CHAPTER – 5
Section - A

Application of Ellman Reagent & Boekelheide rearrangement in the synthesis of 3-chloromethyl-1,2-benzisoxazoles [Zonisamide intermediate]

INTRODUCTION:

Isoxazole and benzisoxazole are important class of nitrogen-oxygen containing heterocycles [105]. They have extensive applications as structural units of various biologically important molecules and are useful intermediates in medicinal chemistry [106]. Among them, 3-substituted-1, 2-benzisoxazole and their derivatives are emerging as potential antipsychotic compounds [107-112]. For example, Zonisamide (1,2-benzisoxazole-3-methane sulfonamide) (117), is an efficient anti-seizure agent available in the market [113]. It is being reported that it blocks the repetitive firing of voltage-sensitive sodium channels and reduces voltage-sensitive T-type calcium currents [113].

\[
\text{SO}_2\text{NH}_2
\]

(117)

LITERATURE BACKGROUND:

117 has been synthesized in various synthetic routes [110-112], [115-122] and [127]. However, it is often synthesized from 3-halomethyl-1,2-benzisoxazole (121) by the reaction of sodium sulfite followed by phosphorus oxychloride and ammonia [114]. 3-Methyl-1,2-benzisoxazole
(128) is, in turn, prepared from o-hydroxyaryl aldoximes and ketoximes [121].

(i) Hitoshi et al. reported the preparation of 117 through the intermediacy of 3-bromomethyl-1,2-benzisoxazole 121 obtained from 1,2-benzisoxazole-3-acetic acid (119), which, in turn, was prepared from 4-hydroxycoumarin (118) and hydroxylamine by Posner reaction. (Scheme 5.1)[115-118]

(ii) Jaweed et al. reported the preparation of 117 through the intermediacy of 119 to sodium-1,2-benzisoxazole-3-methanesulphonate (123) starting from 118. (Scheme 5.2)[119]
(iii) Reddy et al. reported the preparation of 117 through the intermediacy of 125, 126, 127 and 123 starting from methyl salicylate (124). (Scheme 5.3)[120]

(iv) Nasser et al. reported the synthesis of 3-methyl-1,2-benzisoxazole (128) from 2-hydroxyarylaldoximes and ketoximes (129). (Scheme 5.4)[121]
Muralidhar et al. reported the synthesis of 128 from 129 through Microwave-assisted synthesis in ionic liquid. (Scheme 5.5)[122]

Moses et al. reported the synthesis of 128 from o-(trimethylsilyl)aryl triflates (130) [123], [124] and hydroxyimoyl chlorides (131) [125] by TBAF mediated 1,3-dipolar cycloaddition of nitrile oxides and benzyne. (Scheme 5.6)[125]
However, the main drawbacks of above reactions, i.e. low yields and harsh reaction conditions like use of large quantity of concentrated sulfuric acid at higher temperature (i.e. >200°C) and use of toxic chlorosulfonic acid, limit the practical applicability of the above synthetic methods.

On the other hand, Boekelheide rearrangement, i.e. [3,3]-sigmatropic rearrangement of N-oxide to corresponding alcohols or halides (Scheme 5.7) has been used for the synthesis of various heterocyclic derivatives [116 - 118]. Acetic anhydride or trifluoroacetic anhydride was commonly used as catalyst in the above reactions.

\[
\text{N} \quad \begin{array}{c}
\text{O} \\
\end{array} \\
\text{F}_3\text{C} \quad \begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\end{array} \\
\text{O} \\
(132)
\]
\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{F}_3\text{C} \quad \begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\text{O} \\
(133)
\end{array}
\end{array}
\]

TFAA = Trifluoroacetic anhydride

Mechanism:

\[
\text{N} \quad \begin{array}{c}
\text{O} \\
\text{F}_3\text{C} \quad \begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\end{array} \\
\text{O} \\
\end{array} \xrightarrow{\text{acyl transfer}} \begin{array}{c}
\text{N} \\
\text{O} \\
\text{F}_3\text{C} \quad \begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\end{array} \\
\text{O} \\
\end{array} \xrightarrow{\text{[3,3]-sigmatropic rearrangement}} \begin{array}{c}
\text{N} \\
\text{O} \\
\text{F}_3\text{C} \quad \begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\end{array} \\
\text{O} \\
\end{array} \xrightarrow{\text{hydrolysis}} \begin{array}{c}
\text{N} \\
\text{O} \\
\text{F}_3\text{C} \quad \begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\end{array} \\
\text{O} \\
\end{array}
\]

\[\ldots\] (Scheme 5.7)

(vii) Zhang et al. reported the transformation of 2-(1-chloromethyl)-4,5-dimethyloxazoles (136) from 2,3-butanedionemonooxime (134). (Scheme 5.8)[126]
(viii) Goto et al. reported the synthesis and reactions of oxazole N-oxides with phosphoryl chloride and acetic anhydride. \(\text{(Scheme 5.9)}[127]\)

(ix) Boulton et al. reported the synthesis of 3-methyl-1,2-benzisoxazole-2-oxides \(142\) from 1-(2-hydroxyphenyl)ethanone oxime \(129\) with lead tetraacetate or sodium hypochlorite. \(\text{(Scheme 5.10)}[128 - 130]\)

(x) Vidyadhar et al. reported the preparation of 3-methyl-1,2-benzisoxazole-2-oxides \(142\) from 1-(2-hydroxyphenyl)ethanone oxime \(129\) with sodium perborate in glacial acetic acid. \(\text{(Scheme 5.11)}[131]\)
(xi) Rane et al. reported the synthesis of 2-chloromethylpyridines \((143)\) from 2-methylpyridine-N-oxides \((132)\) by Boekelheide rearrangement in the presence p-TSCl and an organic base such as triethylamine. \((\text{Scheme 5.12})\)[132]

(xii) Rao et al. reported the preparation of 2-chloromethylpyridines \((143)\) from 2-methylpyridine-N-oxides \((132)\) with diphosgene or with triphosgene in the presence of amines. \((\text{Scheme 5.13})\)[133]

(xiii) Pews et al. reported the transformation of 2-chloromethylpyridines \((143)\) from 2-methylpyridine-N-oxides \((132)\) with POCl\(_3\) in the presence of triethylamine. \((\text{Scheme 5.14})\)[134]
PRESENT WORK:

It is obvious from the references cited above that a good number of researchers have synthesized 117 and its key intermediate 121. The synthesis of 121 through the intermediacy of 2-hydroxyaryl ketosulfinylimines (145) and 142, starting from 2-hydroxyacetophenone (144) is novel and although Boekelheide rearrangement was reported with various N-oxides, there seems to be no report on the halogen transfer to 3-position of N-oxides of 1,2-benzisoxazoles.

