8} a number of procedures are reported mostly using stoichiometric metal oxidants such as nickel peroxide,\textsuperscript{9} copper reagents in combination with oxygen,\textsuperscript{10} silver reagents,\textsuperscript{11} cobalt peroxide\textsuperscript{12} and lead tetraacetates.\textsuperscript{13} The catalytic oxidations using NiSO\textsubscript{4}/K\textsubscript{2}S\textsubscript{2}O\textsubscript{8},\textsuperscript{14} RuCl\textsubscript{3}/O\textsubscript{2},\textsuperscript{15} RuCl\textsubscript{3}/K\textsubscript{2}S\textsubscript{2}O\textsubscript{8},\textsuperscript{16} and ruthenium complex/O\textsubscript{2},\textsuperscript{17} Ru supported on Alumina/O\textsubscript{2}\textsuperscript{18} have been reported. Nitriles are also obtained by direct electrochemical oxidation\textsuperscript{19} or indirect electrochemical oxidations with mediators.\textsuperscript{20} Recently, molecular iodine in stoichiometric amounts, in combination with aq.NH\textsubscript{3} is used for the above transformation.\textsuperscript{21}
Kaneda and co-workers found out that a hydroxyapatite-bound ruthenium complex could efficiently catalyze the aerobic oxidation of various primary amines to nitriles which are further hydrated to amides in the presence of water (Scheme 9).8a

$$\text{RCH}_2\text{NH}_2 + \text{RuHAP, O}_2 \xrightarrow{\text{Toluene, 110 °C}} \text{RCH}_2\text{CN} \quad 81 - 99\%$$

**Scheme 9**

Chen et al. carried out the same conversion using trichloroisocyanuric acid in the presence of catalytic TEMPO (Scheme 10).8f

$$\text{RCH}_2\text{NH}_2 + \text{TCCA, TEMPO (1 mol%) \xrightarrow{\text{CH}_2\text{Cl}_2, 10 °C}} \text{RCH}_2\text{CN} \quad 80 - 91\%$$

**Scheme 10**

Togo and Iida reported a high-yield procedure for the direct conversion of various primary alcohols, primary, secondary and tertiary amines to the corresponding nitriles with molecular iodine in aq.NH$_3$ or 1,3-diiodo-5,5-dimethylhydantoin (DIH) in aq. NH$_3$ (Scheme 11).8d

$$\text{RCH}_2\text{NH}_2 \xrightarrow{\text{aq. NH}_3 (3.0 \text{ mL}), 60 °C} \text{RCH}_2\text{CN} \quad 56 - 90\%$$

$$\text{RCH}_2\text{NX} \xrightarrow{\text{DIH, aq. NH}_3 (3.0 \text{ mL})} \text{RCN} \quad 65 - 98\%$$

**Scheme 11**

Savelli and co-workers developed an aqueous reaction medium, based on a surfactant solution of dimethyldodecylamine N-oxide (DDAO) for the oxidative dehydrogenation of primary amines using NiSO$_4$ as catalyst and K$_2$S$_2$O$_8$ as oxidant (Scheme 12).14b
Mizuno and Yamaguchi reported the effective aerobic heterogeneous oxidation of various amines to corresponding nitriles or imines using Ru/Al₂O₃ (Scheme 13).¹⁸

The conventional methods and several of these reported procedures often require hazardous reagents, severe reaction conditions, expensive catalysts and additives. To overcome some of these economical and environmental related problems, catalytic methods involving the direct conversion of aldehydes and alcohols to nitriles using commercially available aqueous ammonia or direct conversion primary amines to nitriles via dehydrogenation could be a viable alternative and clean route (Scheme 14).

