Chapter 3

SOCl₂/β-Cyclodextrin: A New and Efficient Catalytic System for Beckmann Rearrangement and Dehydration of Aldoximes Under Aqueous Condition

3.1 Introduction
3.2 Review of Literature
3.3 Present Work
3.4 Conclusion
3.5 Experimental Section
3.6 Spectral Data
3.7 References

Synthetic Communication 2013, 43 (1), 118-128.
3.1 Introduction

The rearrangement of ketoximes to corresponding amides, known as “Beckmann reaction or rearrangement”, is a common method in organic chemistry and is a topic of current interest. The Beckmann rearrangement, named after the German chemist Ernst Otto Beckmann (1853–1923), has been tremendous interest to all practicing organic chemist, as the reaction affects a nitrogen insertion into a carbon framework. It generally proceeds through anti migration. Beckmann rearrangement is industrially important for the manufacture of Nylon-6 precursor, ε-caprolactum. The amide functionality is an important motif in polymers, natural products, and pharmaceuticals. The amide bond is a key functional group in organic and biological chemistry. Beyond conventional methods toward the synthesis of amides, many alternative strategies have been reported. In fact, the development of new amide forming reactions till in demand with improvements by the pharmaceutical industry.

Amide has an immensely important due to its role as a privileged pharmacophore and building block in a myriad of biomolecules as well as pharmaceutically interesting compounds. The benzazepines having amide functionality have been reported, which may be used in the treatment of certain diabetic conditions. Amide derivative of Ibuprofen resulted in improved analgesic, gastroprotective as well as anti-inflammatory activity. Ibuprofen heterocyclic amides are also investigated for their analgesic and toxicological properties. A series of 5,5-diarylpena-2,4-dienoic acids and their amides have been synthesized and evaluated as antimalarial agents. The amides also act as precursors for the synthesis of heterocycles like pyrimidine derivatives, δ-lactams, for the synthesis of sulphenylated oxazolines, oxazines or tetrahydropyrroles, etc. Bioactive amides moieties are shown in Figure 3.1.
Figure 3.1: Bioactive amide derivatives.

The nitrile functionality is a key constituent of numerous natural products and also serves as an important synthetic intermediate for pharmaceuticals, agricultural chemicals, dyes, material sciences and as intermediates in microbial metabolism. Nitriles are also products of the petrochemical industry and are widely used as chemical solvents, recrystallizing agents. Nitriles are of important synthon in preparative organic chemistry due to their conversion into carboxylic acids, aldehydes, amides, amines and ketones. Nitrile compounds are viable precursors for preparation of a variety of nitrogen-containing functional compounds, amino acids by Strecker reaction, synthesis of bioactive heterocycles like 5-aminopyrazoles, aryl 2-oxazolines, tetrahydropyridinethione, pyridopyrimidines, pyridotriazines dihydropyridines and oxazolines etc.

3.2 Review of Literature

The most common methods for the preparation of amides are the reaction between carboxylic acid derivatives particularly acid halides, acid anhydrides, and esters with the amines. Despite their wide scope, limitations are associated with the use of acid halides, anhydrides, and esters. Limitations are mostly due to the limited stability of many acid chlorides, reactions with esters require strongly basic or acidic catalysts. Conventional Beckmann rearrangement usually requires relatively high temperature, large amount of strongly acidic and dehydrating media such as concentrated H$_2$SO$_4$ (forms ammonium sulfate as byproduct), polyphosphoric acid, P$_2$O$_5$-methanesulfonic acid that leads to the large waste products (formation of inorganic salts caused by neutralization) and not applicative to sensitive
substrate. Consequently research is being pursued to make the process mild and catalytic. To avoid these requisite harsh conditions several methodologies in liquid phase, supercritical water, ionic liquid, vapour phase have been developed. Many catalytic systems such as boria hydroxyapatite, metal ilerite, supported oxide and zeolite have been reported. However these processes require high reaction temperature (300 °C), low selectivity and can suffer from rapid decay in the activity of catalyst. Various inorganic catalyst such as terpyridine ruthenium, AlCl₃,6H₂O/KI/H₂O/CH₃CN, metal lewis acid- Ga(OTf)₃, [RhCl(cod)]₂, Au/Ag co-catalytic system, triphosphazene in HIIP or acetonitrile also reported. The other reagent includes cyanuric chloride/DMF, anhydrous oxalic acid, chlorosulfonic acid in toluene. However some of these processes require hazardous high cost solvents like DCM, DMF, acetonitrile, toluene, etc with high reaction time. Therefore, the development of simple, highly efficient and selective Beckmann rearrangement process is still highly demandable.