Therefore, in the present investigation, it was considered worthwhile to study the preparation of 121 through the intermediacy of 145 and 142 from 144 under different conditions.

The present chapter deals with the synthesis of 145 by the reaction of 144 with 1 using the conditions of Ellman reaction [49]. Cyclisation of 145 to get 3-methyl-1,2-benzisoxazole 128, followed by the preparation of N-oxide 142. Finally, chlorination of 142 with different chlorinating agents will yield the required 3-chloromethyl-1,2-benzisoxazole 121 with modified Boekelheide rearrangement.
RESULTS AND DISCUSSION:

2-Hydroxyacetophenone (144) is a commercially available intermediate and 1 was synthesized according to the literature [63, 64] reported earlier in chapter-II.

144 on condensation with 1 in the presence of titanium tetraisopropoxide in THF at 65°-70° C for 24 hours and after work up gave an imine product different from the starting material and homogeneous on TLC. It was assigned 2-methylpropane-2-sulfinic acid [1-(2-hydroxyphenyl)ethylidene]amide (145) structure based on its analytical and spectral data (Scheme 5.15). Thus, its IR in KBr (fig. 5.1) showed diagnostic absorption peak at 3350 - 3450 cm⁻¹ (broad, weak band due to phenolic –OH). Its ¹H-NMR (CDCl₃/TMS) spectrum (fig. 5.2) showed signals at δ1.34 (s, 9H, -(C₃H₃)₃), 2.83 (s, 3H, -CH₃), 6.91 (t, 1H, aromatic -CH), 6.98 (d, 1H, aromatic -CH), 7.41 (t, 1H, aromatic -CH), 7.65 (d, 1H, aromatic -CH) and 13.08 (s, 1H, phenolic -OH). Its ¹³C-NMR (CDCl₃/TMS) spectrum (fig. 5.3) showed signals at δ 20.06, 22.10, 56.74, 118.42, 118.89, 119.42, 129.26, 134.91, 161.75 and 182.27. Its mass spectrum (ESIMS) (fig. 5.4) showed the molecular ion peak at m/z 240 corresponding to a molecular mass of 239 when recorded in the Q+1 mode.
The cyclisation of 145 was tried with simultaneous cleavage of the sulfinyl group by treating with 13% sodium hypo chlorite solution alone, and in combination with different acids like dry HCl in ethyl acetate, p-toluenesulfonic acid and bases like, 25% sodium methoxide in methanol and DBU. But, neither acid nor base medium initiated the cyclisation and in all the cases, the reactions completely reverted to hydroxyacetophenone 144 (Scheme 5.16). 

![Diagram](image)

Proposed mechanism:

[Chemical structures and reactions diagram]
Obtained reaction mechanism:

As the cyclisation reaction was not proceeding with either acids or bases, the sulfinyl derivatives were replaced with keto-oxime derivatives 129, which were prepared by reacting 144 with hydroxylamine hydrochloride in the presence of pyridine. All the oximes were prepared according to known methods in good yields (70-98%) (Scheme 5.17).

Keto-oxime 129, on treatment with 13% aqueous sodium hypochlorite solution furnished the cyclized product different from the starting material and homogeneous on TLC. It was assigned 3-methyl-1,2-benzisoxazole-2-oxide (142) structure based on its analytical and spectral data (Scheme 5.18) [121], [122]. Thus, its IR in KBr (fig. 5.5) showed the absence of broad, medium phenolic -OH peak at 3300-3500
cm$^{-1}$. Its $^1$H-NMR (CDCl$_3$/TMS) spectrum (fig. 5.6) showed signals at $\delta$ 2.43 (s, 3H, -CH$_3$), 7.10 (d, 1H, aromatic -CH), 7.27 (t, 1H, aromatic -CH), 7.42 (d, 1H, aromatic -CH), 7.47 (t, 1H, aromatic –CH). Its $^{13}$C-NMR (CDCl$_3$/TMS) spectrum (fig. 5.7) showed signals at $\delta$ 9.2, 106.6, 116.4, 118.8, 121.1, 129.7, 133.6 and 148.4.

![Reaction mechanism](image)

Finally, the required 3-chloromethyl-1,2-benzisoxazole derivatives 121 were synthesized by the halogen transfer to 3-position of N-oxides via modified Boekelheide rearrangement using phosphorous oxychloride as chlorinating agent in the presence of triethylamine (Scheme 5.19). Its structure was confirmed based on its analytical and spectral data. Thus, its $^1$H-NMR (CDCl$_3$/TMS) spectrum (fig. 5.8) showed signals at $\delta$ 4.92 (s, 2H, -CH$_2$), 7.36 (m, 1H, aromatic -CH), 7.60 (dt, 2H, aromatic -CH) and 7.86 (d, 1H, aromatic –CH) that clearly indicates the absence of methyl signal at $\delta$ 2.43 (s, 3H, -CH$_3$). Its $^{13}$C-NMR (CDCl$_3$/TMS) spectrum (fig. 5.8) showed signals at $\delta$ 9.2, 106.6, 116.4, 118.8, 121.1, 129.7, 133.6 and 148.4.
showed signals at δ 34.9, 110.0, 120.0, 121.6, 123.8, 130.3, 155.0 and 163.6.

![Chemical reaction diagram]

Reaction mechanism:

Initially the usefulness of Boekelheide reaction in the synthesis of 3-acetoxymethyl-1,2-benzisoxazole (147) was investigated using acetic anhydride. But the reaction of 142 with acetic anhydride did not lead to the formation of the required product, but mainly formed 128 and 2-acetyloxyacetophenone (146). (Scheme 5.20)

![Chemical reaction diagram]
Reaction mechanism:

Initially acetic anhydride or trifluoro acetic anhydride was used in Boekelheide reaction, the acetate group (or hydroxy group) is transferred to the adjacent carbon atom and the use of POCl$_3$ in the second step leads to the formation of halogen derivatives instead of acetate or hydroxy derivatives [17], [18], [19], [21] and [22]. Therefore, POCl$_3$ was used in the presence of organic bases such as triethylamine (TEA) or diisopropylethylamine (DIPEA) or DBU for halogen transfer from $N$-oxide of benzisoxazole to result in the formation of 3-chloromethyl-1,2-benzisoxazole.