Moreover, this route will eliminate the additional step involved in the preparation of imines, amides and aldoximes. Although several oxidative procedures using
stoichiometric reagents are known for the synthesis of nitriles, only a few catalytic methods involving dehydrogenation protocols have been reported.\textsuperscript{22}

**Present work**

In this chapter, direct conversion of alcohols, aldehydes and primary amines to their corresponding nitriles selectively using catalytic amount of KI or iodine in combination with TBHP as an external oxidant is described (Scheme 15).

\[ \text{RCH}_2\text{OH} \xrightarrow{\text{KI} / \text{I}_2, \text{TBHP (3.8 mmol)}} \text{aq.NH}_3, 60 \, ^\circ\text{C} \rightarrow \text{RCN} \text{ up to 98\%} \]

\[ \text{RCHO} \xrightarrow{\text{KI} / \text{I}_2, \text{TBHP (2.2 mmol)}} \text{aq.NH}_3, 60 \, ^\circ\text{C} \rightarrow \text{RCN} \text{ up to 92\%} \]

\[ \text{RCH}_2\text{NH}_2 \xrightarrow{\text{KI, TBHP (1.1 mmol)}} \text{H}_2\text{O}, \text{rt} \rightarrow \text{RCN} \text{ up to 78\%} \]

**Scheme 15**

**Results and Discussion**

For the initial optimization studies, 4-methoxy benzyl alcohol was chosen as the model substrate. A mixture of 4-methoxy benzyl alcohol and aq.NH$_3$ solution was stirred under different conditions, and the results are summarized in Table 2. There was no product formation in the absence of either catalyst or oxidant (Table 2, entries 1, 2). Reactions at room temperature provided lower product formation, but by increasing the catalyst loading from 5 mol % to 20 mol %, the conversion improved significantly (Table 2, entries 3-5). Under similar reaction conditions, both KI and I$_2$ have shown same activities (Table 2, entries 5,6). Further, increasing the temperature and decreasing the amount of catalyst led to the quantitative conversion of benzyl alcohol to nitrile (Table 2,
entry 7). The role of other commercially available oxidants such as H$_2$O$_2$ and NaOCl on the model reaction was also examined, but there was no observable product formation (Table 2, entries 9,10). Thus KI or I$_2$ in conjunction with TBHP as the oxidant in aq.NH$_3$ at 60 °C was fixed as the optimum condition for other substrates (Table 2, entries 7,8).

Table 2. Optimization studies for the conversion of alcohol to nitrile$^{[a]}$

<table>
<thead>
<tr>
<th>S.No</th>
<th>Catalyst [mmol]</th>
<th>Oxidant [mmol]</th>
<th>Temp (°c)</th>
<th>Yield [%]$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>TBHP [3.8]</td>
<td>RT</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>KI (0.2)</td>
<td>--</td>
<td>RT</td>
<td>-- (4%)</td>
</tr>
<tr>
<td>3</td>
<td>KI (0.05)</td>
<td>TBHP [2.2]</td>
<td>RT</td>
<td>10 (9)</td>
</tr>
<tr>
<td>4</td>
<td>KI (0.1)</td>
<td>TBHP [2.2]</td>
<td>RT</td>
<td>17 (15)</td>
</tr>
<tr>
<td>5</td>
<td>KI (0.2)</td>
<td>TBHP [2.2]</td>
<td>RT</td>
<td>29 (32)</td>
</tr>
<tr>
<td>6</td>
<td>I$_2$ (0.1)</td>
<td>TBHP [2.2]</td>
<td>RT</td>
<td>29 (31)</td>
</tr>
<tr>
<td>7</td>
<td>KI (0.05)</td>
<td>TBHP [2.2]</td>
<td>60</td>
<td>99 (99)</td>
</tr>
<tr>
<td>8</td>
<td>I$_2$ (0.025)</td>
<td>TBHP [2.2]</td>
<td>60</td>
<td>99 (99.5)</td>
</tr>
<tr>
<td>9</td>
<td>KI (0.05)</td>
<td>H$_2$O$_2$ [2.2]</td>
<td>60</td>
<td>--</td>
</tr>
<tr>
<td>10</td>
<td>KI (0.05)</td>
<td>NaOCl [2.2]</td>
<td>60</td>
<td>--</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: Alcohol (1 mmol), aq. NH$_3$ (3 mL), 15 h. [b] Yields based on $^1$H NMR, GC yields given in parenthesis [c] Aldehyde is the major product.
The general applicability of this method was further evaluated for structurally diverse alcohols under optimized reaction conditions using KI or I₂ as catalyst (Table 3). The reactivity depends on the nature of alcohols used. Thus benzyl alcohols having electron-donating groups were smoothly converted to the corresponding nitriles in good yields (Table 3, entries 1-6), while benzy alcohols with electron-withdrawing groups have shown slightly lower yield (Table 3, entries 8–11).