**Furuya Y. et al. (2005)**

Furuya Y. et al. have reported the commercially available cyanuric chloride as an effective organocatalyst for the Beckmann rearrangement of ketoximes into amides in acetonitrile under refluxing condition (Scheme 3.1).

![Scheme 3.1](image)

**Ramalingan C. et al. (2007)**

Ramalingan C. et al. has found an acetonitrile solution of mercury(II) chloride as an efficient catalytic system for rearrangement of diverse range of ketoximes to their corresponding amides/lactums (Scheme 3.2).

![Scheme 3.2](image)
Li Z. et al. (2008)³⁵

Li Z. et al. developed an efficient and rapid method for Beckmann rearrangement of ketoximes by using recyclable and reusable silica-supported phosphorus chloride as catalyst under microwave irradiation in anhydrous tetrahydrofuran (Scheme 3.3).

\[
\begin{align*}
\text{R}_1\text{N} = \text{OH} & \quad \xrightarrow{\text{SiO}_2\text{-OPC}_2} \quad \text{R}_1\text{N} = \text{O-R}_2 \\
\text{R}_1, \text{R}_2 & = \text{alkyl, aryl}
\end{align*}
\]

Scheme 3.3

Liu X. et al. (2009)³⁶

Liu X. et al. reported a mild, efficient and eco-friendly procedure for Beckmann rearrangement catalyzed by a series of novel Bronsted acidic ionic liquids (ILs) consisting double SO₃H cations mediated zinc chloride (ILs–ZnCl₂) catalytic system (Scheme 3.4). High yields of amides were achieved by using 5 mol % of ILs–ZnCl₂ catalysts. In addition, the catalyst system could be recycled and reused for three times.

\[
\begin{align*}
\text{R}_1\text{N} = \text{OH} & \quad \xrightarrow{\text{Acidic ionic liquid- ZnCl}_2} \quad \text{R}_1\text{N} = \text{O-R}_2 \\
\text{R}_1, \text{R}_2 & = \text{phenyl, alkyl, cycloalkyl}
\end{align*}
\]

Scheme 3.4

Yadav L. D. S. et al. (2010)³⁷

Yadav L. D. S et al. have performed Bromodimethylsulfonium bromide (BDMS)-catalyzed Beckmann rearrangement of a variety of ketoximes in the imidazolium-based ionic liquid [bmim]PF₆ under mild conditions without using any additional co-catalyst or solvent to afford excellent conversion and selectivity (Scheme 3.5). The ionic liquid is recovered and reused for up to three runs without any loss of efficiency.

\[
\begin{align*}
\text{R}_1\text{N} = \text{OH} & \quad \xrightarrow{\text{BDMS}} \quad \text{R}_1\text{N} = \text{O-R}_2 \\
\text{R}_1, \text{R}_2 & = \text{phenyl, alkyl, cycloalkyl}
\end{align*}
\]

Scheme 3.5
Yadav L. D. S. et al. (2010)$^{38}$

Yadav L. D. S et al. has been shown Bromodimethylsulfonium bromide, in combination with zinc chloride, an excellent catalytic system for liquid-phase Beckmann rearrangement of various ketoximes into the corresponding amides/lactams in acetonitrile at reflux temperature (Scheme 3.6) with good to excellent yields.

![Scheme 3.6](image)

Liu L. F. et al. (2011)$^{39}$

Liu L. F. et al. invented aluminum chloride, an inexpensive and commercially available lewis acid catalyst for Beckmann rearrangement. The stoichiometric amounts of catalyst smoothly promote the Beckmann rearrangement of various ketoximes to the corresponding amides in anhydrous acetonitrile under reflux temperature (Scheme 3.7).