With the initial success on the parent compound (as described in Scheme 5.19), which was confirmed as 3-chloromethyl-1,2-benzisoxazole, with all the spectral & analytical data, the rearrangement was studied with different chlorinating agents and different bases for obtaining better yields. The results (Table 5.1) showed that only POCl$_3$ and TEA (Entry: 11) were effective for the rearrangement.
**Table 5.1**: Optimization of rearrangement conditions for best conversion of 142 to 121

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Chlorinating agent</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield * (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>POCl₃</td>
<td>DIPEA</td>
<td>40</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>POCl₃</td>
<td>DBU</td>
<td>40</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>POCl₃</td>
<td>PhNMe₂</td>
<td>40</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>POCl₃</td>
<td>Pyridine</td>
<td>40</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>POCl₃</td>
<td>DMAP</td>
<td>40</td>
<td>1</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>POCl₃ &amp; PCl₅</td>
<td>----</td>
<td>40</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>SOCl₂</td>
<td>TEA</td>
<td>40</td>
<td>72</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
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<td>SOCl₂</td>
<td>DIPEA</td>
<td>40</td>
<td>72</td>
<td>Nil</td>
</tr>
<tr>
<td>9</td>
<td>C₂H₄Cl₂</td>
<td>(EtO)₂P(O)Cl</td>
<td>TEA</td>
<td>80</td>
<td>72</td>
<td>Nil</td>
</tr>
<tr>
<td>10</td>
<td>C₂H₄Cl₂</td>
<td>p-TSCl</td>
<td>TEA</td>
<td>80</td>
<td>72</td>
<td>Nil</td>
</tr>
<tr>
<td>11</td>
<td>CH₂Cl₂</td>
<td>POCl₃</td>
<td>TEA</td>
<td>40</td>
<td>48</td>
<td>50</td>
</tr>
</tbody>
</table>

* Isolated yield

After establishing the best conditions for rearrangement (entry 11, Table 5.1), the effect of different substituents on benzene ring as well as methyl group of benzisoxazole was examined on this rearrangement. The presence of Me, Et, Ph, Cl, Br substituents on benzene ring (Table 5.2), behaved normally in the rearrangement process whereas the presence of nitro (5q, 5r) or methoxy (5s) substituents has drastically affected the rearrangement and failed to generate the expected products. When
dimethyl (5o) and isopropyl (5p) substituents were present on the side chain of benzisoxazole the formation of rearranged products were not observed and chlorination with de-methylation at C-3 was observed to some extent (Scheme 5.22), (Scheme 5.23) which was confirmed by the absence of dimethyl and isopropyl signals in $^1$H NMR spectrum and major portion of the N-oxide was decomposed. However, methyl, ethyl, phenyl substituents on the side chain behaved normally.

\[
\begin{align*}
\text{Scheme 5.22} & : \\
\text{Scheme 5.23} & :
\end{align*}
\]
Apart from general spectral characterization, some of the 3-chloromethyl-1,2-benzisoxazoles were confirmed by single-crystal X-ray analysis. The ORTEP diagrams that are showed below also confirmed the structures of 3-chloromethyl-6,7-dimethyl-1,2-benzisoxazole \((121j)\) and 3-[chloro(phenyl)methyl]-6-methyl-1,2-benzisoxazole \((121m)\).
ORTEP diagram of 121j

ORTEP diagram of 121m
Table 5.2: Yield of substituted 3-chloromethyl-1,2-benzisoxazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>121a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>50</td>
</tr>
<tr>
<td>121b</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>55</td>
</tr>
<tr>
<td>121c</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>52</td>
</tr>
<tr>
<td>121d</td>
<td>H</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>50</td>
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<td>H</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>65</td>
</tr>
<tr>
<td>121f</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>53</td>
</tr>
<tr>
<td>121g</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>49</td>
</tr>
<tr>
<td>121h</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
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</tr>
<tr>
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<td>H</td>
<td>Br</td>
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<td>H</td>
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<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
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<td>H</td>
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<td>H</td>
<td>Et</td>
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<td>H</td>
<td>H</td>
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<td>32</td>
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<td>H</td>
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</tr>
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<td>121o</td>
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<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me₂</td>
<td>NR</td>
</tr>
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<td>121p</td>
<td>H</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>CHMe₂</td>
<td>NR</td>
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<td>H</td>
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<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>NR</td>
</tr>
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<td>H</td>
<td>NHAc</td>
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<td>H</td>
<td>H</td>
<td>10</td>
</tr>
</tbody>
</table>

*Isolated yield
Experimental Section:

5.1) Preparation of 145 from 144 & 1 (General Procedure):

1 (8.9 gm) was added to a solution of titanium tetraisopropoxide (41.75 gm) and 144 (10.0 gm) in tetrahydrofuran (150.0 mL) under N₂ atmosphere and the mixture was heated to 65° to 70°C for 24 hours. Upon completion of reaction, the mixture was cooled to room temperature and diluted with ethyl acetate. It was washed with saturated brine solution and the resulting solids were filtered off through celite bed. Then the organic layer was separated from the aqueous layer and washed successively with water. The organic portions were dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain the crude product, which was purified through column chromatography to obtain pure 145.

Yield 6.0 g (60%); M. R. 57.4 - 59.7°C; IR (KBr): 3 421 (vb, -OH), 1586 (vs, C=N), 1083 (vs, sharp, S=O) cm⁻¹; ¹H NMR (CD₃OD/TMS): δ 1.34 (s, 9H, -(CH₃)₃), 2.83 (s, 3H, -CH₃), 6.91 (t, 1H, aromatic -CH), 6.98 (d, 1H, aromatic -CH), 7.41 (t, 1H, aromatic -CH), 7.65 (d, 1H, aromatic -CH), 13.08 (s, 1H, phenolic -OH); ¹³C NMR (CD₃OD/TMS): δ 20.06, 22.10, 56.74, 118.42, 118.89, 119.42, 129.26, 134.91, 161.75 and 182.27; MS (m/z): 240 [Q+1]⁺
5.2a) **Preparation of 128 from 145 with NaOCl:**

To 145 (1.0 gm) was added 13% aq.sodium hypochlorite solution (2.8 mL) at RT under N₂ atmosphere and stirred till completion of the starting material. The reaction mixture was quenched in dil.HCl solution to get neutral pH and extracted with ethyl acetate (10.0 mL). The organic layer was washed with water, then separated and dried over anhydrous sodium sulfate. Filtered and concentrated under vacuum to get the crude product. IR and GC results showed that the reaction completely reverted to 144.

5.2b) **Preparation of 128 from 145 with NaOCl and NaOMe:**

145 (1.0 gm) dissolved in diisopropyl ether (10.0 mL) and to this solution was added sodium methoxide powder (0.33 gm) and 13% aq.sodium hypochlorite solution (2.8 mL) at RT under N₂ atmosphere and stirred till completion of the starting material. The reaction mass was quenched in water and separated the organic layer. The organic layer is washed with water until pH comes to neutral, then separated and dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get the crude product. IR and GC results showed that the reaction completely reverted to 144.