In case of p-(Methylthio)benzyl alcohol (Table 3, entry 4), apart from the desired, p-(Methylthio)benzonitrile, p-methanesulfinyl benzonitrile was also observed as a minor product (10% by GC analysis). The reaction with p-nitrobenzyl alcohol under optimized condition resulted in the formation of p-nitrobenzamide as the major product, but when the reaction was carried out at room temperature with 20 mol % of KI as catalyst, 70% of desired product was obtained (Table 3, entry 12). In the case of primary aliphatic alcohols such as 1-octanol and 1-decanol, the reactions under optimized reaction condition provided very lower conversions. However, increasing the amount of catalyst to 20 mol % led to moderate conversions (Table 3, entries 13 and 14). Similarly the reaction with cinnamyl alcohol led to cinnamoniitrile in 30% isolated yield. In the case of heteroaromatics, the reaction with 2-pyridyl carbinol was tested which provided amide as the major product along with the required nitrile product which was analyzed by ¹H NMR and further confirmed by GC and GC–MS.
Table 3. KI/I\(_2\)–TBHP catalysed oxidative conversion of alcohols to nitriles \(^a\)

| Entry | Substrate | Product | Yield (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>KI (5 mol%)</td>
</tr>
<tr>
<td>1</td>
<td>MeO–CH(_2)OH</td>
<td>MeO–CN</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>OMe–CH(_2)OH</td>
<td>CN</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>OMe–OMe</td>
<td>OMe–CN</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>MeS–CH(_2)OH</td>
<td>MeS–CN</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)OH</td>
<td>Me–CN</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>Me–CH(_2)OH</td>
<td>Me–CN</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)OH</td>
<td>CN</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>Cl–CH(_2)OH</td>
<td>Cl–CN</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>CH(_2)OH</td>
<td>CN</td>
<td>79</td>
</tr>
<tr>
<td>10</td>
<td>Br–CH(_2)OH</td>
<td>Br–CN</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^a\) Reactions performed under anhydrous conditions at room temperature for 24 h.
<table>
<thead>
<tr>
<th>Entry</th>
<th>substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>KI (5 mol%)</strong></td>
</tr>
<tr>
<td>11</td>
<td>[F - CH&lt;sub&gt;2&lt;/sub&gt;OH]</td>
<td>[F - CN]</td>
<td>72</td>
</tr>
<tr>
<td>12</td>
<td>[O&lt;sub&gt;2&lt;/sub&gt;N - CH&lt;sub&gt;2&lt;/sub&gt;OH]</td>
<td>[O&lt;sub&gt;2&lt;/sub&gt;N - CN]</td>
<td>5 (70)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>[6 CH&lt;sub&gt;2&lt;/sub&gt;OH]</td>
<td>[6 CN]</td>
<td>41&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td>[8 CH&lt;sub&gt;2&lt;/sub&gt;OH]</td>
<td>[8 CN]</td>
<td>29&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>[benzyl OH]</td>
<td>[benzyl CN]</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>[pyridine OH]</td>
<td>[pyridine CN]</td>
<td>36</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: Alcohol (1 mmol), aq.NH<sub>3</sub> (3 mL), TBHP (3.8 mmol), 60 °C, 15 h. [b] Isolated yield. [c] Reaction at rt with 20 mol% of KI. [d] Yields based on <sup>1</sup>H NMR.