![Scheme 3.7](image)

At the same time, dehydration of aldoximes to nitriles is also an important transformation in organic synthesis and a number of methods have been developed.$^{40}$ There are many methods using SOCl$_2$ for dehydration of aldoximes to nitriles has been reported like silica gel/SOCl$_2$, SOCl$_2$-benztriazole, Na$_2$CO$_3$/SOCl$_2$. Although the methods developed so far have their own limitations for example, the use of extremely anhydrous reaction condition, toxic and hazardous chemicals and the need of cumbersome work-up procedures.$^{42}$ One of the most general methods for synthesis of alkyl nitriles is direct nucleophilic substitution of alkyl halides with inorganic cyanides, although the reaction is frequently accompanied by elimination of hydrogen halides, especially with bulky alkyl halides.$^{43}$ They were also usually prepared by regenerating CN group via oxidation, rearrangement or elimination. The direct preparation of nitriles from aldehydes was generally achieved by the dehydration of the corresponding aldoximes using classical reagents or other new
reagents like trichloroisocyanuric acid,\textsuperscript{47} trichloroacetyl chloride/triethylamine, dicyclohexyl carbodiimide, phosphonitrilic chloride,\textsuperscript{40b} CuCl\textsubscript{2},\textsuperscript{48} chlorosulfonyl isocyanate, triphenylphosphine, Burgess reagent\textsuperscript{49} and also include the use of expensive (2,4-dinitrophenyl hydroxyl amine),\textsuperscript{50} (hydroxylamine-o-sulfonic acid),\textsuperscript{51} hazardous (selenium dioxide),\textsuperscript{52} or corrosive (formic acid)\textsuperscript{53} reagents. Some other method for synthesis of nitriles includes use of hypervalent iodine (III) reagent in aqueous ammonium acetate,\textsuperscript{54} microwave reaction with catalytic amount of pyridine,\textsuperscript{55} microwave mediated solvent free reaction in presence of TiO\textsubscript{2},\textsuperscript{56} CuCl\textsubscript{2} in acetonitrile under ultrasound irradiation,\textsuperscript{57} etc.

**Yang S. H. et al. (2001)\textsuperscript{58}**

Yang S. H. et al. performed catalytic dehydration of aldoximes with catalytic system [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2}/molecular sieves under essentially neutral and mild conditions resulting into various types of cyano compounds with good to excellent yields (Scheme 3.8).

\[
R\overset{H}{\overset{\text{OH}}{\overset{\text{N}}{\overset{\text{OH}}{}}} + [\text{RuCl}_{2}(\text{p-cymene})]_{2}} \xrightarrow{\text{MS 4 A}^0, \text{CH}_3\text{CN, 80 °C, 10-60 min}} R\overset{\text{CN}}{\text{O}}
\]

**Scheme 3.8**

**Lee K. et al. (2004)\textsuperscript{59}**

Lee K. et al. reported the various aliphatic, aromatic and heterocyclic aromatic type of aldoximes conversion to corresponding nitriles in good to excellent yields using 2-chloro-1-methylpyridinium iodide (CMPI) as a dehydrating agent using triethylamine in dichloromethane under Argon atmosphere (Scheme 3.9).

\[
R\overset{\text{H}}{\overset{\text{OH}}{\overset{\text{N}}{}}} \xrightarrow{\text{CMPI, Et}_3\text{N, CH}_2\text{Cl}_2, \text{rt, 1-2 h, Ar}} R\overset{\text{CN}}{\text{O}}
\]

**Scheme 3.9**

**Saini A. et al. (2005)\textsuperscript{60}**

Saini A. et al. developed an efficient method for the transformation of aldoximes to nitriles induced by zinc-iodine system in good to excellent yields in acetonitrile at room temperature (Scheme 3.10).
Gucma M. et al. (2008)\textsuperscript{61}

Gucma M. et al. have mentioned the transformation of benzaldehyde aldoximes with electron donating group to corresponding nitriles with the help of N-chlorosuccinimide and pyridine in acetonitrile (Scheme 3.11). In this method for the simple benzaldehyde oxime and alkanal aldehyde oximes get deprotected into corresponding benzaldehyde.

\[
\begin{align*}
\text{ArCH}=\text{NOH} & \quad + \quad \text{NCl} \\
\quad & \quad \xrightarrow{\text{pyridine, MeCN}} \quad \text{ArCN} + \quad \text{NH} & \quad + \quad \text{py.HCl}
\end{align*}
\]

