CHAPTER-5

LIQUID-LIQUID PHASE TRANSFER CATALYSED HETEROAROMATIC NUCLEOPHILIC SUBSTITUTION IN 4,6-DISUBSTITUTED 2-CHLORO-3-CYANOPYRIDINES

5.1 Introduction

A nucleophilic substitution reaction in which the substrate is a heteroaromatic compound containing a leaving group and the nucleophile is a group which brings electron pair to the substrate, is called substitution nucleophilic heteroaromatic (SNHet-Ar).

Phase transfer was used to catalyse nucleophilic aromatic substitution by Makosza in 1974. Zoltewicz has given a good early review of various methods and has compared other techniques that make use of polar solvents, transition metals and monoelectron transfers.

In principle, phase transfer catalysis can be used for heterocyclic $S_{N}Ar$ as well. Moreover, as the approximate order of activating and deactivating ability of substituents is $NO_{2} > N$(heterocycle) $> SO_{2}Me > CF_{3} > CN > H > Me > OMe$, reactions with azaaromatic molecules must be easier than the reactions with similar aromatic molecules. Therefore, unsubstituted monohalogeno heterocycles were expected to undergo $S_{N}-Ar$ reactions under phase transfer conditions.

Formation of ether linkage (O-alkylation, O-arylation) is an important example of nucleophilic substitution reaction. Following examples illustrate the versatility and applicability of phase transfer catalysis in such nucleophilic substitution reactions, where the products are ethers of various types.

Phase transfer catalysis provided a simple and convenient method for conducting Williamson ether synthesis (Scheme-92).
\[
RX + R'OH \xrightarrow{\text{Catalyst}} R-O-R' \quad \text{NaOH (aq)}
\]

Scheme - 92

Sam and Simmons\textsuperscript{283} showed that using potassium hydroxide-18-crown-6 complex, o-dichlorobenzene (173) was converted selectively into o-chloroanisole (174) in 40-50\% yield (Scheme-93)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{173} & \quad \text{K}^+ \cdot \text{Crown} + \text{CH}_3\text{O}^- \\
\quad & \quad \text{Cl} \\
\quad & \quad \text{OCH}_3 \\
\end{align*}
\]

Scheme - 93

Freedman and Dubois\textsuperscript{284} found that a variety of ethers could be prepared by the reaction with primary alkyl chlorides in the presence of excess of concentrated aqueous sodium hydroxide solution and tetrabutylammoniumhydrogen sulfate (TBHSO\textsubscript{4}) as phase transfer catalyst (Scheme-94).

\[
n-\text{C}_4\text{H}_9\text{OH} + n-\text{C}_6\text{H}_{13}\text{Cl} \xrightarrow{\text{aq. NaOH}} n-\text{C}_4\text{H}_9\text{O} - n-\text{C}_6\text{H}_{13} \quad \text{Bu}_4\text{NHSO}_4
\]

Scheme - 94

5-Chloro-2-nitropyridine (175) reacted with alkali metal alkoxides to form pyridyl alkyl ethers\textsuperscript{285} (176) (Scheme-95).
2-Chloropyridines (177, 180) when reacted with phenols (178) and alcohols (181) under liquid-liquid and solid-liquid phase transfer conditions, phenoxy pyridines (179) and alkoxo pyridines (182) were obtained in good yields (Scheme-96).

Transformation of 2-chloropyridines (183) to the corresponding phenoxy picolines (184) was carried out using phase transfer catalyst (Scheme-97).
The reaction of 2-chloropyridines (185) with polyethylene glycols (186) in toluene-potassium hydroxide system yielded monoethers (187) or diethers (188) selectively depending on the amount of base (Scheme-98).

Duggen et al.\textsuperscript{286} carried out heteroaromatic nucleophilic substitution of 2-chloro-3-cyanopyridines (189) with (S)-3-t-butyl-5-hydroxymethyl-2-phenyloxazolidine (190) to give the corresponding alkoxide (191) (Scheme-99).
Phase transfer catalyzed heteroaromatic nucleophilic substitution was used to prepare 4/5-alkoxy substituted pyridazine-3(2H)-ones (194) possessing hypotensive and β-blocking activity (Scheme-100). In this case solid-liquid system was found to be more effective than liquid-liquid system.

Scheme - 99

(1) = PhCl, Bu4N+Br-, 30% NaOH, 85°C, 2-10 hrs.
(2) = MeCN, Bu4N+HSO4-, K2CO3, reflux, 4-6 hrs.
X=4-, 5-Cl, 4-, 5-Br; Z=O; R=R1=CH3; Z=NC6H4-t; R=R1=H, C6H5

Scheme - 100
The reaction of 2,4-dichloro-6,7-dimethoxyquinazoline (195) with o-nucleophiles occurs regiospecifically at position-4 to give the corresponding 4-alkoxy derivatives\(^\text{200}\) (196, 197) (Scheme-101).

\[
\begin{align*}
\text{PhCl / Bu}_4\text{N}^+\text{Br} & \quad 20\% \text{NaOH, r.t / 2 hrs.} \\
\end{align*}
\]

The alkylation of substituted phenols (198) with 4-chloromethyl-1,3-dioxolane (199) provided phenylethers (200) in good yield. The effect of substrate structure, solvent and phase transfer catalyst on the yield of product has been reported\(^\text{201}\) (Scheme-102).
5.2 Present work

The application of phase transfer catalysis to heteroaromatic nucleophilic substitution reactions ($S_N$ Het-Ar) employing alkoxide ions is very recent and only a few cases have been described on 2-chloropyridine derivatives.\textsuperscript{286, 288, 292}

With an aim of developing new biologically active compounds, in present work, a $\beta$-adrenergic blocking moiety namely isopropylidene glycerol\textsuperscript{293} is incorporated in position-2 of 4,6-disubstituted 2-chloro-3-cyanopyridines. This $S_N$-Heteroaromatic type of reaction was carried out at room temperature under liquid-liquid phase transfer conditions. The resulting products i.e. 4,6-disubstituted 2-($O,O$-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII) were further subjected to acid hydrolysis at room temperature to give the corresponding 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV).

5.3 Results and Discussion

5.3.1 Synthesis of 4,6-disubstituted 2-($O,O$-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134):

4,6-Disubstituted 2-chloro-3-cyanopyridines (V) were used as starting material for the synthesis of 4,6-disubstituted 2-($O,O$-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines
The nucleophilic substitution of chlorine in 2-chloropyridines derivatives normally require a hard base like sodium hydride and a polar aprotic solvent like N,N-dimethylformamide.

The substitution reaction of 4,6-disubstituted 2-chloro-3-cyanopyridines (V, 56-70) with isopropylideneglycerol (XII) was carried out under liquid-liquid phase transfer conditions at room temperature using tetra-n-butylammonium bromide (TBAB) as a phase transfer catalyst.

