2.1 Introduction:

It is evident from the introduction and literature survey given in chapter-1 that benzimidazole derivatives are useful intermediates / subunits for the development of new chemical entities and molecules of potential interest\textsuperscript{1, 2}. The synthetic studies on benzimidazoles are devided into three sections namely, Section – A, Section – B and Section- C. Section – A deals with the preparation of 2-acetylbenzimidazole and its reactions, Section – B discusses the reactions of 2-(α-hydroxyethyl)benzimidazole and Section – C describes reactions of 2-(α-chloroethyl)benzimidazole with aniline.

SECTION – A

2A: Preparation and reactions of 2 – Acetylbenzimidazole

2A.1. Literature Survey:

Danghui et. al. reported\textsuperscript{3} the condensation of 1 with lactic acid (2) resulting in 2-(α-hydroxyethyl)benzimidazole (3) which on oxidation in acetic acid gave 2-acetylbenzimidazole (4). The latter on treatment with potassium glycinate (5) in refluxing methanol yielded the corresponding Schiff base 6 of 4.
Kalirajan et al reported the synthesis of pyrazole substituted benzimidazole from 2-acetylbenzimidazole under micro-wave irradiation conditions.

2A. 2.1. Preparation of 2-acetylbenzimidazole:

o-Phenylenediamine (1) was condensed with lactic acid (2) under Phillip’s conditions to obtain the previously known 2-(α-hydroxyethyl)benzimidazole (3) as a crude, fairly water soluble product.
3, which is a recemic mixture of two optically active enantiomeric compounds, could be readily purified by dissolving in hot acetone, treating with charcoal in hot condition, filtration, concentration and cooling to yield a crystalline precipitate of 3, which was found to be pure on TLC.

Oxidation\(^{12-16}\) of 3 with potassium dichromate in 5% sulphuric acid gave the previously reported\(^{17-20}\) 2-acetylbenzimidazole (4). The reported procedures for the preparation of 4 involve oxidation of 3 with oxidising agent in dil. Sulphuric acid followed by careful neutralisation of the reaction mixture with aq. ammonia to a pH of 5.5 – 6.0, resulting in the formation of 4, which is filtered, washed with water and dried. Yield is to be reported around 60% with the product being sufficiently pure on TLC. Similar were the results obtained in our work.

![Scheme 2.4](image)

It has been observed that in the above reaction, the pH of the solution during neutralisation with aq. ammonia should be close to neutral, preferably exceeds 7.0, i.e., if it goes to basic side, then the yield of the product 4 goes down considerably, as 4 is reasonably soluble on dil. aq. alkaline solutions and the product purity suffers due to improper precipitations of chromium salts in reduced oxidation states formed as a result of reduction of the dichromate.
2A.2.2. Oxidation Studies:

In the above reaction, involving oxidation of 3, it was observed in a series of runs that the yields tapered off to around 60%. Since 2-acetylbenzimidazole (4) was needed in the present work in reasonably large amounts, it was considered worthwhile to explore alternative methods for the preparation of 4.

The oxidation reaction of 3 to 4 was studied with different oxidising agents with a view to see if 4 can be obtained in higher yields, greater purity and using a reagent cheaper than the analar dichromate.

**Table: 2.1**

**Preparation of 4 from 3 by oxidising using different reagents:-**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Substrate</th>
<th>Oidising agent</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Reaction Status</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>K$_2$Cr$_2$O$_7$</td>
<td>Stirring at RT</td>
<td>4</td>
<td>Completed</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>MnO$_2$</td>
<td>Refluxing/ 3-4hrs</td>
<td>4</td>
<td>Not moving</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>MnO$_2$</td>
<td>Physical grinding</td>
<td>4</td>
<td>Not moving</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>H$_2$O$_2$ in AcOH</td>
<td>Stirring RT/ 3hrs</td>
<td>4</td>
<td>Completed</td>
<td>55%</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>CaOCl$_2$</td>
<td>Refluxing/ 3hrs</td>
<td>4</td>
<td>Not moving</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>m-CPBA</td>
<td>Stirring RT/ 3-4hrs</td>
<td>4</td>
<td>Not moving</td>
<td>Nil</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>10% HNO$_3$</td>
<td>Stirring RT / 3-4hrs</td>
<td>4</td>
<td>Not moving</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>50% HNO$_3$</td>
<td>Stirring RT / 3-4hrs</td>
<td>4</td>
<td>Not moving</td>
<td>Nil</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>50% HNO$_3$</td>
<td>△/100°C / 3-4hrs</td>
<td>4</td>
<td>Not moving</td>
<td>Nil</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>CAN</td>
<td>MEK/ RT/ 3-4hrs</td>
<td>4</td>
<td>Completed</td>
<td>50%</td>
</tr>
</tbody>
</table>
The oxidising agents used were MnO$_2$, H$_2$O$_2$ in glacial acetic acid, bleaching powder, m-CPBA, Ceric ammonium nitrate, cupric acetate (in acetic acid) and nitric acid. The results are shown in Table 2.1.