5.2c) **Preparation of 128 from 145 with NaOCl and DBU:**

145 (1.0 gm) dissolved in diisopropyl ether (10.0 mL) and to this solution was added DBU (0.95 gm) and 13% aq.sodium hypochlorite solution (2.8
mL) at RT under N₂ atmosphere and stirred till completion of the starting material. The reaction mixture was quenched in water and separated the organic layer. The organic layer was washed with water until pH comes to neutral, then separated and dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get the crude product. IR and GC results showed that the reaction completely reverted to 144.

5.2d) Preparation of 128 from 145 with acid hydrolysis:

145 (1.0 gm) dissolved in methanol (10.0 mL) and to this was added 10% dry HCl in ethyl acetate (3.0 mL) at RT under N₂ atmosphere and stirred till completion of the starting material. Methanol was distilled out, diluted with ethyl acetate and the reaction mass was quenched in water. The organic layer was washed with water until pH comes to neutral, then separated and dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get the crude product. 87% of the product was comparing with 144 in IR and there is no product of 128. Reaction completely reverted to hydroxyacetophenone 144.

IR (Neat): 3050 (vb, -OH), 1642 (vs, C=O) cm⁻¹; ¹H NMR (CD₃OD/TMS): δ 2.65 (s, 3H, -CH₃), 6.91 (t, 1H, aryl proton), 6.98 (d, 1H, aryl proton), 7.47 (t, 1H, aryl proton), 7.75 (d, 1H, aryl proton), 12.27 (s, 1H, phenolic -OH); GC Purity: 92.5%
5.2e) Preparation of 128 from 145 with p-TSA:

145 (1.0 gm) dissolved in diisopropyl ether (10.0 mL) and to this solution was added p-toluenesulfonicacid (0.08 gm) at RT under N₂ atmosphere and stirred till completion of the starting material. The reaction mixture was quenched in water and separated the organic layer. The organic layer was washed with water until pH comes to neutral, then separated and dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get the crude product. IR and GC purity results showed that the reaction completely reverted to 144.

5.3) General procedure for the preparation of 142a – t:

Phenolic oxime (1.0 mole) was dissolved in aqueous NaOH solution (1.1 mole of NaOH dissolved in water) and the obtained solution was cooled to 0 - 10°C. 13% aq.sodium hypochlorite solution (1.2 moles) was added slowly at 0 - 10°C over a period of 15 min and stirred for 30 min. The precipitated solid was filtered, washed with water, dried and recrystallized from ethyl acetate to obtain pure compound.

142a Yield 4.9 g (50%); M. R. 93-95°C; HPLC purity 98%; ¹HNMR (CDCl₃/TMS): δ 2.43 (s, 3H), 7.10 (d, 1H, J = 8.0Hz), 7.27 (t, 1H, J = 8.0Hz), 7.42 (d, 1H, J = 8.0Hz), 7.47 (t, 1H, J = 8.0Hz); ¹³CNMR (CDCl₃/TMS): δ 9.2, 106.6, 116.4, 118.8, 121.1, 129.7, 133.6 and 148.4.

142b Yield 5.14 g (52%); M. P. 70-71°C; HPLC purity 99%; ¹HNMR (CDCl₃/TMS): δ 2.34 (s, 3H), 2.38 (s, 6H), 7.01 (s, 1H), 7.07 (s, 1H);
$^{13}$CNMR (CDCl$_3$/TMS): δ 9.3, 14.7, 21.0, 116.1, 117.0, 117.2, 120.6, 130.8, 133.7 and 147.3.

**142c** Yield 5.4 g (55%); M. R. 152-154°C; HPLC purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 2.35 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 6.91 (d, 1H, J = 8.0Hz), 7.11 (d, 1H, J = 8.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 11.3, 14.3, 18.3, 115.2, 117.7, 119.0, 125.3, 128.1, 129.0 and 148.8.

**142d** Yield 6.0 g (61%); HPLC purity 97%; $^1$HNMR (CDCl$_3$/TMS): δ 1.27 (t, 3H, J = 8.0Hz), 2.41 (s, 3H), 2.72 (q, 2H, J = 8.0Hz), 7.08 (d, 1H, J = 8.0Hz), 7.21 (s, 1H), 7.31 (dd, 1H, $J_1$ = 8.0Hz, $J_2$ = 1.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.2, 15.8, 28.5, 106.7, 116.4, 117.6, 121.0, 128.6, 140.1 and 148.44.

**142e** Yield 4.8 g (48.5%); M. R. 118-120°C; HPLC purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 2.46 (s, 3H), 7.24 (d, 1H, J = 8.0Hz), 7.38 (m, 1H), 7.47 (m, 2H), 7.57 (m, 2H), 7.67 (dd, 1H, $J_1$ = 8.0Hz, $J_2$ = 2.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.3, 107.1, 116.2, 117.3, 121.6, 127.1, 127.5, 127.9, 128.8, 137.6, 140.1 and 149.4.

**142f** Yield 5.53 g (56%); M. R. 75-79°C; HPLC purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 2.39 (s, 3H), 2.42 (s, 3H), 7.04 (d, 1H, J = 8.0Hz), 7.20 (d, 1H, J = 8.0Hz) 7.26 (dd, 1H, $J_1$ = 8.0Hz, $J_2$ = 2.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.2, 21.1, 106.6, 116.3, 118.8, 121.0, 129.6, 133.6 and 148.3.

**142g** Yield 5.23 g (53%); M. R. 101-103°C; HPLC purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 2.40 (s, 3H), 2.46 (s, 3H), 7.01 (s, 1H), 7.09 (d, 1H, J =
8.0Hz) 7.27 (d, 1H, J = 8.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.3, 21.9, 107.2, 116.3, 118.5, 118.6, 125.2, 139.5 and 150.4.

142h Yield 5.45 g (55%); M. R. 99-101°C; HPLC purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 2.40 (s, 3H), 7.05 (d, 1H, J = 8.0Hz), 7.54 (m, 2H); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.2, 108.4, 114.9, 116.5, 121.6, 123.0, 131.2 and 148.6.

142i Yield 5.53 g (56%); M. R. 112-115°C; HPLC purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 2.40 (s, 3H), 7.11 (d, 1H, J = 8.0Hz), 7.39 (d, 1H, J = 2.0Hz), 7.43 (dd, 1H, $J_1$ = 8.0Hz, $J_2$ = 2.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.3, 108.0, 115.3, 118.6, 122.5, 128.5, 129.4 and 148.2.

142j Yield 5.1 g (51%); M. R. 82-85°C; HPLC purity 99%; $^1$HNMR (CDCl$_3$/TMS): δ 2.30 (s, 3H), 2.37 (s, 3H), 2.39 (s, 3H), 7.08 (d, 1H, J = 8.0Hz), 7.13 (d, 1H, J = 8.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.2, 11.6, 19.3, 115.7, 116.0, 117.3, 118.3, 125.8, 137.7 and 149.2.