The organic phase consisted of chlorobenzene, while aqueous phase consisted of 50% (w/v) sodium hydroxide solution. At the end of the reaction (tlc), the chlorobenzene layer was separated, washed with water till neutral, dried over anhydrous magnesium sulphate and distilled in vacuo to obtain the 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134) in 80-90% yield (Scheme-103).

The mechanism for such a heteroaromatic nucleophilic substitution reaction is proposed in scheme-104.
From the mechanism it is clear that, initially tetrabutylammonium bromide (TBAB) undergoes exchange reaction with sodium hydroxide to form tetrabutylammonium hydroxide.
The tetrabutylammonium hydroxide thus formed abstracts the proton from isopropylidene glycerol to form alkoxide ion, which gets enough organic structure from the quaternary ammonium salt to get extracted into organic layer. In organic layer, the alkoxide ion, which is loosely bound with quaternary ammonium cation, undergoes nucleophilic substitution reaction with 4,6-disubstituted 2-chloro-3-cyanopyridines (V, 56-70) to form 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134). The quaternary salt is generated back by a series of exchange reactions and it once again performs the same set of reactions. Some of the other findings of this work were:

1. Attempts to carry out these nucleophilic substitution reactions at higher temperatures (70-80°C) resulted in decyanation of same 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII).

2. At lower than 50% (w/v) concentrations of aqueous sodium hydroxide, the reaction rates were very low (more than 24 hours).

3. Solid-liquid phase transfer catalysis conditions resulted in comparable yields.

4. During the course of these nucleophilic substitution reactions, there was no emulsion formation observed, suggesting that these reactions were not of interfacial type.

5.3.2 Synthesis of 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145):

Hydrolysis of 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134) with 6N hydrochloric acid (HCl) using methanol as solvent, provided the 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145) in excellent yield. The reaction was carried out at room temperature under stirring. After comple-
tion of the reaction (tlc), the mixture was poured onto the crushed ice, neutralized with ammonia to obtain the titled products (Scheme-105)

\[
\begin{align*}
\text{R}_1 \text{CN} & \quad \text{R}_1 \text{CN} \\
\text{R}_2 \text{OH} & \quad \text{R}_2 \text{OH} \\
\text{XIII} & \quad \text{XIV}
\end{align*}
\]

Scheme - 105

4,6-Disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134) were crystalline compounds soluble in N,N-dimethylformamide, dimethylsulfoxide, methylene chloride, methanol and ethanol while sparingly soluble in benzene and toluene. Physical constants of 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134) are reported in table-48.
Table-48: Physical constants of 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XI, 124-134).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Yield (%)</th>
<th>M P °C</th>
<th>Mol Formula</th>
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<td>124</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
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<td>108-10</td>
<td>C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;22&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>125</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>85</td>
<td>132-34</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;24&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>126</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>80</td>
<td>157-59</td>
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<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>83</td>
<td>127-29</td>
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<td>4-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>84</td>
<td>130-32</td>
<td>C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;24&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>129</td>
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<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;26&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;</td>
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<td>131</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>115-17</td>
<td>C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;21&lt;/sub&gt;ClN&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>132</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>160-62</td>
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<td>133</td>
<td>2-Furyl</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>82</td>
<td>231-33</td>
<td>C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;22&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>134</td>
<td>2-Thienyl</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
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</table>

IR(KBr) Spectral data of 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134) are recorded in table-49. IR(KBr) Spectra of 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134) did not exhibit any absorption in the region 3450-3400 cm<sup>-1</sup> responsible for -OH group indicating the complete O-alkylation of isopropylidene glycerol. The absorption bands at 1597-1516 cm<sup>-1</sup> were assigned to C=C, C=N (ring) stretching vibrations.
Table-49: IR Spectral data of 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>v C-H cm(^{-1})</th>
<th>v C=(\equiv)N cm(^{-1})</th>
<th>v C=C, C=N cm(^{-1})</th>
<th>(\delta) C-H cm(^{-1})</th>
<th>(\delta) C-O, C-N cm(^{-1})</th>
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<td>1301, 1220</td>
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</table>