Scheme 3.11

Singh M. K. et al. (2009)\textsuperscript{62}

Singh M. K. et al. have converted an easily synthesized aldoximes to the corresponding nitriles by a reaction with \textit{1H}-benzotriazol-1-ylxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and DBU in CH\textsubscript{2}Cl\textsubscript{2}, THF, or DMF (Scheme 3.12). As an alternative reagent that eliminates the formation of hexamethylphosphoramide as a byproduct, use of \textit{1H}-benzotriazol-1-yl-4-methylbenzenesulfonate (Bt-OTs) and DBU was also investigated.

\[
\begin{align*}
\text{Ar or R} = \text{N} & \quad \xrightarrow{\text{DBU, CH}_2\text{Cl}_2} \quad \text{Ar or R} = \text{CN}
\end{align*}
\]

Scheme 3.12

Saha D. et al. (2009)\textsuperscript{63}

Saha D. et al. described a simple and convenient procedure for the synthesis of nitriles by dehydration of aldoximes using an ionic liquid, 1-pentyl-3-methylimidazolium tetrafluoroborate, [pmim]BF\textsubscript{4} under organic solvent-free condition (Scheme 3.13). A variety of aromatic, heteroaromatic and aliphatic
aldoximes were converted to the corresponding nitriles. The ionic liquid was recovered and reused for subsequent reactions.

\[
\text{RCH=NOH} \xrightarrow{[\text{pimim}]\text{BF}_4 \text{, 90 °C}} \text{RCN}
\]

\(\text{R} = \text{aryl, heteroaryl, alkyl}\)

**Scheme 3.13**

**Rad M. N. S. et al. (2010)**

Rad M. N. S. et al. reported a facile and efficient method for dehydration of aldoximes into nitriles using N-(p-toluenesulfonyl) imidazole (TsIm) (**Scheme 3.14**). In this method, aldoximes were refluxed with TsIm in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in dimethylformamide (DMF) to afford the corresponding nitriles in good yields. This methodology is highly efficient for various structurally diverse aldoximes including aromatic, heteroaromatic and aliphatic oximes.

**Scheme 3.14**

**Li Y. T. et al. (2011)**

Li Y. T. et al. invented catalytic dehydration of aldoximes efficiently with NiCl\(_2\) in acetonitrile under neutral condition and in \(\text{N}_2\) atmosphere. Under these conditions, various functionalized aldoximes produce the corresponding nitriles in good to excellent yields (**Scheme 3.15**).

**Scheme 3.15**

**Rad M. N. S. et al. (2012)**

Rad M. N. S. et al. developed a rapid and highly convenient synthesis of nitriles from the corresponding aldoximes using 8-bromocaffeine (8-BC) (**Scheme 3.16**). In this protocol, aldoximes react with 8-BC in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and \(N,N\)-dimethylformamide (DMF) to
furnish the corresponding nitriles under both microwave-assisted and/or conventional heating (reflux) conditions in short times and in good to excellent yields.

\[ \text{Scheme 3.16} \]

3.3 Present Work

In comparison with some inflammable and toxic organic solvents, water may serve as superior solvent that is safe to use in organic reactions. The low cost of water renders the chemical processes more economical. In many cases, water can be recycled to improve the problem of solvent disposal. Furthermore, using water as a solvent may also have advantages of simple operation and high efficiency in many organic reactions. Synthetic chemists continue to explore new methods to carry out chemical transformations. Herein we present our results on highly selective SOCl₂/β-cyclodextrin catalyzed Beckmann rearrangement and dehydration of aldoximes to corresponding nitriles (Scheme 3.17). As the Beckmann rearrangement usually requires electrophilic activation of oxime hydroxy group, we hypothesized that β-CD facilate the transformation of ketoximes to amide or dehydration of aldoximes by hydrogen bonding with β-CD hydroxyl groups by supramolecular interaction. The hydrogen bonding with oxygen may also force up for departing of leaving group and accelerate the rate of migration or rate of dehydration.

\[ \text{Scheme 3.17} \]

In order to explore the best reaction condition the 4-bromoacetophenone oxime was selected as a model molecule under various reaction conditions (Table 3.1).
Table 3.1: Screen of reaction conditions.\textsuperscript{a}

\begin{align*}
\begin{array}{ccc}
\text{Entry} & \text{Temp. (°C)} & \text{Time (h)} & \text{Yield (%)} \\
\hline
1 & \text{Room temp.} & 12 & 30 & 68 \\
2 & 40 & 2.45 & 38 & 53 \\
3 & 60 & 0.5 & 47 & 50 \\
4 & 80 & 0.41 & 85 & - \\
\end{array}
\end{align*}