142k Yield 4.5 g (45%); HPLC purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 1.35 (t, 3H, J = 7.6Hz), 2.40 (s, 3H), 2.83 (q, 2H, J = 7.6Hz), 7.04 (d, 1H, J = 8.0Hz), 7.23(s, 1H), 7.25 (d, 1H, J = 8.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 1.1, 17.8, 20.6, 106.7, 117.0, 127.4, 129.7, 131.2, 155.6 and 164.0.

142l Yield 5.93 g (60%); HPLC purity 97%; $^1$HNMR (CDCl$_3$/TMS): δ 1.02 (t, 3H, J = 7.4Hz), 1.82 (h, 2H, J = 7.4Hz), 2.43 (s, 3H), 2.79 (t, 2H, J = 7.4Hz), 7.04 (d, 1H, J = 8.4Hz), 7.22 (s, 1H), and 7.25 (d, 1H, J = 8.4Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 21.1, 30.4, 106.6, 118.4, 119.0, 120.4, 127.3, 128.7, 128.8, 129.5, 133.6, 134.6 and 148.4.
142m Yield 5.94 g (60%); M. R. 73-74°C; HPLC purity 97%; $^{1}$H NMR (CDCl$_3$/TMS): δ 2.42 (s, 3H), 4.14 (s, 2H), 6.99 (m, 3H), and 7.3 (m, 5H); $^{13}$CNMR (CDCl$_3$/TMS): δ 21.8, 30.6, 107.2, 117.8, 118.4, 119.0, 125.2, 127.4, 128.8, 128.8, 134.6, 139.3 and 150.5.

142n Yield 6.54 g (66%); M. R. 113-116°C. HPLC purity 97%; $^{1}$HNMR (CDCl$_3$/TMS): δ 2.35 (s, 3H), 4.14 (s, 2H), 6.96 (s, 1H), 7.04 (d, 1H, $J$ = 8.4Hz), 7.22 (d, 1H, $J$ = 8.4Hz), 7.25 to 7.33 (m, 5H); $^{13}$CNMR (CDCl$_3$/TMS): δ 21.1, 30.4, 106.6, 118.4, 119.0, 120.4, 127.3, 128.7, 128.8, 129.5, 133.6, 134.6 and 148.4.

142o Yield 8.41 g (85%); HPLC purity 97%; $^{1}$HNMR (CDCl$_3$/TMS): δ 1.40 (d, 6H, $J$ = 7.1Hz), 2.39 (s, 3H), 3.26 (m, 1H), 7.0 (d, 1H, $J$ = 8.4Hz), 7.21 (d, 1H, $J$ = 8.4Hz), 7.29 (s, 1H); $^{13}$CNMR (CDCl$_3$/TMS): δ 18.5, 21.1, 26.0, 106.5, 119.3, 119.7, 122.9, 129.1, 133.2 and 148.4.

142p Yield 8.62 g (87%); HPLC purity 97%; $^{1}$HNMR (CDCl$_3$/TMS): δ 1.01 (d, 6H, $J$ = 6.7Hz), 1.25 (t, 3H, $J$ = 7.6Hz), 2.25 (m, 1H), 2.69 (d, 2H, $J$ = 7.6Hz), 2.7 (q, 2H, $J$ = 7.6Hz), 7.05 (d, 1H, $J$ = 8.4Hz), 7.22 (s, 1H), 7.28 (dd, 1H, $J_1$ = 8.4Hz, $J_2$ = 1.3); $^{13}$CNMR (CDCl$_3$/TMS): δ 15.9, 22.4, 26.5, 28.5, 32.9, 106.6, 117.8, 119.1, 121.2, 128.4, 140.0 and 148.4.

142q Yield 4.45 g (45%); M. R. 157.8-159.1°C; HPLC purity 97%; $^{1}$HNMR (CDCl$_3$/TMS): δ 2.42 (s, 3H), 7.51 (d, 1H, $J$ = 9.0Hz), 8.36 (dd, 1H, $J_1$ = 9.0Hz, $J_2$ = 2.3Hz), 8.63 (d, 1H, $J$ = 2.2Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.4, 107.9, 115.8, 117.2, 122.3, 124.6, 144.3 and 152.9.
Yield 4.25 g (43%); M. R. 161-163.9°C; HPLC purity 97%; $^1$H NMR (CDCl$_3$/TMS): δ 2.42 (s, 3H), 7.50 (t, 1H, $J = 8.0$Hz), 8.09 (d, 1H, $J = 8.0$Hz), 8.27 (d, 1H, $J = 8.0$Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.4, 106.9, 115.8, 117.2, 122.3, 124.6, 144.34 and 153.1.

Yield 1.5 g (15%); M. R. 112.6-118.4°C; HPLC purity 95%; $^1$HNMR (CDCl$_3$/TMS): δ 2.43 (s, 3H), 3.87 (s, 3H), 6.7 (d, 1H, $J = 2.0$Hz), 6.88 (dd, 1H, $J_1 = 8.0$Hz, $J_2 = 5.5$Hz), 7.27 (d, 1H, $J = 8.0$Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.2, 55.7, 91.9, 112.6, 119.5 and 161.3.

Yield 3.0 g (30%); M. R. 178-180°C; IR (KBr): 3320 (-NH), 1682 (-C=O) cm$^{-1}$; $^1$HNMR (CDCl$_3$/TMS): δ 2.06 (s, 3H), 2.32 (s, 3H), 7.32 (d, 1H, $J = 8.0$Hz), 7.55 (d, 1H, $J = 8.0$Hz), 7.77 (s, 1H), 10.26 (s, 1H); $^{13}$CNMR (CDCl$_3$/TMS): δ 9.2, 24.4, 97.0, 115.6, 116.0, 120.5, 140.7, 150.2 and 169.1.

### 5.4) General procedure for the rearrangement of 142 to 121:

To a solution of $N$-oxide (1.0 mole) in methylene dichloride (10 volumes) was added POCl$_3$ (2.0 moles) drop wise at 20°C over a period of 5 min and stirred for 5 min at 20°C. Then triethylamine (2.0 moles) was added drop wise at 20°C over a period of 10 min in such a rate that the reaction temperature does not exceed 30°C. Then the mixture was stirred at reflux temperature for 48 hours and cooled to 10°C, washed with chilled water, followed by 10% aq.Na$_2$CO$_3$ solution to get neutral pH. The aqueous layer is extracted with methylene dichloride (25.0 mL X 2). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and the
solvent was removed under reduced pressure to get the crude product, which was purified by column chromatography or by recrystallization.

121a Yield 5.6 g (50%); M. R. 66-67°C; HPLC purity 99%; $^1$HNMR (CDCl$_3$/TMS): δ 4.92 (s, 2H), 7.36 (m, 1H), 7.60 (dt, 2H, $J_1 = 2.6$ Hz, $J_2 = 1.0$ Hz) and 7.86 (d, 1H, $J = 7.0$ Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 34.9, 110.0, 120.0, 121.6, 123.8, 130.3, 155.0 and 163.6; Mass: m/z = 338.6.