\(^1\)HNMR Spectral data of 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134) are given in table-50.
Table-50 : $^1$HNMR Spectral data of 4,6-disubstituted 2-($O,O$-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$^1$H NMR (CDCl$_3$, $\delta$ ppm)</th>
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<tr>
<td>124</td>
<td>C$_6$H$_5$</td>
<td>C$_6$H$_5$</td>
<td>1.43-1.52(2s, 6H, 2CH$_3$), 4.03-4.08(m, 1H, 4'Hd), 4.20-4.25(m, 1H, 4'Hc), 4.53-4.64(m, 2H, CH$_2$), 4.75-4.79(m, 1H, 5'Hb), 7.26-8.19(m, 11H, Ar-H)</td>
</tr>
<tr>
<td>125</td>
<td>C$_6$H$_5$</td>
<td>4-CH$_3$C$_6$H$_4$</td>
<td>1.42-1.52(2s, 6H, 2CH$_3$), 4.02-4.08(m, 1H, 4'Hd), 2.48(s, 3H, CH$_3$), 4.19-4.23(m, 1H, 4'Hc), 4.53-4.64(m, 2H, CH$_2$), 4.75-4.79(m, 1H, 5'Hb), 7.06-8.00(m, 10H, Ar-H)</td>
</tr>
<tr>
<td>126</td>
<td>C$_6$H$_5$</td>
<td>4-OCH$_3$C$_6$H$_4$</td>
<td>1.42-1.50(2s, 6H, 2CH$_3$), 3.89(s, 3H, OCH$_3$), 4.02-4.07(m, 1H, 4'Hd), 4.19-4.24(m, 1H, 4'Hc), 4.51-4.63(m, 2H, CH$_2$), 4.73-4.78(m, 1H, 5'Hb), 7.26-8.19(m, 10H, Ar-H)</td>
</tr>
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<td>127</td>
<td>C$_6$H$_5$</td>
<td>4-ClC$_6$H$_4$</td>
<td>1.43-1.53(2s, 6H, 2CH$_3$), 4.01-4.08(m, 1H, 4'Hd), 4.20-4.23(m, 1H, 4'Hc), 4.53-4.65(m, 2H, CH$_2$), 4.75-4.79(m, 1H, 5'Hb), 7.00-8.19(m, 10H, Ar-H)</td>
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<tr>
<td>128</td>
<td>4-CH$_3$C$_6$H$_4$</td>
<td>C$_6$H$_5$</td>
<td>1.43-1.51(2s, 6H, 2CH$_3$), 2.47(s, 3H, CH$_3$), 4.02-4.09(m, 1H, 4'Hd), 4.18-4.20(m, 1H, 4'Hc), 4.51-4.63(m, 2H, CH$_2$), 4.75-4.78(m, 1H, 5'Hb), 7.16-8.00(m, 11H, Ar-H)</td>
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<tr>
<td></td>
<td>Structure</td>
<td>NMR Data</td>
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<tr>
<td>129</td>
<td>4-OCH₃C₆H₄</td>
<td>C₆H₅</td>
<td>1.42-1.51 (2s, 6H, 2CH₃), 3.90 (s, 3H, OCH₃), 4.02-4.08 (m, 1H, 4′Hd), 4.18-4.24 (m, 1H, 4′Hc), 4.51-4.63 (m, 2H, CH₂), 4.75-4.78 (m, 1H, 5′Hb), 7.24-8.10 (m, 10H, Ar-H)</td>
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<tr>
<td>130</td>
<td>4-OCH₃C₆H₄</td>
<td>4-OCH₃C₆H₄</td>
<td>1.43-1.52 (2s, 6H, 2CH₃), 3.89 (s, 6H, 2OCH₃), 4.01-4.07 (m, 1H, 4′Hd), 4.19-4.23 (m, 1H, 4′Hc), 4.50-4.65 (m, 2H, CH₂), 4.73-4.77 (m, 1H, 5′Hb), 7.26-8.19 (m, 9H, Ar-H)</td>
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<td>131</td>
<td>4-ClC₆H₄</td>
<td>C₆H₅</td>
<td>1.42-1.52 (2s, 6H, 2CH₃), 4.02-4.08 (m, 1H, 4′Hd), 4.19-4.24 (m, 1H, 4′Hc), 4.51-4.65 (m, 2H, CH₂), 4.74-4.79 (m, 1H, 5′Hb), 7.28-8.19 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>132</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>1.42-1.52 (2s, 1, 6H, 2CH₃), 4.03-4.08 (m, 1H, 4′Hd), 4.20-4.25 (m, 1H, 4′Hc), 4.53-4.64 (m, 2H, CH₂), 4.75-4.79 (m, 1H, 5′Hb), 7.26-8.19 (m, 9H, Ar-H)</td>
</tr>
<tr>
<td>133</td>
<td>2-Furyl</td>
<td>4-CH₃C₆H₄</td>
<td>1.43-1.52 (2s, 6H, 2CH₃), 2.48 (s, 3H, CH₃), 4.02-4.08 (m, 1H, 4′Hd), 4.20-4.25 (m, 1H, 4′Hc), 4.51-4.65 (m, 2H, CH₂), 4.76-4.79 (m, 1H, 5′Hb), 7.26-8.19 (m, 8H, Ar-H)</td>
</tr>
<tr>
<td>134</td>
<td>2-Thienyl</td>
<td>C₆H₅</td>
<td>1.44-1.52 (2s, 6H, 2CH₃), 4.03-4.08 (m, 1H, 4′Hd), 4.20-4.25 (m, 1H, 4′Hc), 4.53-4.64 (m, 2H, CH₂), 4.75-4.79 (m, 1H, 5′Hb), 7.26-8.19 (m, 9H, Ar-H)</td>
</tr>
</tbody>
</table>
Figure 14
In $^1$HNMR(CDC$_3$) spectra of 4,6-disubstituted 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyanopyridines (XIII, 124-134), two singlets were observed in the region of $\delta$ 1.42-1.52 due to presence of geminal dimethyl group in the isopropylidene glycerol ring. The proton of isopropylidene glycerol moiety (Ar-0-CH$_2$-CH-CH$_2$) were found to resonate at $\delta$ 4.03-4.79 in form of a multiplet integrating for 5H. Resonance due to aromatic protons was observed between $\delta$ 7.24-8.19 as a multiplet.

$^1$HNMR(CDC$_3$) Spectrum of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4,6-diphenylpyridine (124) (Figure-14) displayed two singlets at $\delta$ 1.43 and $\delta$ 1.52 integrating for 3H each, due to geminal dimethyl group of the isopropylidene glycerol ring. The multiplet due to the protons of isopropylidene glycerol functionality (Ar-0-CH$_2$-CH-CH$_2$) was found in the region $\delta$ 4.03-4.79 integrating for five protons. The aromatic protons (11H) were resonated at $\delta$ 7.26-8.10 as a multiplet.

$^1$HNMR(CDC$_3$) Spectrum of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-methoxyphenyl)pyridine (126) (Figure-15) exhibited two singlets at $\delta$ 1.42 and $\delta$ 1.52 integrating for 3H each, due to the presence of geminal dimethyl group of isopropylidene glycerol ring. The multiplet due to the protons of isopropylidene glycerol functionality (Ar-O-CH$_2$-CH-CH$_2$) was found in the region between $\delta$ 4.02-4.78 integrating for 5H. A singlet observed at $\delta$ 3.89 integrating for 3H was suggestive of methoxy functionality. The aromatic protons were resonated at $\delta$ 6.99-8.08 in form of a multiplet integrating for 9H.

Mass spectrum of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4,6-diphenylpyridine (124) displayed a molecular ion peak at m/e=386 and base peak at m/e=274. Some important fragments are depicted in scheme-106.
Scheme - 106
4,6-Disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145) were off-white to yellow in colour, soluble in methanol, chloroform, methylene chloride, dimethylsulfoxide and N,N-dimethylformamide, while sparingly soluble in hexene and petroleum ether. The physical constants of 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145) were reported in table-51.

**Table-51 :** Physical constants of 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
<th>M.P. °C</th>
<th>Mol. Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>92</td>
<td>90-91</td>
<td>C₂₁H₁₈N₂O₃</td>
</tr>
<tr>
<td>136</td>
<td>C₆H₅</td>
<td>4-CH₃ C₆H₄</td>
<td>89</td>
<td>122-24</td>
<td>C₂₂H₂₀N₂O₃</td>
</tr>
<tr>
<td>137</td>
<td>C₆H₅</td>
<td>4-OCH₃ C₆H₄</td>
<td>90</td>
<td>147-48</td>
<td>C₂₂H₂₀N₂O₄</td>
</tr>
<tr>
<td>138</td>
<td>C₆H₅</td>
<td>4-ClC₆H₄</td>
<td>92</td>
<td>142-44</td>
<td>C₂₁H₁₇ClN₂O₃</td>
</tr>
<tr>
<td>139</td>
<td>4-CH₃ C₆H₄</td>
<td>C₆H₅</td>
<td>91</td>
<td>149-50</td>
<td>C₂₂H₂₀N₂O₃</td>
</tr>
<tr>
<td>140</td>
<td>4-OCH₃ C₆H₄</td>
<td>C₆H₅</td>
<td>90</td>
<td>140-41</td>
<td>C₂₂H₂₀N₂O₄</td>
</tr>
<tr>
<td>141</td>
<td>4-OCH₃ C₆H₄</td>
<td>4-OCH₃ C₆H₄</td>
<td>89</td>
<td>125-26</td>
<td>C₂₃H₂₂N₂O₃</td>
</tr>
<tr>
<td>142</td>
<td>4-ClC₆H₄</td>
<td>C₆H₅</td>
<td>92</td>
<td>130-31</td>
<td>C₂₁H₁₇ClN₂O₃</td>
</tr>
<tr>
<td>143</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>90</td>
<td>138-40</td>
<td>C₂₁H₁₆Cl₂N₂O₃</td>
</tr>
<tr>
<td>144</td>
<td>2-Furyl</td>
<td>4-CH₃ C₆H₄</td>
<td>89</td>
<td>185-86</td>
<td>C₁₉H₁₈N₂O₄</td>
</tr>
<tr>
<td>145</td>
<td>2-Thienyl</td>
<td>C₆H₅</td>
<td>87</td>
<td>127-28</td>
<td>C₁₉H₁₈N₂O₃S</td>
</tr>
</tbody>
</table>

IR(KBr) Spectral data of 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145) (Table-52) exhibited an absorption band in the region 3449-3430 cm⁻¹ due to
the presence of the hydroxyl groups indicative of complete hydrolysis of compounds (XIII, 124-134). A distinct absorption band for cyano (-C≡N) functionality was observed in the region 2210-2205 cm⁻¹.