\textsuperscript{a}Reaction condition: To a solution of 4-bromoacetophenone oxime in acetone, SOCl\textsubscript{2} added dropwise at 0-10 °C. Then clear solution of β-CD dissolved in distilled water (10 mL) was added at room temperature and stir at given temperature. A mole ratio of oxime: SOCl\textsubscript{2}: β-CD = 5: 6: 0.5 \textsuperscript{b} Isolated yield.

Table 3.2: Transformation of ketoximes to amide using different amount of catalyst at 80 °C.\textsuperscript{a}

\begin{align*}
\begin{array}{ccc}
\text{Entry} & \text{Catalyst (mmol)} & \text{Time (min.)} & \text{Yield (%)} \\
\hline
1 & 0.5 & 25 & 85 \\
2 & 1 & 25 & 84 \\
3 & 2 & 28 & 84 \\
4 & 4 & 30 & 80 \\
5 & 5 & 40 & 80 \\
6 & - & 35 & 41 \\
\end{array}
\end{align*}

\textsuperscript{a} A mole ratio of oxime: SOCl\textsubscript{2} = 5: 6 was used.

The effect of temperature for above reaction has been studied and it was found that at lower temperature (entry 1, Table 3.1), the rate of migration was very slow, require high reaction time and leading to the side product identified as 4-bromoacetophenone (by TLC comparison and Mp with authentic sample). Increase in
temperature fevers the rate of migration and best result was found at 80 °C (entry 4, 85%, Table 3.1). The reactions were also carried out by varying amount of catalyst (Table 3.2) at 80 °C. When we have increased the amount of catalyst from 0.5 to 5 mmol, no yield improvements were observed. When same reaction was carried out at 80 °C without β-CD catalyst, formation amide and starting carbonyl compound takes place. The efficiency of catalyst have been studied for the structurally divers ketoxime (Table 3.3). The reactions were found to be complete within 5 – 25 min. As per usual migratory aptitude of Beckmann rearrangement, here only migration of aryl group was observed. The naphthalene and diphenyl compounds also show good results (entry  6d – 6g, Table 3.3). In our results the electronic effect of substituents on aromatic ring was not more pronouns.

**Table 3.3:** Catalytic conversions of various ketoximes to amide using SOCl₂/β-CD as catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Time (min.)</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Measured</td>
</tr>
<tr>
<td>6a</td>
<td><img src="image" alt="Amide 6a" /></td>
<td>5</td>
<td>86</td>
<td>113</td>
</tr>
<tr>
<td>6b</td>
<td><img src="image" alt="Amide 6b" /></td>
<td>8</td>
<td>88</td>
<td>150</td>
</tr>
<tr>
<td>6c</td>
<td><img src="image" alt="Amide 6c" /></td>
<td>25</td>
<td>85</td>
<td>165-167</td>
</tr>
<tr>
<td>6d</td>
<td><img src="image" alt="Amide 6d" /></td>
<td>20</td>
<td>90</td>
<td>159-166</td>
</tr>
<tr>
<td>6e</td>
<td><img src="image" alt="Amide 6e" /></td>
<td>15</td>
<td>91</td>
<td>129-132</td>
</tr>
</tbody>
</table>
Table 3.4: Reuse of β-CD for 6c.

<table>
<thead>
<tr>
<th>No. of use</th>
<th>Yield (%)</th>
<th>Recovery of β-CD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>85</td>
</tr>
</tbody>
</table>