121b Yield 6.0 g (55%); M. R. 54-56°C; HPLC purity 99%; $^1$HNMR (CDCl$_3$/TMS): δ 2.45 (s, 3H), 2.53 (s, 3H), 4.88 (s, 2H), 7.18 (s, 1H) and 7.41 (s, 1H); $^{13}$CNMR (CDCl$_3$/TMS): δ 15.0, 21.0, 35.1, 117.8, 119.6, 120.2, 132.4, 133.9, 154.8 and 161.7; Mass: m/z = 196.3 (M$^+$) & 198.3 (M+2).

121c Yield 5.75 g (52%); HPLC Purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 2.52 (s, 3H), 2.70 (s, 3H), 4.94 (s, 2H), 7.01 (d, 1H, $J = 7.3$ Hz) and 7.22 (d, 1H, $J = 7.3$ Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 14.6, 18.4, 35.5, 118.1, 118.3, 125.1, 130.1, 130.7, 155.2 and 163.3; Mass: m/z = 196.2 (M$^+$) & 198.3 (M+2).

121d Yield 5.57 g (50.5%); HPLC Purity 99%; $^1$HNMR (CDCl$_3$/TMS): δ 1.30 (t, 3H, $J = 7.6$ Hz), 2.79 (q, 2H, $J = 7.6$ Hz), 4.90 (s, 2H), 7.42 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 1.6$ Hz), 7.49 (d, 1H, $J = 8.6$ Hz) and 7.61 (s, 1H); $^{13}$CNMR (CDCl$_3$/TMS): δ 15.9, 28.5, 35.0, 109.7, 119.5, 120.1, 131.0, 140.2, 154.7 and 162.4; Mass: m/z = 196.2 (M$^+$) & 198.3 (M+2).

121e Yield 7.0 g (65%); M. R. 78-80°C; HPLC Purity 98%; $^1$HNMR (CDCl$_3$/TMS): δ 4.95 (s, 2H), 7.39 (m, 1H), 7.48 (t, 2H, $J = 7.6$ Hz), 7.65
(m, 2H), 7.81 (dd, 1H, \(J_1 = 8.7\)Hz, \(J_2 = 1.7\)Hz) and 7.99 (d, 1H, \(J = 1.7\)Hz);

\(^{13}\)CNMR (CDCl\(_3\)/TMS): \(\delta \) 34.9, 110.2, 119.6, 120.7, 127.3, 127.5, 128.8, 130.2, 137.8, 140.0, 155.1 and 163.1; Mass: m/z = 244.6 (M\(^+\)).

**121f** Yield 5.9 g (53%); HPLC Purity 98%; \(^1\)HNMR (CDCl\(_3\)/TMS): \(\delta \) 2.49 (s, 3H), 4.89 (s, 2H), 7.38 (dd, 1H, \(J_1 = 8.6\)Hz, \(J_2 = 1.4\)Hz), 7.46 (d, 1H, \(J = 8.6\)Hz) and 7.60 (s, 1H); \(^{13}\)CNMR (CDCl\(_3\)/TMS): \(\delta \) 21.0, 34.9, 109.5, 120.1, 120.6, 131.9, 133.6, 154.6 and 162.28; Mass: m/z = 182.3 (M\(^+\)) \& 184.4 (M+2).

**121g** Yield 5.45 g (49%); HPLC Purity 98%; IR (Neat): 3014, 2968, 2921, 1623, 1437, 1379, 805 cm\(^{-1}\); \(^1\)HNMR (CDCl\(_3\)/TMS): \(\delta \) 2.53 (s, 3H), 4.89 (s, 2H), 7.18 (d, 1H, \(J = 8.0\)Hz), 7.39 (s, 1H) and 7.69 (d, 1H, \(J = 8.0\)Hz); \(^{13}\)CNMR (CDCl\(_3\)/TMS): \(\delta \) 21.9, 35.0, 109.8, 117.7, 120.9, 125.6, 141.4, 154.7 and 164.2; Mass: m/z = 182.3 (M\(^+\)) \& 184.4 (M+2).

**121h** Yield 5.51 g (51%); M. P. 64-67\(^\circ\)C; HPLC Purity 97%; \(^1\)HNMR (CDCl\(_3\)/TMS): \(\delta \) 4.88 (s, 2H), 7.57 (d, 2H, \(J = 1.9\)Hz) and 7.83 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\)/TMS): \(\delta \) 34.6, 111.5, 116.8, 121.9, 124.2, 133.4, 154.4 and 162.5.

**121i** Yield 5.17 g (47%); M. R. 87-90\(^\circ\)C; HPLC Purity 98%; \(^1\)HNMR (CDCl\(_3\)/TMS): \(\delta \) 4.89 (s, 2H), 7.55 (d, 2H, \(J = 1.0\)Hz) and 7.84 (s, 1H); \(^{13}\)CNMR (CDCl\(_3\)/TMS): \(\delta \) 34.7, 111.1, 121.0, 121.3, 129.5, 130.8, 154.6 and 162.1.

**121j** Yield 6.62 g (60%); M. R. 59-60.5\(^\circ\)C; HPLC purity 99%; \(^1\)HNMR (CDCl\(_3\)/TMS): \(\delta \) 2.43 (s, 3H), 2.47 (s, 3H), 4.88 (s, 2H), 7.17 (d, 1H, \(J = \)
8.0Hz) and 7.52 (d, 1H, J = 8.0Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 11.7, 19.1, 35.1, 117.5, 117.7, 118.7, 126.5, 139.0, 155.1 and 163.5; Mass: m/z = 196.1 (M$^+$) & 198.2 (M+2).

121k Yield 6.1 g (55%); HPLC Purity 95%; $^1$HNMR (CDCl$_3$/TMS): δ 2.05 (d, 3H, J = 6.9Hz), 2.49 (s, 3H), 5.42 (q, 1H, J = 6.9Hz), 7.37 (dd, 1H, $J_1$ = 8.5Hz, $J_2$ = 0.7Hz), 7.46 (d, 1H, J = 8.5Hz) and 7.66 (s, 1H); $^{13}$C NMR (CDCl$_3$/TMS): δ 21.0, 23.4, 48.8, 109.5, 119.4, 121.2, 131.7, 133.4, 158.4 and 162.4; Mass: m/z = 196.2 (M$^+$) & 198.2 (M+2).