Table- 52 : IR(KBr) Spectral data of 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145)

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>ν O-H cm⁻¹</th>
<th>ν C-H cm⁻¹</th>
<th>νC≡N cm⁻¹</th>
<th>ν C=C, C=N cm⁻¹</th>
<th>δ C-H cm⁻¹</th>
<th>δ C-C, C-N cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>3438</td>
<td>3030, 2944, 2852</td>
<td>2220</td>
<td>1585, 1530</td>
<td>1445</td>
<td>1378, 1255</td>
</tr>
<tr>
<td>136</td>
<td>3449</td>
<td>3010, 2970, 2837</td>
<td>2218</td>
<td>1587, 1534</td>
<td>1434</td>
<td>1354, 1236</td>
</tr>
<tr>
<td>137</td>
<td>3440</td>
<td>3010, 2995, 2878</td>
<td>2214</td>
<td>1585, 1532</td>
<td>1440</td>
<td>1360, 1238</td>
</tr>
<tr>
<td>138</td>
<td>3438</td>
<td>3010, 2944, 2838</td>
<td>2210</td>
<td>1590, 1525</td>
<td>1424</td>
<td>1350, 1258</td>
</tr>
<tr>
<td>139</td>
<td>3444</td>
<td>3020, 2970, 2878</td>
<td>2224</td>
<td>1585, 1534</td>
<td>1443</td>
<td>1360, 1240</td>
</tr>
<tr>
<td>140</td>
<td>3448</td>
<td>3020, 2994, 2870</td>
<td>2218</td>
<td>1587, 1530</td>
<td>1428</td>
<td>1347, 1220</td>
</tr>
<tr>
<td>141</td>
<td>3436</td>
<td>3010, 2958, 2838</td>
<td>2220</td>
<td>1580, 1550</td>
<td>1430</td>
<td>1348, 1256</td>
</tr>
<tr>
<td>142</td>
<td>3430</td>
<td>3010, 2978, 2852</td>
<td>2210</td>
<td>1599, 1534</td>
<td>1424</td>
<td>1378, 1235</td>
</tr>
<tr>
<td>143</td>
<td>3435</td>
<td>3005, 2950, 2830</td>
<td>2221</td>
<td>1580, 1555</td>
<td>1456</td>
<td>1370, 1250</td>
</tr>
<tr>
<td>144</td>
<td>3438</td>
<td>3010, 2975, 2870</td>
<td>2220</td>
<td>1587, 1540</td>
<td>1440</td>
<td>1360, 1276</td>
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<tr>
<td>145</td>
<td>3440</td>
<td>3020, 2980, 2840</td>
<td>2218</td>
<td>1582, 1535</td>
<td>1445</td>
<td>1354, 1240</td>
</tr>
</tbody>
</table>

¹¹HNMR Spectral data of 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145) are given in table-53
Table-53: $^1$H NMR Spectral data of 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>$^1$H NMR (CDCl$_3$, δ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>C$_6$H$_5$</td>
<td>C$_6$H$_5$</td>
<td>3.71-3.90 (m, 2H, CH$_2$OH), 4.12-4.25 (q, 1H, CHO), 4.65-4.75 (m, 2H, OCH$_2$), 7.42-8.03 (m, 11H, Ar-H)</td>
</tr>
<tr>
<td>136</td>
<td>C$_6$H$_5$</td>
<td>4-CH$_3$C$_6$H$_4$</td>
<td>3.71-3.90 (m, 2H, CH$_2$OH), 2.48 (s, 3H, CH$_3$), 4.12-4.25 (q, 1H, CHO), 4.65-4.75 (m, 2H, OCH$_2$), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>137</td>
<td>C$_6$H$_5$</td>
<td>4-OCH$_2$C$_6$H$_4$</td>
<td>3.71-3.90 (m, 2H, CH$_2$OH), 3.98 (s, 3H, OCH$_3$), 4.12-4.25 (q, 1H, CHO), 4.65-4.75 (m, 2H, OCH$_2$), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>138</td>
<td>C$_6$H$_5$</td>
<td>4-ClC$_6$H$_4$</td>
<td>3.71-3.90 (m, 2H, CH$_2$OH), 4.12-4.25 (q, 1H, CHO), 4.65-4.75 (m, 2H, OCH$_2$), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>139</td>
<td>4-CH$_3$C$_6$H$_4$</td>
<td>C$_6$H$_5$</td>
<td>3.71-3.90 (m, 2H, CH$_2$OH), 2.48 (s, 3H, CH$_3$), 4.12-4.25 (q, 1H, CHO), 4.65-4.75 (m, 2H, OCH$_2$), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>140</td>
<td>4-OCH$_3$C$_6$H$_4$</td>
<td>C$_6$H$_5$</td>
<td>3.71-3.90 (m, 2H, CH$_2$OH), 3.98 (s, 3H, OCH$_3$), 4.12-4.25 (q, 1H, CHO), 4.65-4.75 (m, 2H, OCH$_2$), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>141</td>
<td>4-OCH₃C₆H₄</td>
<td>4-OCH₃C₆H₄</td>
<td>3.71-3.90 (m, 2H, CH₂OH), 3.98 (s, 6H, 2OCH₃), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>142</td>
<td>4-ClC₆H₄</td>
<td>C₆H₅</td>
<td>3.71-3.90 (m, 2H, CH₂OH), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>143</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>3.71-3.90 (m, 2H, CH₂OH), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>144</td>
<td>2-Furyl</td>
<td>4-CH₃C₆H₄</td>
<td>3.71-3.90 (m, 2H, CH₂OH), 2.48 (s, 3H, CH₃), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
<tr>
<td>145</td>
<td>2-Thienyl</td>
<td>C₆H₅</td>
<td>3.71-3.90 (m, 2H, CH₂OH), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)</td>
</tr>
</tbody>
</table>

¹H NMR (CDCl₃) Spectra of 4,6-disubstituted 2-(2,3-dihydroxypropoxy)-3-cyanopyridines (XIV, 135-145) show a multiplet in the region of δ 3.75-3.93 integrating for 2H due to the presence of -CH₂OH functionality of the dihydroxypropoxy side chain. A quintet
integrating for 1H was found in the region of $\delta$ 4.15-4.28 responsible for -CHOH functionality of dihydroxypropoxy side chain. A multiplet integrating for 2H resonated at $\delta$ 4.59-4.72 due to OCH$_2$ functionality. The aromatic protons resonated giving a multiplet between $\delta$ 7.40-8.08.