The present catalytic system was further examined for the direct conversion of aldehydes to nitriles, and the results are summarized in Table 4. The conversion was very good irrespective of the electronic nature of the aldehydes. Moreover, these reactions were found to be faster than alcohols. In case of <i>p</i>-nitrobenzaldehyde, amide was observed as the major product which was similar to the reaction with <i>p</i>-nitrobenzyl alcohol. With aliphatic aldehyde, (octanal) the yields are comparable to that of alcohol ones.
### Table 4. KI/I$_2$ –TBHP catalysed oxidative conversion of aldehydes to Nitriles$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>KI</td>
</tr>
<tr>
<td>1</td>
<td>MeO-(\text{CHO})</td>
<td>MeO-(\text{CN})</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>(\text{CHO})</td>
<td>(\text{CN})</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>(\text{CHO})</td>
<td>(\text{CN})</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>(\text{CHO})</td>
<td>(\text{CN})</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>(\text{CHO})</td>
<td>(\text{CN})</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>(\text{CHO})</td>
<td>(\text{CN})</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>Cl-(\text{CHO})</td>
<td>Cl-(\text{CN})</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>Br-(\text{CHO})</td>
<td>Br-(\text{CN})</td>
<td>85</td>
</tr>
</tbody>
</table>
The catalytic studies were extended for the direct conversion of primary amines to nitriles, and the products were analyzed by GC and were confirmed by GC–MS. Initial optimization was carried out using benzyl amine as the model substrate (Table 5). Reaction without catalyst and oxidant does not yield the required nitrile product. The reaction was carried out in various solvents, among which water proves to be the better one with respect to yields as well as its benign nature. By increasing the temperature and decreasing the catalyst loading, conversions are lower. The optimized reaction condition was, benzyl amine treated with 5 mol % of KI, 1.1 mmol of TBHP at room temperature in water, to afford 73% of the desired nitrile product (Table 4, entry 3).

### Table 5: Conversion of Primary Amines to Nitriles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>K&lt;sub&gt;1&lt;/sub&gt;</th>
<th>I&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>F-CH=CHO</td>
<td>F-CH=CN</td>
<td>73 67</td>
<td>73</td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td>F-CHO</td>
<td>F-CN</td>
<td>68 67</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>OHC-F-CN</td>
<td>NC-F-CN</td>
<td>72 67</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>12</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;N-CH=CHO</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;N-CH=CN</td>
<td>amide 12</td>
<td>40 42</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>6-CHO</td>
<td>6-CN</td>
<td>40 42</td>
<td>40</td>
<td>42</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: Aldehyde (1 mmol), aq. NH<sub>3</sub> (3 mL), TBHP (2.2 mmol), 60 °C, 8h. [b] Yields based on H NMR.
Table 5. Optimization studies for the conversion of amine to nitrile

\[
\text{NH}_2 \xrightarrow{\text{Cat, Oxidant, Solvent, Temp}} \text{CN}
\]