121l Yield 5.7 g (52%); HPLC Purity 95%; $^1$HNMR (CDCl$_3$/TMS): δ1.11 (t, 3H, J = 7.3Hz), 2.34 (m, 2H), 2.49 (s, 3H), 5.19 (t, 1H, J = 7.3Hz), 7.37 (dd, 1H, $J_1$ = 8.5Hz, $J_2$ = 0.7Hz), 7.46 (d, 1H, J = 8.5) and 7.65 (s, 1H); $^{13}$CNMR (CDCl$_3$/TMS): δ 11.3, 21.0, 30.4, 55.2, 109.5, 119.4, 121.2, 131.7, 133.3, 157.7 and 162.4.

121m Yield 3.44 g (32%); M. R. 59-64°C; HPLC Purity 97%; $^1$HNMR (CDCl$_3$/TMS): δ 2.49 (s, 3H), 6.46 (s, 1H), 7.08 (d, 1H, J = 8.0Hz), 7.35 (m, 5H), 7.52 (s, 1H) and 7.55 (d, 1H, J = 8.0Hz); $^{13}$C NMR (CDCl$_3$/TMS): δ 21.8, 54.8, 109.8, 117.1, 121.7, 125.5, 127.4, 128.7, 128.7, 137.0, 141.2, 157.6 and 164.5; MS m/z 258.3 (Q+1)$^+$. 

121n Yield 3.2 g (30%); HPLC Purity 97%; $^1$HNMR (CDCl$_3$/TMS): δ 2.42 (s, 3H), 6.48 (s, 1H), 7.34 (m, 4H), 7.45 (d, 1H, J = 1.3Hz), 7.48 (s, 1H) and 7.57 (d, 1H, J = 1.3Hz); $^{13}$CNMR (CDCl$_3$/TMS): δ 21.7, 55.6, 110.7, 118.1, 123.7, 124.5, 128.4, 128.7, 128.7, 137.9, 140.5, 158.6 and 164.5; MS m/z 258.2 (Q+1)$^+$. 
121t Yield 1.08 g (10%); M. R. 185-188°C; IR (Neat): 3313 (NH), 1669 (-C=O) cm\(^{-1}\); \(^1\)HNMR (CDCl\(_3\)/TMS): \(\delta\) 2.10 (s, 3H), 5.14 (s, 2H), 7.40 (dd, 1H, \(J_1 = 8.0\)Hz, \(J_2 = 1.4\)Hz), 7.83 (d, 1H, \(J = 8.0\)Hz), 8.22 (s, 1H) and 10.44 (s, 1H); \(^{13}\)CNMR (CDCl\(_3\)/TMS): \(\delta\) 24.5, 35.0, 98.8, 115.1, 116.8, 122.5, 142.2, 155.6, 164.1 and 169.5; MS m/z 223.3 (Q-1) & 225.3 (Q-2).
CHAPTER – 5
Section - B

Study on stability of tert-butanesulfinamide
[Termal rearrangement]

INTRODUCTION:

Since its introduction in 1997, tert-butanesulfinamide (in R- & S-forms) is proved to be versatile reagent for the asymmetric synthesis of chiral amine containing compounds. It is being applied across various research areas, including the development of pharmaceutical agents, natural products, agrochemicals and the preparation of chemical tools for a wide range of biological investigations [17]. A number of factors have led to the popularity of 1, in particular, the tert-butylsulfinyl group showed high levels of asymmetric induction in many processes.

PRESENT WORK:

As per the literature survey [17], it is obvious that no stability study work have been done on 1. The present section deals with the studies on the stability of 1 and the thermal rearrangement of 1 to N-(tert-butylthio)-tert-butylsulfonamide (150) and also chemical synthesis of 150 from tert-butylsulfanyl chloride (151) and tert-butylsulfonamide (152).

RESULTS AND DISCUSSIONS:

Condensation of 1 with phenylacetic acid (153) in the presence of boric acid in toluene at reflux temperature for 1h, yielded a
product homogeneous on TLC, different from the starting material. Its IR (KBr) spectrum (Fig. 5.10) showed a sharp absorption centering around 3300-3200 cm\(^{-1}\) due to –NH- group and a sharp absorption centering around 1400-1300 cm\(^{-1}\) due to –SO\(_2\)- group. Its PMR spectrum (CDCl\(_3\)/TMS) (Fig. 5.11) showed signals at \(\delta 1.31\) (s, 9H, –C(CH\(_3\)_3)), 1.42 (s, 9H, –C(CH\(_3\)_3)), 5.37 (br, s, 1H, D\(_2\)O exchangeable –NH-). Its \(^{13}\)C-NMR (CDCl\(_3\)/TMS) spectrum (fig. 5.12) showed signals at \(\delta\) 24.6, 28.0, 48.4, and 61.1. Its Mass spectrum (Fig. 5.13), showed the molecular ion peak at 224 (Q-1) corresponding to a molecular mass of 225. Its molecular structure was confirmed by single-crystal X-ray analysis (ORTEP diagram, Fig. 5.14). Thus, on the basis of spectral data, the product was found to be \(N\)-\((\text{tert}-\text{butylthio})\)-\(\text{tert}-\text{butylsulfonamide}\) 150, instead the expected \(N\)-phenylacetyl-\(N\)-\(\text{tert}-\text{butanesulfinamide}\) (154). (Scheme 5.24)
Fig. 5.14: ORTEP diagram of 150

A plausible mechanisms for the formation of 150 as given below:

\[
\begin{align*}
\text{S} &\rightarrow \text{S} \\
\text{O} &\rightarrow \text{O} \\
\text{NH}_2 &\rightarrow \text{NH}_2 \\
\end{align*}
\]