$^1$HNMR Spectrum of 2-(2,3-dihydroxypropoxy)-3-cyano-4,6-diphenylpyridines (135) (Figure-16) shows a multiplet in the region of $\delta$ 3.77-3.90 integrating for 2H due to the presence of -CH$_2$OH functionality of the dihydroxypropoxy side chain. A quintet integrating for 1H was found in the region of $\delta$ 4.18-4.25 responsible for -CHOH functionality of dihydroxypropoxy side chain. A multiplet integrating for 2H resonated at $\delta$ 4.62-4.70 due to OCH$_2$ functionality. The aromatic protons resonated giving a multiplet between $\delta$ 7.41-8.03 integrating for 11H.

The Mass spectrum of 2-(2,3-dihydroxypropoxy)-3-cyano-4,6-diphenylpyridine (135) is depicted in scheme-107.
The $^{13}$C NMR (CDCl$_3$) spectral data of 2-($O,O$-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4,6-diphenylpyridine (124) and 2-(2,3-dihydroxypropoxy)-3-cyano-4,6-diphenylpyridine (135) are recorded in table-54.

![Chemical structures of 124 and 135](image)

**Table-54. $^{13}$C NMR Data for compound 124 and 135**

<table>
<thead>
<tr>
<th>Compound 124 carbon no.</th>
<th>Compound 135 carbon no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>157 42</td>
<td>158 17</td>
</tr>
<tr>
<td>114.56</td>
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<tr>
<td>163 60</td>
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<td>128.38</td>
<td>129.00</td>
</tr>
<tr>
<td>127 79</td>
<td>128.33</td>
</tr>
</tbody>
</table>
Table-54 shows that 2', 2'a and 2'b are absent in compound 135.

5.4 Experimental:

Melting points were uncorrected and determined on Toshniwal melting point apparatus in open capillary tubes. Carbon, hydrogen and nitrogen of all compounds were estimated gravimetrically using Column Model-33 carbon, hydrogen and nitrogen analyser. The elemental analysis was performed at Ahmedabad Textile Industrial Research Association (ATIRA), Ahmedabad.

IR(KBr) Spectra of compounds XIII and XIV were recorded on Buck-500 spectrophotometer. Samples were run in form of pellets, which were prepared by smearing 2 mg compound in 150 mg KBr powder.

$^1$HNMR of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4,6-diphenylpyridine (XIII, 124-134) and 2-(2,3-dihydroxypropoxy)-3-cyano-4,6-diphenyl-pyridine (XIV, 135-145) were recorded on Varian Model- 400 spectrometer using TMS as an internal standard. The values are given in $\delta$ ppm.

The purity of compounds VIII, and XIV was checked routinely by TLC (1-mm thickness) silica gel-G and spots were visualized by exposing the dry plates in iodine vapours.
General method for the preparation of dl-isopropylidenglycerol \(^{295}\) (XII):

In a round bottom flask fitted with a water separator were placed acetone (4.09 mole, 300 ml), glycerol (1.09 mole, 100 g), petroleum ether (bp-40-60) (300 ml) and p-toluenesulphonic acid monohydrate (3 g). The mixture was heated upto reflux under stirring and water was collected in the water trap. The heating and stirring were continued till no more water gets collected in the trap.

The mixture was cooled to room temperature, to this was added powdered fused sodium acetate (3 g). The mixture was then filtered and the petroleum ether and acetone were removed by distillation. The residual liquid is distilled in a Claisen flask and the fraction obtained between 80-81 °C/11 mm is collected.

Synthesis of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4,6-diarylpyridine (XIII, 124-134):

2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4,6-diphenylpyridine (124):

To a solution of sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.161 g), chlorobenzene (15 ml) and 2-chloro-3-cyano-4,6-diphenylpyridine (57, 0.005 mole, 1.45 g) was added dl-isopropylidenglycerol (XII, 0.006 mole, 0.792 g). The mixture was stirred for 1 hour and the completion of reaction was determined by tlc (benzene : ethanol, 8:2). The water (25 ml) was added to the reaction mixture and stirring was continued for 5 minutes. The phases were then separated and the aqueous phase was extracted with chlorobenzene (15 ml). The combined organic layers were dried over anhydrous magnesium sulphate and chlorobenzene was removed in vacuo to obtained the crude solid product which was crystallized from ethanol.

Yield : 87 %

mp 108-10 °C

Analysis : C\(_{24}\)H\(_{22}\)N\(_2\)O\(_3\) (386.44)

Calcd. : C 74.58 H 5.73 N 7.25 %

Found . C 74.75 H 5.59 N 7.40 %
IR(KBr) cm⁻¹  3010, 2980, 2870 (CH), 2220 (CN), 1588, 1545 (C=C, C=N)

¹HNMR(δ ppm) : 1.43-1.52(2s, 6H, 2CH₃), 4.03-4.08(m, 1H, 4’Hd), 4.20-4.25(m, 1H, 4’He), 4.53-4.64 (m, 2H, CH₂), 4.75-4.79(m, 1H, 5’Hb), 7.26-8.19(m, 1H, Ar-H).

2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-methylphenyl)pyridine (125):

dl-Isopropylideneglycerol (XII, 0.006 mole, 0.792 g) was added to a mixture of sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.161 g), chlorobenzene (15 ml) and 2-chloro-3-cyano-4-phenyl-6-(4-methylphenyl)pyridine (59, 0.005 mole, 1.52 g). The mixture was stirred for 1 hour and stirring was continued for 5 minutes. After completion of the reaction, work-up was done according to the procedure described for 124.

Yield 85 %

mp : 132-34 °C

Analysis : C₂₅H₂₄N₂O₃ (400.48 )

Calcd.  C 74.97 H 6.04 N 6.99 %

Found . C 75.02 H 5.92 N 7.01 %

IR(KBr) cm⁻¹ : 3005, 2990, 2932 (CH), 2224 (CN), 1586, 1517 (C=C, C=N)

¹HNMR(δ ppm): 1.42-1.52(2s, 6H, 2CH₃), 4.02-4.08(m, 1H, 4’Hd), 2.48(s, 3H, CH₃), 4.19-4.23(m, 1H, 4’He), 4.53-4.64(m, 2H, CH₂), 4.75-4.79(m, 1H, 5’Hb), 7.06-8.00(m, 10H, Ar-H)

2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-methoxyphenyl)pyridine (126):

To a solution of sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.161 g), chlorobenzene (15 ml) and 2-chloro-3-cyano-4-phenyl-6-(4-methoxyphenyl)pyridine (59, 0.005 mole, 1.60 g) was added dl-isopropylideneglycerol (XII, 0.006 mole, 0.792 g). The mixture was stirred for 1 hour and stirring was continued for 5
minutes. The further work-up was carried out as per the procedure described for 124.