Table 3.5: Catalytic dehydration of aldoximes to corresponding nitriles using SOCl₂/β-CD as a catalyst.\(^{a}\)

\[
\text{R}^\equiv\text{N}^\text{OH} \xrightarrow{\text{i. SOCl}_2, \text{Acetone}} \xrightarrow{\text{ii. β-CD (0.5 mmol), H}_2\text{O, 80 °C}} \text{R'}^\equiv\text{N}^\text{CN}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile</th>
<th>Time (min.)</th>
<th>Yield (^b) (%)</th>
<th>Melting point (°C) Measured</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>CN</td>
<td>15</td>
<td>90</td>
<td>190 (Bp)</td>
<td>191(^{70})</td>
</tr>
<tr>
<td>7b</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>8</td>
<td>98</td>
<td>116-118</td>
<td>118°</td>
</tr>
<tr>
<td>7c</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>10</td>
<td>91</td>
<td>148</td>
<td>149°</td>
</tr>
<tr>
<td>7d</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>10</td>
<td>96</td>
<td>96</td>
<td>96°</td>
</tr>
<tr>
<td>7e</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>15</td>
<td>91</td>
<td>112</td>
<td>113°</td>
</tr>
<tr>
<td>7f</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>20</td>
<td>94</td>
<td>180-182</td>
<td>179-182°</td>
</tr>
<tr>
<td>7g</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>12</td>
<td>91</td>
<td>112</td>
<td>113°</td>
</tr>
<tr>
<td>7h</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>12</td>
<td>91</td>
<td>58</td>
<td>57-59°</td>
</tr>
<tr>
<td>7i</td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>15</td>
<td>92</td>
<td>92-94</td>
<td>-</td>
</tr>
<tr>
<td>7j</td>
<td><img src="image9" alt="Chemical Structure" /></td>
<td>15</td>
<td>94</td>
<td>44</td>
<td>43-46°</td>
</tr>
<tr>
<td>7k</td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td>20</td>
<td>92</td>
<td>216-218</td>
<td>218° (Bp)</td>
</tr>
<tr>
<td>7l</td>
<td><img src="image11" alt="Chemical Structure" /></td>
<td>25</td>
<td>93</td>
<td>84</td>
<td>85-87°</td>
</tr>
<tr>
<td>7m</td>
<td><img src="image12" alt="Chemical Structure" /></td>
<td>10</td>
<td>89</td>
<td>96-98</td>
<td>97° (Bp)</td>
</tr>
</tbody>
</table>

\[ a \text{ A molar ratio of aldoximes: SOCl}_2: \beta-\text{CD} = 5:6:0.5. \text{ b Isolated yield after column chromatography.} \]
With promising results in hand for the formation of amide from ketoximes, we next tested for the aldoximes to examine generality of this reaction under identical condition. Aldoximes were found to be undergoing dehydration furnishes the corresponding nitriles in good to excellent yields and within short reaction time (8 - 25 min, Table 3.5). On comparison of the overall reactivity of aldoximes and ketoximes in our results with respect to time and yields, aldoximes were found to be more reactive. The effect of substituent on aromatic ring like nitro, halide, hydroxyl, methoxy, and methyl was found to be less on reaction efficiency and selectivity. The same reaction proceeds much slowly when reaction carried out in acetonitrile at similar condition affording side product (monitor by TLC). Not only aromatic aldoximes were efficiently converted to aromatic cyano compounds but heterocyclic (entry 7f) as well as aliphatic aldoxime (entry 7m) could also be employed as a good substrate with similar selectivity to affords the corresponding nitriles. Compounds entry 7a, 7d, 7h, 7k were isolated in 90, 96, 91 and 92% yields in shorter reaction time while using a literature procedure these compounds were isolated in 82, 87, 82 and 85% yields in 1 h reaction time. Furthermore catalytic activity of recovered catalyst (β-CD) was examined. As shown in Table 3.6, the yield of 3-nitrobenzonitrile in second and third use of catalyst not found to be decreasing much more. In each case almost > 86% of β-CD was easily recovered by cooling of aqueous layer. However when these reactions were carried out in presence of simple oligosaccharides such as glucose or dextrose, the reaction was completed in 30 min. and 20 min. with yields only 45% and 55% for 4-bromoacetophenone oxime and 4-nitrobenzaldehyde oxime respectively. It confirms that cyclodextrin may form complex with oxime, thus yields of reaction increased to 85% and 91% respectively. Glucose or dextrose also not recovered from aqueous layer quantitatively.

**Table 3.6:** Reuse of β-CD for 7b.

<table>
<thead>
<tr>
<th>Number of use</th>
<th>Yield (%)</th>
<th>Recovery of β-CD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>86</td>
</tr>
</tbody>
</table>
3.4 Conclusion

In conclusion, we have described a highly efficient protocol for conversion of ketoximes to amide and dehydration of aldoximes to nitrile using nontoxic and inexpensive β-CD catalyst in water. The advantages of this protocol includes a simple reaction set-up not requiring specialized equipment, mild reaction condition, high product yields, very short reaction time, reusable catalyst and eliminating the use of hazardous solvents.