From the single-crystal structure, it is assumed that the product 150 is formed only by the degradation of reagent 1. To confirm the thermal degradation of 1, various experiments were carried out. Summary table of different conditions for the comparison of yields is given below.
Table 5.3: Screening of rearrangement conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
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<tr>
<td></td>
<td>STM Reagent / condition type Solvent</td>
<td>Temp (°C)</td>
</tr>
<tr>
<td>1</td>
<td>(R)-isomer - -</td>
<td>110</td>
</tr>
<tr>
<td>2</td>
<td>(R)-isomer - toluene</td>
<td>110</td>
</tr>
<tr>
<td>3</td>
<td>(R)-isomer - o-xylene</td>
<td>140</td>
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<tr>
<td>4</td>
<td>(R)-isomer - EDC</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>(R)-isomer - CHCl₃</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>(R)-isomer - toluene</td>
<td>110</td>
</tr>
<tr>
<td>7</td>
<td>(R)-isomer Boric acid (1.0 equi) toluene (u/N₂)</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>(R)-isomer Boric acid (1.0 equi) toluene</td>
<td>110</td>
</tr>
<tr>
<td>9</td>
<td>(R)-isomer Boric acid (0.5 equi) toluene</td>
<td>110</td>
</tr>
<tr>
<td>10</td>
<td>(R)-isomer MeSO₃H toluene</td>
<td>110</td>
</tr>
<tr>
<td>11</td>
<td>(R)-isomer Tartaric acid toluene</td>
<td>110</td>
</tr>
<tr>
<td>12</td>
<td>(R)-isomer Citric acid toluene</td>
<td>110</td>
</tr>
<tr>
<td>13</td>
<td>(R)-isomer p-TSA toluene</td>
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</tr>
<tr>
<td>14</td>
<td>(R)-isomer Sonication CHCl₃ RT</td>
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</tr>
<tr>
<td>15</td>
<td>(R)-isomer Sonication DMF RT</td>
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</tr>
<tr>
<td>16</td>
<td>(R)-isomer Sonication Ethyl acetate RT</td>
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<tr>
<td>17</td>
<td>(R)-isomer Sonication + Boric acid CHCl₃ RT</td>
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</tr>
<tr>
<td>18</td>
<td>(R)-isomer Sonication + p-TSA CHCl₃ RT</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>(R)-isomer</td>
<td>-</td>
</tr>
<tr>
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<tr>
<td>19</td>
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<td></td>
</tr>
<tr>
<td>20</td>
<td>(R)-isomer</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>(R)-isomer</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>(R)-isomer</td>
<td>Benzoyl peroxide</td>
</tr>
<tr>
<td>23</td>
<td>(R)-isomer</td>
<td>TEMPO</td>
</tr>
<tr>
<td>24</td>
<td>(R)-isomer</td>
<td>2,6-di-tert-butyl phenol</td>
</tr>
<tr>
<td>25</td>
<td>(S)-isomer</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>(R)-isomer</td>
<td>MW 150 Watts</td>
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</table>

a. Isolated yield, b. % conversion in HPLC, c. recovered STM with SOR+5°

Experiments in the presence of acids (Table 5.3, entries 7 to 13) or the absence of acids (entries 1 to 6), under sonication (entries 14 to 18) and with microwave irradiation (entry 26), confirmed the assumption that the reagent is thermally unstable. Also the rearrangement is likely not to proceed by a homolytic fission (radical) mechanism, because the rate of reaction is not affected either by benzoyl peroxide, by TEMPO a radical initiator (entries 22 and 23) or by a radical inhibitor 2,6-di-tert-butylphenol (entry 24).

When the reagent 1 alone was subjected to thermal rearrangement (entry 1), complete consumption of starting material was observed. Only 27% product was isolated and 73% of the material was lost by vaporization. When the reaction was carried out in the presence of solvents such as
toluene (entries 2, 6 and 24), o-xylene (entry 3), or solvents with reagents such as boric acid (entries 7 to 9), methanesulphonic acid (entry 10), p-TSA (entry 13), benzoyl peroxide (entry 22), 2,6-di-tertbutylphenol (entry 23) or with microwave irradiation (entry 25), complete consumption of starting material was observed. In other cases (entries 4, 5, 11 and 12), 10 to 30% of the starting material was recovered without racemization.

Finally, the rearranged product 150 was also confirmed by comparing with the chemically synthesized product from 151 and 152, which were prepared according to literature procedures [135, 136]. 151 was treated with 152 in the presence of DBU at room temperature afforded 150 in 30% yield. (Scheme 5.25).

\[
\text{S-Cl} + \text{H}_2\text{N-SO}_3 \xrightarrow{\text{DBU, RT}} \text{SO}_3\text{NH-S-Cl}
\]

(151) (152) (150)
**Experimental Section:**

5.5) **Preparation of 154 from 153**:

To a solution of 153 (5.0 g, 0.036 M) in toluene (50.0 mL) was added 1 (4.45 g, 0.036 M) and boric acid (0.22 g, 0.0036 M) and heated to reflux temperature and stirred for 48 hours (Progress of the reaction is monitored through TLC and the spots are visualized in Iodine vapour). The solution was cooled to RT and washed with water (50.0 mL X 2). Separated organic layer was dried over anhydrous Na$_2$SO$_4$ (10.0 g) and concentrated under vacuum. The obtained residue was passed through column chromatography in n-Hexane and ethylacetate mixture solvent. The product obtained in 2-4% ethylacetate in n-hexane solvent was concentrated and filtered to get white crystalline solid (94% purity), which is recrystallized from ethyl acetate. The starting material 153 was completely recovered and reagent 1 was absent in crude product.

Yield 2.0 g; M. R. 160 – 164°C; HPLC Purity: 99%; [α]$_{D}^{20}$ (C=1.0, CHCl$_3$): 0°: IR (cm$^{-1}$, KBr): 3300 - 3200 (s, -NH), 1400 - 1300 (s, –SO$_2$); $^1$HNMR (TMS/CDCl$_3$): δ 1.32 (s, 9H, C(CH$_3$)$_3$), 1.43 (s, 9H, C(CH$_3$)$_3$), 5.18 (s, 1H, -NH). $^{13}$CNMR (TMS/CDCl$_3$): δ 24.62, 28.0, 48.46 and 61.14. ESI-MS m/z (%,- mode): 224 [Q -1].

5.6) **Preparation of 154 from 1**:
1 (10.0 g, 0.08 M) was dissolved in toluene (100.0 mL) at room temperature. The resulted colorless clear solution was heated to reflux temperature and stirred for 48 hours. The solution was cooled to RT and washed with water (50.0 mL x 2). Separated organic layer was dried over anhydrous Na$_2$SO$_4$ (10.0 g) and concentrated under vacuum. The obtained solid is slurred in n-Hexane (50.0 mL) at RT and filtered to get white crystalline solid (94% purity), which is recrystallized from ethyl acetate.

Yield 7.0 g (70%); m.p: 162 – 164°C; HPLC Purity: 99.5%; [α]$_{D}^{20}$ (C=1.0, CHCl$_3$): 0°.

5.7) Preparation of 154 from 151 & 152:

152 (2.4 g, 0.017 M) was dissolved in ethyl acetate (12.0 mL) and DBU (5.3 g, 0.034 mol) was added at ambient temperature. 151 (~2.2 g, 0.017 M) in n-pentane (10.0 mL) was added drop-wise at 25 – 30°C over a period of 10 minutes. After complete addition, the pale yellow sticky precipitate was stirred for 1 hour. Water (10.0 mL) was added and the layers were separated. The aqueous layer is extracted once with ethyl acetate (10.0 mL), the combined organic layers are washed with water (10.0 mL x 2) and dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent under vacuum results in a residue, which is mixed with ether (10.0 mL) and n-Hexane (20.0 mL) and the crystals are filtered and washed with ether (1.5 mL). The product is purified through column chromatography with 4% ethyl acetate:n-Hexane as eluent to afford 1.18 g of 3 as white crystals.

Yield 30%; m.p: 159.8 – 161.8°C; HPLC Purity: 99%