Yield : 80 %  
mp : 157-59 °C

Analysis :  
Calcd  
Found  

IR(KBr) cm⁻¹ : 3010, 2985, 2899 (CH), 2221 (CN), 1587, 1524 (C=C, C=N)

¹HNMR(δ ppm): 1.42-1.50(2s, 6H, 2CH₃), 3.89(s, 3H, OCH₃), 4.02-4.07(m, 1H, 4'Hd), 4.19-4.23(m, 1H, 4'Hc), 4.51-4.63(m, 2H, CH₂), 4.73-4.78(m, 1H, 5'Hb), 7.26-8.19(m, 10H, Ar-H)

2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-chlorophenyl)pyridine (127)

To a mixture of 2-chloro-3-cyano-4-phenyl-6-(4-chlorophenyl)pyridine (60, 0.005 mole, 1.62 g), sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.005 mole, 0.161 g) in chlorobenzene (15 ml), was added dl-isopropylideneglycerol (XII, 0.006 mole, 0.792 g). The mixture was stirred for 1 hour and and stirring was continued for 5 minutes. On completion of the reaction, the titled product was obtained after work-up as per the procedure described for compound 124.

Yield : 83 %  
mp : 127-29 °C

Analysis :  
Calcd  
Found  

IR(KBr) cm⁻¹ : 3010, 2980, 2902 (CH), 2226 (CN), 1588, 1544 (C=C, C=N)

¹HNMR(δ ppm): 1.43-1.53(2s, 6H, 2CH₃), 4.01-4.08(m, 1H, 4'Hd), 4.20-4.23(m, 1H, 4'Hc), 4.53-4.65(m, 2H, CH₂), 4.75-4.79(m, 1H, 5'Hb), 7.00-8.19(m, 10H, Ar-H)
2-((O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-methylphenyl)-6-phenylpyridine (128):

To a solution of sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.161 g), chlorobenzene (15 ml) and 2-chloro-3-cyano-4-(4-methyl-phenyl)-6-phenylpyridine (61, 0.005 mole, 1.52 g) was added dl-isopropylidenglycerol (XII, 0.006 mole, 0.792 g). The mixture was stirred for 1 hour and and stirring was continued for 5 minutes. The further work-up was carried out as per the procedure described for 124.

Yield: 84 %  
mp: 130-32 °C

Analysis: C25H24N2O3 (400.48)
Calcld.: C 74.97 H 6.04 N 6.99 %
Found: C 75.10 H 6.14 N 6.70 %

IR(KBr) cm⁻¹: 3010, 2988, 2854 (CH), 2220 (CN), 1584, 1524 (C=C, C=N)

¹H NMR (δ ppm): 1.43-1.51 (2H, 6H, 2CH₃), 2.47 (s, 3H, CH₃), 4.02-4.09 (m, 1H, 4'Hd), 4.18-4.20 (m, 1H, 4'Hc), 4.51-4.63 (m, 2H, CH₂), 4.75-4.78 (m, 1H, 5'Hb), 7.16-8.00 (m, 11H, Ar-H)

2-((O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-methoxyphenyl)-6-phenylpyridine (129):

dl-Isopropylidenglycerol (XII, 0.006 mole, 0.792 g) was added to a solution of sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.161 g), chlorobenzene (15 ml) and 2-chloro-3-cyano-4-(4-methoxyphenyl)-6-phenylpyridine (63, 0.005 mole, 1.60 g). The mixture was stirred for 1 hour and and stirring was continued for 5 minutes. The further work-up was carried out as per the procedure described for 124.

Yield: 85 %  
mp: 154-55 °C

Analysis: C26H24N2O4 (416.48)
Calcd. . C 72.09 H 5.80 N 6.72 %
Found : C 71.97 H 5.78 N 6.90 %
IR(KBr) cm⁻¹ : 3020, 2986, 2901 (CH), 2225 (CN), 1587, 1516 (C=C, C=N)
¹HNMR(δ ppm): 1.42-1.51(2s, 6H, 2CH₃), 3.90(s, 3H, OCH₃), 4.02-4.08
(m, 1H, 4'Hd), 4.18-4.24(m, 1H, 4'Hc), 4.51-4.63(m, 2H, CH₂),
4.75-4.78(m, 1H, 5'Hb), 7.24-8.10(m, 10H, Ar-H).

2-(O.O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-methoxyphenyl)-6-(4-methoxy-
phenyl)pyridine (130):

To a solution of sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide
(TBAB) (0.0005 mole, 0.161 g), chlorobenzene (15 ml) and 2-chloro-3-cyano-4-(4-
methoxyphenyl)-6-(4-methoxyphenyl)pyridine (65, 0.005 mole, 1.75 g) was added dl-
isopropylideneglycerol (XII, 0.006 mole, 0.792 g). The mixture was stirred for 1 hour and and
stirring was continued for 5 minutes. On completion of the reaction, the titled product was
obtained after work-up as per the procedure described for compound 124.

Yield : 86 %
mp : 119-20 °C
Analysis : C₂₆H₂₆N₂O₅ (446.48)
Calcd. : C 70.10 H 5.65 N 6.28 %
Found : C 70.22 H 5.52 N 6.20 %
IR(KBr) cm⁻¹ : 3010, 2989, 2950 (CH), 2224 (CN), 1582, 1544 (C=C, C=N)
¹HNMR(δ ppm): 1.43-1.52(2s, 6H, 2CH₃), 3.89(s, 6H, 2OCH₃), 4.01-4.07
(m, 1H, 4'Hd), 4.19-4.23(m, 1H, 4'Hc), 4.50-4.65(m, 2H, CH₂),
4.73-4.77(m, 1H, 5'Hb), 7.26-8.19(m, 9H, Ar-H).

2-(O.O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-chlorophenyl)-6-phenylpyridine
(131):

dl-Isopropylideneglycerol (XII, 0.006 mole, 0.792 g) was added to a solution of so-
dium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.16
g), chlorobenzene (15 ml) and 2-chloro-3-cyano-4-(4-chlorophenyl)-6-phenylpyridine (66, 0.005 mole, 1.62 g). The mixture was stirred for 1 hour and and stirring was continued for 5 minutes. On completion of the reaction, the titled product was obtained after work-up as per the procedure described for compound 124.