3.5 Experimental Section

Chemicals required for the synthesis were obtained from Aldrich, Spectrochem. Melting points were taken in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR IRAffinity-1 using KBr. $^1$H NMR spectra were recorded with a Varian Mercury at 300 MHz in CDCl$_3$ with TMS as an internal standard. Mass spectra were under ESI mode, on Thermo Finnigan (Model-LCQ Advantage MAX) mass spectrometer.

**Typical procedure for transformation of oximes into amide and nitriles**

To a solution of oxime (5 mmol) in acetone (2 mL), SOCl$_2$ (6 mmol) was added dropwise with stirring at 0-10 °C. Then clear solution of β-CD (0.5 mmol) in distilled water (10 mL) was added at room temperature and stir at 80 °C for appropriate time (monitored by TLC, Hexane: Ethyl acetate 9:1). The organic material was extracted in ethyl acetate (3 x 20 mL). The aqueous layer was cooled to 0 °C; in which β-CD reappeared as a white solid. The obtained white solid mass was filtered, dried to recover β-CD and reused. The organic phase dried over anhydrous Na$_2$SO$_4$, solvent was evaporated under reduced pressure, the crude product purified by column chromatography using hexane-ethyl acetate (9:1) as eluent to afford pure product.

The selected products were characterized by FTIR, NMR, Mass spectroscopy, whereas the remaining products characterized by their physical constants, comparative TLC and are found to be in good agreement with the authentic samples.
3.6 Spectral Data

\textbf{N-p-Tolyacetamide:}
Molecular formula: C_{9}H_{11}NO
Molecular weight: 149
Mp: 150 °C
IR (KBr, cm\(^{-1}\)) \(\nu\): 3300, 2922, 1664, 1602, 817
\(^{1}\)H NMR (CDCl\(_{3}\), 300 MHz, ppm) \(\delta\): 7.36 (d, 2H, J = 8 Hz, Aromatic), 7.20 (brs, 1H, NH), 7.11 (d, 2H, J = 8 Hz, Aromatic), 2.30 (s, 3H, COCH\(_{3}\)), 2.15 (s, 3H, CH\(_{3}\))
MS (m/e): 150 [M+1]

\textbf{N-(Naphthalene-6-yl) acetamide:}
Molecular formula: C_{12}H_{11}NO
Molecular weight: 185
Mp: 129-132 °C
IR (KBr, cm\(^{-1}\)) \(\nu\): 3284, 2983, 1668, 1589
\(^{1}\)H NMR (CDCl\(_{3}\), 300 MHz, ppm) \(\delta\): 8.17 (s, 1H, NH), 7.79 – 7.76 (m, 3H, Aromatic), 7.45 – 7.39 (m, 4H, Aromatic), 2.23 (s, 3H, COCH\(_{3}\))
MS (m/e): 186 [M+1]

\textbf{N-Phenylbenzamide:}
Molecular formula: C_{13}H_{11}NO
Molecular weight: 197
Mp: 162 °C
IR (KBr, cm\(^{-1}\)) \(\nu\): 3344, 3053, 1654, 1598, 750
\(^{1}\)H NMR (DMSO-d\(_{6}\), 300 MHz, ppm) \(\delta\): 10.2 (brs, 1H, NH), 7.96 – 7.07 (m, 10H, Aromatic)
MS (m/e): 198 [M+1]

\textbf{4-Chloro-N-phenylbenzamide:}
Molecular formula: C_{13}H_{10}CINO
Molecular weight: 231
Mp: 197-200 °C
IR (KBr, cm\(^{-1}\)) \(\nu\): 3350, 3057, 1653, 1598, 848
\(^{1}\)H NMR (CDCl\(_{3}\), 300 MHz, ppm) \(\delta\): 7.85 – 7.16 (m, 9H, Aromatic), 7.74 (s, 1H, NH)
MS (m/e) : 232 [M+1]

4-Nitrobenzonitrile:
Molecular formula: C₇H₄N₂O₂
Molecular weight : 148
Mp : 148 °C
IR (KBr, cm⁻¹) ν : 2223, 1600, 1348, 860
¹H NMR (CDCl₃, 300 MHz, ppm) δ :
8.36 (d, 2H, Aromatic), 7.90 (d, 2H, Aromatic)