<table>
<thead>
<tr>
<th>S.No</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Yield [%]^[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[mmol]</td>
<td>[mmol]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>--</td>
<td>TBHP [1.1]</td>
<td>RT</td>
<td>H₂O</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>KI (0.2)</td>
<td>--</td>
<td>RT</td>
<td>H₂O</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>KI (0.2)</td>
<td>TBHP [1.1]</td>
<td>RT</td>
<td>H₂O</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>KI (0.05)</td>
<td>TBHP [1.1]</td>
<td>80</td>
<td>H₂O</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>KI (0.2)</td>
<td>TBHP [1.1]</td>
<td>RT</td>
<td>CH₃CN</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>KI (0.2)</td>
<td>TBHP [1.1]</td>
<td>RT</td>
<td>CHCl₃</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>KI (0.2)</td>
<td>TBHP [1.1]</td>
<td>RT</td>
<td>CH₃OH</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>KI (0.2)</td>
<td>TBHP [1.1]</td>
<td>RT</td>
<td>THF</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>KI (0.2)</td>
<td>TBHP [2.2]</td>
<td>RT</td>
<td>aq. NH₃</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>KI (0.2)</td>
<td>TBHP [1.1]</td>
<td>RT</td>
<td>aq.NH₃:THF(2:1)</td>
<td>6</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: Amine (1 mmol), solvent (3 mL), 15 h. [b] Yields based on GC.
Further the feasibility of this reaction was examined for various amine as substrates and the results are summarized in Table 6. Moderate yields were obtained for both electron rich and electron deficient systems (Table 6, entry 1-5). Aliphatic amines were also converted to nitriles smoothly under the optimized reaction conditions (Table 6, entry 6-8). However, the conversion was low for aliphatic amines, which may be due to solubility problem of the long chain aliphatic amines. In case of hexadecyl amine, when the reaction was carried out with acetonitrile as the solvent, there was slight increase in the conversion (Table 6, entry 6). This was due to the increased solubility of the reactant in acetonitrile. In case of heteroaromatic system, pyridyl 2-methanamine, the nitrile product was observed in moderate yield. All the products were analyzed by $^1$H NMR and further confirmed by GC and GC-MS.

Since the aromatic nitriles are very useful and expensive products, the feasibility of the present catalytic system on multi-gram scale was examined for the synthesis of p-methoxy benzonitrile. Reaction of p-methoxybenzyl alcohol (5 g, 36.2 mmol) with 20 mol % of KI and 3.2 equiv of TBHP at 60 °C provided pure nitrile product quantitatively after 24 h.
Table 6. KI–TBHP catalysed oxidative conversion of alcohols to Nitriles

<table>
<thead>
<tr>
<th>S.No</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[CH2NH2]</td>
<td>[CN]</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>MeO—^~^-CH2NH2</td>
<td>MeO—^~^-CN</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Me—^~^-CH2NH2</td>
<td>Me—^~^-CN</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>F—^~^-CH2NH2</td>
<td>F—^~^-CN</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Cl—^~^-CH2NH2</td>
<td>Cl—^~^-CN</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>CH3-(CH2)15-NH2</td>
<td>CH3-(CH2)14-CN</td>
<td>58 (70)c</td>
</tr>
<tr>
<td>7</td>
<td>CH3-(CH2)11-NH2</td>
<td>CH3-(CH2)10-CN</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>CH3-(CH2)17-NH2</td>
<td>CH3-(CH2)16-CN</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>phenyl—^~^-NH2</td>
<td>phenyl—^~^-CN</td>
<td>59</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: Amine (1 mmol), H2O (3 mL), KI(0.20 mmol), TBHP(1.1 mmol), RT, 8 h. [b] Yields based on 1H NMR. [c] CH3CN used as the solvent.

**Plausible mechanism:**

Based on the present results, the following mechanism was proposed as shown in Scheme 16. In the case of alcohol a, formation of aldehyde b could be an intermediate, which can be achieved by using either KI or I2 as a catalyst (Scheme 16 a). Aldehyde b, thus formed reacts with ammonia to form an imine c. Imine further reacts with iodine to form N-iodo aldime d, which finally transforms into nitrile by β-elimination of HI with...
ammonia (Scheme 16b). In case of direct conversion of primary amines to nitrile, a similar mechanism via imine and N-iodo aldime was expected.\textsuperscript{4c}

Scheme 16a KI/I\textsubscript{2} catalyzed oxidation of alcohol to aldehydes

It has been proposed earlier that under alkaline conditions, iodine involves in multiple equilibriums, in which hypoiodous acid is one of the possible intermediates.\textsuperscript{23a} Similar intermediate was also proposed under acidic conditions with NaI and H\textsubscript{2}O\textsubscript{2} for the a-iodination of ketones.\textsuperscript{23b} The catalytic cycle was established as the oxidant TBHP re-oxidise iodide to iodine and vice versa.