Yield: 81%  
mp: 115-17 °C

Analysis:  
Calcd.  C 68.64 H 5.02 N 6.65%  
Found  C 68.78 H 4.92 N 6.72%

IR(KBr) cm⁻¹:  3010, 2990, 2980 (CH), 2226 (CN), 1583, 1524 (C=C, C=N)

¹H NMR (δ ppm):  1.42-1.52 (2s, 6H, 2CH₃), 4.02-4.08 (m, 1H, 4'Hd), 4.19-4.24 (m, 1H, 4'Hc), 4.51-4.65 (m, 2H, CH₂), 4.74-4.79 (m, 1H, 5'Hb), 7.28-8.19 (m, 10H, Ar-H)

2-('O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-chlorophenyl)-6-(4-chlorophenyl)pyridine (132)

To a solution of sodium hydroxide (50% w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.161 g), chlorobenzene (15 ml) and 2-chloro-3-cyano-4-(4-chlorophenyl)-6-(4-chlorophenyl)pyridine (68, 0.005 mole, 1.45 g) was added dl-isopropylidene-glycerol (XII, 0.006 mole, 0.792 g) The mixture was stirred for 1 hour and and stirring was continued for 5 minutes. The further work-up was carried out as per the procedure described for 124.

Yield: 80%  
mp: 160-62 °C

Analysis:  
Calcd.  C 63.43 H 4.21 N 6.16%  
Found  C 63.52 H 4.01 N 6.36%
IR(KBr) cm⁻¹ : 3020, 2980, 2925 (CH), 2224 (CN), 1587, 1545 (C=C, C=N)

¹HNMR(δ ppm): 1.42-1.5 (2s, 1H, 2CH₃), 4.03-4.08 (m, 1H, 4'Hd), 4.20-4.25 (m, 1H, 4'Hc), 4.50-4.56 (m, 2H, CH₂), 4.75-4.79 (m, 1H, 5'Hb), 7.26-8.19 (m, 9H, Ar-H)

2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(2-furyl)-6-(4-methylphenyl)pyridine (133):

To a solution of 2-chloro-3-cyano-4-(2-furyl)-6-(methylphenyl)pyridine (69, 0.005 mole, 1.47 g), sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.161 g) and chlorobenzene (15 ml), was added dl-isopropylideneglycerol (XII, 0.006 mole, 0.792 g). The mixture was stirred for 1 hour and stirring was continued for 5 minutes. The further work-up was carried out as per the procedure described for 124.

Yield : 82 %

Analysis : C₂₃H₂₂N₂O₄ (390.53)

Calcd. : C 74.50 H 5.81 N 5.99 %

Found : C 74.70 H 5.92 N 5.79 %

IR(KBr) cm⁻¹ : 3020, 2995, 2924 (CH), 2226 (CN), 1597, 1556 (C=C, C=N)

¹HNMR(δ ppm): 1.43-1.52 (2s, 6H, 2CH₃), 2.48 (s, 3H, CH₃), 4.02-4.08 (m, 1H, 4'Hd), 4.20-4.25 (m, 1H, 4'Hc), 4.51-4.65 (m, 2H, CH₂), 4.76-4.79 (m, 1H, 5'Hb), 7.26-8.19 (m, 8H, Ar-H)

2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(2-thienyl)-6-phenylpyridine (134):

To a solution of 2-chloro-3-cyano-4-(2-thienyl)-6-phenylpyridine (69, 0.005 mole, 1.45 g) sodium hydroxide (50 % w/v, 3 ml), tetrabutylammonium bromide (TBAB) (0.0005 mole, 0.161 g) and chlorobenzene (15 ml), was added dl-isopropylideneglycerol (XII, 0.006 mole, 0.792 g). The mixture was stirred for 1 hour and stirring was continued for 5 minutes. The further work-up was carried out as per the procedure described for 124.
Yield 84 %
Analysis C_{23}H_{22}N_{2}O_{3}S (406 42)
Calcd. : C 67 96 H 5 45 N 6 89
Found . C 67 78 H 5 56 N 7 01
IR(KBr) cm^{-1} : 3010, 2995, 2859 (CH), 2230 (CN), 1587, 1535 (C=C, C=N)
{\textsuperscript{1}}HNMR(δ ppm): 1.44-1.52(2s, 6H, 2CH_{3}), 4.03-4.08(m, 1H, 4' Hd), 4.20-4.25
(m, 1H, 4'Hd), 4.53-4.64(m, 2H, CH_{2}), 4.75-4.79(m, 1H, 5'Hb),
7.26-8.19 (m, 9H, Ar-H)

**Synthesis of 2-(2,3-dihydroxypropoxy)-3-cyano-4,6-diarylpyridines (XIV. 135-145):**

2-(2,3-Dihydroxypropoxy)-3-cyano-4,6-diphenylpyridine (135):

To a mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4,6-diphenyl-
pyridine (124, 0.005 mole, 1.92 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5
ml) was stirred for 0.5 hour. The end point of the reaction was confirmed by tlc (hexane:ethyl
acetate, 8:2) The reaction mixture was poured onto the crushed ice, the solid separated was
filtered and washed with water till neutral Which was then dried at 50 °C and crystallized
from ethanol to get the titled product

Yield : 92 %
Analysis : C_{21}H_{18}N_{2}O_{3} (346 37)
Calcd. : C 72 82 H 5 23 N 8 08 %
Found . C 72 90 H 5 29 N 7 95 %
IR(KBr) cm^{-1} : 3438 (OH), 3030, 2944, 2852 (CH), 2220 (CN),
1585, 1530 (C=C, C=N)
{\textsuperscript{1}}HNMR(δ ppm) 3 71-3 90(m, 2H, CH_{2}OH), 4.12-4.25 (q, 1H, CHOH),
4.65-4.75(m, 2H, OCH_{2}), 7.42-8.03 (m, 11H, Ar-H)
2-(2,3-Dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-methylphenyl)pyridine (136):

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-methylphenyl)pyridine (125, 0.005 mole, 1.99 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 89%  
mp: 122-24 °C

Analysis
Calcld.  C 73.31 H 5.59 N 7.77 %
Found  C 73.43 H 5.60 N 7.59 %

IR(KBr) cm⁻¹: 3449 (OH), 3010, 2970, 2837 (CH), 2218 (CN), 1587, 1534 (C=C, C=N)

¹HNMR(δ ppm): 3.71-3.90 (m, 2H, CH₂OH), 2.48 (s, 3H, CH₃), 4.12-4.25 (q, 1H, CHO₃), 4.65-4.75 (m, 2H, OCHA), 7.42-8.03 (m, 10H, Ar-H)

2-(2,3-Dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-methoxyphenyl)pyridine (137):

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-methoxyphenyl)pyridine (126, 0.005 mole, 2.07 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 90%  
mp: 147-48 °C

Analysis
Calcld.  C 70.20 H 5.35 N 7.44 %
Found  C 70.02 H 5.25 N 7.32 %

IR(KBr) cm⁻¹: 3440 (OH), 3010, 2995, 2878 (CH), 2214 (CN), 1585, 1532 (C=C, C=N)
1H NMR (δ ppm): 3.71-3.90 (m, 2H, CH₂OH), 3.98 (s, 3H, OCH₃), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)

2-(2,3-Dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-chlorophenyl)pyridine (138):

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-phenyl-6-(4-chlorophenyl)pyridine (127, 0.005 mole, 2.10 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 92%  mp: 142-44 °C

Analysis

Calcd.