1H-Indole-3-carbonitrile:
Molecular formula: C₉H₆N₂
Molecular weight : 142
Mp : 180-182 °C
IR (KBr, cm⁻¹) ν : 3230, 3122, 2227
¹H NMR (CDCl₃, 300 MHz, ppm) δ :
8.68 (brs, 1H, NH), 7.80 – 7.26 (m, 5H, Aromatic)
MS (m/e) : 143 [M+1]

4-Hydroxybenzonitrile:
Molecular formula: C₇H₅NO
Molecular weight : 119
Mp : 112 °C
IR (KBr, cm⁻¹) ν : 3275, 3169, 2233, 1610, 1166, 839
¹H NMR (CDCl₃, 300 MHz, ppm) δ :
7.56 (d, 2H, Aromatic), 6.93 (d, 2H, Aromatic), 6.09 (s, 1H, OH)
MS (m/e) : 120 [M+1]

4-Methoxybenzonitrile:
Molecular formula: C₈H₇NO
Molecular weight : 133
Mp : 58 °C
IR (KBr, cm⁻¹) ν : 3024, 2843, 2218, 1604, 1024, 829
¹H NMR (CDCl₃, 300 MHz, ppm) δ :
7.60 (d, 2H, Aromatic), 6.98 (d, 2H, Aromatic), 3.88 (s, 3H, OCH₃)
MS (m/e) : 134 [M+1]
2-Chlorobenzonitrile:
Molecular formula: C\(_7\)H\(_4\)ClN
Molecular weight : 137
Mp : 44 °C
IR (KBr, cm\(^{-1}\)) \(\nu\) : 3093, 2229, 1591, 759
\(^1\)H NMR (CDCl\(_3\), 300 MHz, ppm) \(\delta\) : 7.69 – 7.34 (m, 4H, Aromatic)

4-Hydroxy-3-methoxybenzonitrile:
Molecular formula: C\(_8\)H\(_7\)NO\(_2\)
Molecular weight : 149
Mp : 84 °C
IR (KBr, cm\(^{-1}\)) \(\nu\) : 3226, 3028, 2225, 1028
\(^1\)H NMR (CDCl\(_3\), 300 MHz, ppm) \(\delta\) : 7.26 – 6.95 (m, 3H, Aromatic), 6.06 (s, 1H, OH), 3.93 (s, 3H, OCH\(_3\))
MS (m/e) : 150 [M+1]

### 3.6.1 Spectra

Table 3.7: FTIR, \(^1\)H NMR and Mass spectra of selected compounds.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FTIR of N-(p)-Tolyacetamide</td>
</tr>
<tr>
<td>2</td>
<td>(^1)H NMR of N-(p)-Tolyacetamide</td>
</tr>
<tr>
<td>3</td>
<td>Mass of N-(p)-Tolyacetamide</td>
</tr>
<tr>
<td>4</td>
<td>FTIR of N-(Naphthalene-6-yl) acetamide</td>
</tr>
<tr>
<td>5</td>
<td>(^1)H NMR of N-(Naphthalene-6-yl) acetamide</td>
</tr>
<tr>
<td>6</td>
<td>Mass of N-(Naphthalene-6-yl) acetamide</td>
</tr>
<tr>
<td>7</td>
<td>FTIR of 4-Hydroxy-3-methoxybenzonitrile</td>
</tr>
<tr>
<td>8</td>
<td>(^1)H NMR of 4-Hydroxy-3-methoxybenzonitrile</td>
</tr>
<tr>
<td>9</td>
<td>Mass of 4-Hydroxy-3-methoxybenzonitrile</td>
</tr>
</tbody>
</table>
2. $^1$H NMR of N-p-Tolyacetamide
3. Mass of N-p-Tolyacetamide
4. FTIR of N-(Naphthalene-6-yl)acetamide
5. $^1$H NMR of N-(Naphthalene-6-yl)acetamide
6. Mass of N-(Naphthalene-6-yl) acetamide
8. $^1$H NMR of 4-Hydroxy-3-methoxybenzonitrile
9. Mass of 4-Hydroxy-3-methoxybenzonitrile
3.7 References