Scheme 16b KI/I\textsubscript{2} catalyzed oxidation of aldehydes to nitrile with ammonia.
Chapter III

Conclusion:

It can be concluded that a simple and convenient method has been developed for the direct conversion of alcohols, aldehydes and primary amines to their corresponding nitriles selectively using catalytic amount of KI or iodine in combination with TBHP as an external oxidant. The present method avoids the use of expensive metal catalysts and hypervalent iodine reagents. Moreover, the present non-transition metal catalytic system also provides an easy scale-up and separation protocol.

Experimental Section

General

$^1$H NMR spectra were recorded on a Gemini-200 MHz or an Avance-300 MHz spectrometer in CDC$_3$ with TMS as an internal standard. GC were recorded on Schimuzu using BP-01 (30M X 0.25 mm X 1.0 μm) column. GC-MS spectra were recorded on Trace DSQ GC-MS spectrometer using BP-01 (30M X 0.25 mm X 1.0 μm) column.

Synthesis of Nitriles from Alcohols and Aldehydes:

To a solution of alcohol (1.0 mmol), potassium iodide (0.05 mmol) in 3 mL of aq. NH$_3$, a solution of 70% aqueous TBHP (3.8 mmol) was added dropwise over a period of 30 min at room temperature, followed by stirring at 60 °C. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was quenched with saturated aqueous Na$_2$S$_2$O$_3$, washed with brine, extracted with ethyl acetate and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using hexane / ethyl acetate (9:1) mixture and was analyzed by $^1$H NMR, GC and GC-MS. Similar procedure was
followed for synthesis of nitriles from aldehydes but with lesser amount of TBHP (2.2 mmol).

Spectral data:

4-Methoxy-benzonitrile: (Table 2 Entry 1)

\[
\text{MeO-} \quad \text{CN}
\]

Isolated yield = 98%; \textsuperscript{1}H NMR \(\delta\) (300 MHz, CDCl\textsubscript{3}) 7.60 (d, \(J = 8.3\) Hz, Ar, 2H), 6.97, (d, \(J = 9.0\) Hz, Ar, 2H), 3.90 (s, \(-\text{OCH}_3\), 3H).

GC-MS m/z 132.9 (M\textsuperscript{+} peak), 102.9, 89.9, 62.9.

2-Methoxy-benzonitrile: Table 2 Entry:2

\[
\text{MeO-} \quad \text{CN}
\]

Isolated yield = 98%; \textsuperscript{1}H NMR \(\delta\) (300 MHz, CDCl\textsubscript{3}) 7.52 (m, Ar, 2H), 6.98, (m, Ar, 2H), 3.94, (s, \(-\text{OCH}_3\), 3H). GC-MS m/z 133.0 (M\textsuperscript{+} peak), 104.0, 90.0, 63.0.

2,6-di Methoxy-benzonitrile: Table 2 Entry:3

\[
\text{OMe} \quad \text{CN}
\]

Isolated yield = 98%; \textsuperscript{1}H NMR \(\delta\) (300 MHz, CDCl\textsubscript{3}) 7.20 (m, Ar, 2H), 6.90, (m, Ar, 1H), 3.94 (s, \(-\text{OCH}_3\), 3H), 3.82 (s, \(-\text{OCH}_3\)). GC-MS m/z 162.9 (M\textsuperscript{+} peak), 147.9, 119.9, 92.0, 78.9, 65.0.