Found

IR (KBr) cm⁻¹: 3438 (OH), 3010, 2944, 2838 (CH), 2210 (CN), 1590, 1525 (C=C, C=N)

1H NMR (δ ppm): 3.71-3.90 (m, 2H, CH₂OH), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)

2-(2,3-Dihydroxypropoxy)-3-cyano-4-(4-methylphenyl)-6-phenylpyridine (139):

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-methylphenyl)-6-phenylpyridine (128, 0.005 mole, 1.99 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 91%  mp: 149-50 °C

Analysis

Calcd.

Found

IR (KBr) cm⁻¹: 3444 (OH), 3020, 2970, 2878 (CH), 2224 (CN), 1585, 1534 (C=C, C=N)
$^1$HNMR (δ ppm): 3.71-3.90 (m, 2H, CH$_2$OH), 2.48 (s, 3H, CH$_3$), 4.12-4.25 (q, 1H, CH$_2$OH), 4.65-4.75 (m, 2H, OCH$_2$), 7.42-8.03 (m, 10H, Ar-H)

2-(2,3-Dihydroxypropoxy)-3-cyano-4-(4-methoxyphenyl)-6-phenylpyridine (140):

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-methoxyphenyl)-6-phenylpyridine (129, 0.005 mole, 2.07 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 90 %

mp: 140-41 °C

Analysis

C$_{22}$H$_{20}$N$_2$O$_4$ (376.40)
Calcd.: C 70.20 H 5.35 N 7.44 %
Found: C 70.12 H 5.27 N 7.34 %

IR (KBr) cm$^{-1}$: 3448 (OH), 3020, 2994, 2870 (CH), 2218 (CN), 1587, 1530 (C=C, C=N)

$^1$HNMR (δ ppm): 3.71-3.90 (m, 2H, CH$_2$OH), 3.98 (s, 3H, OCH$_3$), 4.12-4.25 (q, 1H, CH$_2$OH), 4.65-4.75 (m, 2H, OCH$_2$), 7.42-8.03 (m, 10H, Ar-H)

2-(2,3-Dihydroxypropoxy)-3-cyano-4-(4-methoxyphenyl)-6-(4-methoxyphenyl)pyridine (141):

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-methoxyphenyl)-6-(4-methoxyphenyl)pyridine (130, 0.005 mole, 2.22 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 87 %

mp: 125-26 °C

Analysis

C$_{23}$H$_{22}$N$_2$O$_3$ (390.40)
Calcd.: C 70.76 H 5.67 N 7.17 %
Found: C 70.59 H 5.50 N 7.20 %

IR (KBr) cm$^{-1}$: 3436 (OH), 3010, 2958, 2838 (CH), 2220 (CN), 1580, 1550 (C=C, C=N)
1H NMR (δ ppm): 3.71-3.90 (m, 2H, CH₂OH), 3.98 (s, 6H, 2OCH₃), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)

(2,3-Dihydroxypropoxy)-3-cyano-4-(4-chlorophenyl)-6-phenylpyridine (142):

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-chlorophenyl)-6-phenylpyridine (131, 0.005 mole, 2.10 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 92%  mp 130-31 °C

Analysis:
Calcd.  C 66.22  H 4.49  N 7.35%
Found  C 66.42  H 4.62  N 7.32%

IR (KBr) cm⁻¹: 3430 (OH), 3010, 2978, 2852 (CH), 2210 (CN), 1599, 1534 (C=C, C=N)

1H NMR (δ ppm): 3.71-3.90 (m, 2H, CH₂OH), 3.98 (s, 6H, 2OCH₃), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH₂), 7.42-8.03 (m, 10H, Ar-H)

(2,3-Dihydroxypropoxy)-3-cyano-4-(4-chlorophenyl)-6-(4-chlorophenyl)pyridine (143):

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(4-chlorophenyl)-6-(4-chlorophenyl)pyridine (132, 0.005 mole, 2.27 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 90%  mp 138-40 °C

Analysis:
Calcd.  C 60.72  H 3.88  N 6.74%
Found  C 60.90  H 3.98  N 6.50%

IR (KBr) cm⁻¹: 3435 (OH), 3005, 2950, 2830 (CH), 2221 (CN), 1580, 1555 (C=C, C=N)
\[ ^{1} \text{HNMR(} \delta \text{ ppm) } 3.71-3.90 (m, 2H, CH_2OH), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH_2), 7.42-8.03 (m, 10H, Ar-H) \]

**2-(2,3-Dihydroxypropoxy)-3-cyano-4-(2-furyl)-6-(4-methylphenyl)pyridine (144):**

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(2-furyl)-6-(4-methylphenyl)pyridine (133, 0.005 mole, 1.94 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 87 %  
mp: 185-86 °C

**Analysis**
- C_{19}H_{18}N_{2}O_{4} (338.37)
- Calcd: C 68.05, H 4.50, N 8.35 %
- Found: C 68.25, H 4.70, N 8.45 %

**IR(KBr) cm^{-1}**
- 3438 (OH), 3010, 2975, 2870 (CH), 2200 (CN), 1587, 1540 (C=C, C=N)

\[ ^{1} \text{HNMR(} \delta \text{ ppm) } 3.71-3.90 (m, 2H, CH_2OH), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH_2), 7.42-8.03 (m, 10H, Ar-H) \]

**2-(2,3-Dihydroxypropoxy)-3-cyano-4-(2-thienyl)-6-(4-methylphenyl)pyridine (145):**

A mixture of 2-(O,O-isopropylidene-2,3-dihydroxypropoxy)-3-cyano-4-(2-thienyl)-6-(4-methylphenyl)pyridine (134, 0.005 mole, 1.92 g) dissolved in methanol (20 ml) and 6N hydrochloric acid (5 ml) was stirred for 0.5 hour. After the completion of reaction, work-up was carried out according to the procedure described for 135.

Yield: 87 %  
mp: 127-28 °C

**Analysis**
- C_{19}H_{18}N_{2}O_{3}S (354.36)
- Calcd: C 64.40, H 5.11, N 7.90 %
- Found: C 64.31, H 5.20, N 7.82 %

**IR(KBr) cm^{-1}**
- 3440 (OH), 3020, 2980, 2840 (CH), 2218 (CN), 1582, 1535 (C=C, C=N)

\[ ^{1} \text{HNMR(} \delta \text{ ppm) } 3.71-3.90 (m, 2H, CH_2OH), 4.12-4.25 (q, 1H, CHOH), 4.65-4.75 (m, 2H, OCH_2), 7.42-8.03 (m, 10H, Ar-H) \]