\(p\)-methylsulfanyl-benzonitrile: Table 2 Entry:4

\[
\text{S} \quad \text{CN}
\]

Isolated yield = 75%; \textsuperscript{1}H NMR \(\delta\) (300 MHz, CDCl\textsubscript{3}) 7.58 (d, \(J = 8.8\) Hz, Ar, 2H), 7.28, (d, \(J = 8.7\) Hz, Ar, 2H), 2.55 (s, \(-\text{SCH}_3\), 3H). GC-MS m/z 148.9 (M\textsuperscript{+} peak), 133.9, 115.9, 104.0, 102.9.

2-Methyl-benzonitrile: Table 2 Entry:5

\[
\text{CN}
\]

Isolated yield = 92%; \textsuperscript{1}H NMR \(\delta\) (300 MHz, CDCl\textsubscript{3}) 7.60 (d, \(J = 8.3\) Hz, Ar, 1H), 7.50 (m, Ar, 1H), 7.20-7.35 (m, Ar, 2H), 2.60 (s, \(-\text{CH}_3\), 3H). GC-MS m/z 117.0 (M\textsuperscript{+} peak), 90.0, 63.0.
4-Methyl-benzonitrile: Table 2 Entry: 6

\[ \text{Isolated yield} = 90\%; \quad ^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 7.50 (d, J = 8.3 \text{ Hz, Ar}, 2\text{H}), 7.25 (d, J = 7.80 \text{ Hz, Ar}, 2\text{H}), 2.40 (s, -CH}_3, 3\text{H}). \quad \text{GC-MS } m/z 117.0 (M^+ \text{ peak}), 90.0, 63.0. \]

Benzonitrile: Table 2 Entry: 7

\[ \text{Isolated yield} = 75\%; \quad ^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 7.80 (d, J = 8.0 \text{ Hz, Ar}, 2\text{H}), 7.40-7.5. \quad \text{GC-MS } m/z 102.8 (M^+ \text{ peak}), 75.7, 49.9. \]

4-Chloro-benzonitrile: Table 2 Entry: 8

\[ \text{Isolated yield} = 77\%; \quad ^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 7.65 (d, J = 8.8 \text{ Hz, Ar}, 2\text{H}), 7.50 (d, J = 8.8 \text{ Hz, Ar}, 2\text{H}). \quad \text{GC-MS } m/z 138.9 (M^+ \text{ peak}), 137.1, 101.8, 74.9, 49.9. \]

2-Chloro-benzonitrile: Table 2 Entry: 9

\[ \text{Isolated yield} = 79\%; \quad ^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 7.70-7.75 (m, Ar, 1\text{H}), 7.54-7.58 (m, Ar, 2\text{H}), 7.38-7.44 (m, Ar, 1\text{H}). \quad \text{GC-MS } m/z 138.8 (M^+ \text{ peak}), 136.8, 101.9, 74.9, 49.9. \]

4-Bromo-benzonitrile: Table 2 Entry: 10

\[ \text{Isolated yield} = 81\%; \quad ^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 7.66 (d, J = 8.3 \text{ Hz, Ar}, 2\text{H}), 7.55 (d, J = 8.3 \text{ Hz, Ar}, 2\text{H}). \quad \text{GC-MS } m/z 182.9 (M^+ \text{ peak}), 180.8 (M^+), 101.9, 75.0, 50.9. \]

4-Fluoro-benzonitrile: Table 2 Entry: 11

\[ \text{Isolated yield} = 81\%; \quad ^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 7.56-7.68 (m, Ar, 2\text{H}), 7.14-7.24 (m, Ar, 2\text{H}). \quad \text{GC-MS } m/z 120.9 (M^+ \text{ peak}), 93.8. \]

4-Nitro-benzonitrile: Table 2 Entry: 12

\[ \text{Isolated yield} = 70\%; \quad \text{at Room temperature}; \quad ^1\text{H NMR } \delta(300 \text{ Hz, CDCl}_3) 8.35 (d, J = 9.55 \text{ Hz, Ar}, 2\text{H}), 7.88 (d, J = 8.8 \text{ Hz Ar}, 2\text{H}). \quad \text{GC-MS } m/z 147.9 (M^+ \text{ peak}), 101.9, 74.9, 51.0. \]
3-Phenyl-acrylonitrile: Table 2 Entry: 15

\[
\text{isolated yield} = 30\%; \quad ^1\text{H NMR} \delta(300 \text{ MHz, CDCl}_3) 7.35 - 7.45 \text{ (b, s, Hz, Ar + Ph-CH, 6H), 5.88 (d, } J = 16.9 \text{ Hz, -CH-CN, 1H). GC-MS } m/z 129.0 \text{ (M}^+\text{ peak), 102.0, 51.0.}
\]

4-Isopropyl-benzonitrile: Table 3 Entry: 3

\[
^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 7.60 \text{ (d, } J = 8.8 \text{ Hz, 2H), 7.30 (d, } J \text{ = 8.1 Hz, 2H), 2.95 (sep, } -\text{CH-}-(\text{CH}_3)_3, 1\text{H), 1.30(s, } -\text{CH}_3,3\text{H), 1.25(s, } -\text{CH}_3,3\text{H). GC-MS } m/z 145.0 \text{ (M}^+\text{ peak), 130.0, 103.0, 77.0, 51.0.}
\]

Naphthalene-1-carbonitrile: Table 3 Entry: 6

\[
^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 8.22 \text{ (d, } J = 8.3 \text{ Hz, Ar, 1H), 8.04 (d, } J \text{ = 8.3 Hz, Ar, 1H), 7.90 (t, } J = 7.6 \text{ m, Ar), 7.50 (t, } J = 8.3 \text{ Hz, Ar, 1H). GC-MS } m/z 152.9 \text{ (M}^+\text{ peak), 125.9, 76.9, 62.9.}
\]

2-Fluoro-benzonitrile: Table 3 Entry: 10

\[
^1\text{H NMR } \delta(300 \text{ MHz, CDCl}_3) 8.50 \text{ (m, Ar, 1H), 7.58 (m, Ar, 1H), 7.30 (m, Ar, 2H). GC-MS } m/z 120.9 \text{ (M}^+\text{ peak), 93.9, 74.9,43.8.}
\]

\begin{center}
\textit{Synthesis of Nitriles from Amines:}
\end{center}

To a solution of amine (1.0 mmol), potassium iodide (0.20 mmol) in 3 mL of H₂O was added a solution of 70% aqueous TBHP (1.1 mmol) drop wise over a period of 30 min and stirred at room temperature. Progress of the reaction was monitored by TLC and after completion of the reaction; mixture was quenched with saturated aqueous Na₂S₂O₃, washed with brine, extracted with ethyl acetate and dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using hexane/ethyl acetate mixture and was analyzed by \(^1\text{H NMR, GC and GC-MS.}\)
Chapter III

Gram scale preparation of 4-methoxy benzonitrile:

To a suspension of alcohol (5.0 g, 36.2 mmol) in 115 mL of aq. NH₃, KI (20 mol %), and a solution of 70% aqueous TBHP (3.8 equiv) was added drop-wise over a period of 30 min at room temperature and then stirred at 60 °C. Progress of the reaction was monitored by TLC. After completion of the reaction (24 h), the mixture was quenched with saturated aqueous Na₂S₂O₃, washed with brine, extracted with ethyl acetate and dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum afforded the crude product.
Figure 3. $^1$H NMR spectrum of 4-Methoxy-benzonitrile.

Figure 4. GC-MS spectrum of 4-Methoxy-benzonitrile.
Figure 5. $^1$H NMR spectrum of Naphthalene-1-carbonitrile.

Figure 6. GC-MS spectrum of Naphthalene-1-carbonitrile.
Reference:


Chapter III