It is obvious from these results that only a few oxidising agents like ceric ammonium nitrate and hydrogen peroxide (in glacial acetic acid) gave comparable yields to potassium dichromate. The other did not fare well.

2A. 2.3: Alkylation studies on 2-acetylbenzimidazole:

Maynard and co-workers studied$^{21}$ the alkylation of 9 with benzyl chloride in the presence of sodium hydride in acetone giving 10.

\[
\begin{align*}
\text{H} & \quad \text{Cl}^–\text{CH}_2\text{C}_6\text{H}_5 \\
\text{N} & \quad \text{NaH} / \text{acetone} \\
\text{N} & \quad \text{H}_2\text{C}^–\text{C}_6\text{H}_5 \\
\text{N} & \quad \text{S} \\
(9) & \quad \text{S} \\
(10) & \quad \text{Scheme} – 2.5
\end{align*}
\]

The reaction seems to occur by an initial abstraction of proton from –NH- of imidazole ring by the hydride ion followed by attack by the electrophilic cation of the alkyl halide on the imide anion. The probable mechanism for the alkylation of 9 to 10 is shown below in scheme – 2.6.
Murphy and Musco studied the alkylation of 11 with dimethyl sulphate in the presence of sodium carbonate in aqueous acetone giving 12.

The reaction in this case seems to occur by the initial nucleophillic attack by the sp² or pyridine nitrogen of the imidazole ring on the electrophillic carbon of the alkylating agent followed by the abstraction of hydrogen of imidazole –NH- from the quaternary species by the weak base (scheme – 2.8).
Sawlewickz and co-workers synthesised\textsuperscript{23} 14 by treatment of ethyl benzimidazole-2-carboxylate (13) with ethylene oxide in ethanol in the presence of traces of pyridine on heating.

Probably, the reaction occurs by initial attack by the nucleophillic sp\textsuperscript{2} or pyridine nitrogen of the imidazole ring on the electrophillic carbon of the epoxide followed by the abstraction of hydrogen of the –NH- of imidazole ring by the pyridine molecule.

From the literature cited above, it is evident that N-alkylation of benzimidazoles has been widely studied. The substitution is most commonly brought about by replacing the hydrogen on pyrrole nitrogen with alkyl or aralkyl groups. Most of these procedures involve alkyl halides as alkylating agents in the presence of bases\textsuperscript{24-25} like NaNH\textsubscript{2}, NaH, NaoEt, NaOH etc. A disadvantage in these reactions is
the reduction of the alkylating agent by the bases, thus reducing the yield of the product. To a certain extent this disadvantage can be overcome by the use of excess of alkylating agent. Reports on the use of anhydrous media and phase-transfer catalyst for alkylations have also appeared in literature$^{26-27}$.

\[ \begin{array}{c}
\text{H} \\
R \overset{\text{X}}{\rightarrow} R \\
\downarrow \quad \downarrow \\
\text{Na} \overset{\text{X}}{\rightarrow} \text{Na} \\
\end{array} \]

It was reported$^{28}$ from our laboratory earlier that alkylation of 2-acetylbenzimidazole with alkylating agents in acetonitrile at room temperature using potassium carbonate and triethylbenzylammonium chloride as phase-transfer catalyst gave the corresponding N-alkylated-2-acetylbenzimidazole in $\approx 90\%$ yield.

\[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{C-CH}_3 \\
\text{N} \\
\text{N} \\
\text{(4)} \\
\end{array} \quad \xrightarrow{\text{Alkylating agent}} \quad 
\begin{array}{c}
\text{CH}_3 \\
\text{O} \\
\text{C-CH}_3 \\
\text{N} \\
\text{N} \\
\text{(15)} \\
\end{array} \\
\text{K}_2\text{CO}_3/\text{TEBAC}/\text{CH}_3\text{CN}/\text{RT}/3\text{hrs}
\]

Scheme – 2.10

A plausible mechanism for alkylation under PTC conditions is shown below.
The above method involves the use of acetonitrile or alternatively dimethyl formamide as non-green solvents. It also involves extraction of the product after the completion of reaction with chloroform or ethyl acetate as solvents from the aqueous solution during work up which is probably less desired.

**Present work:**

There was thus a need to explore other methods, preferably Green methods, to prepare 15. These may be divided into three types, namely, solid phase, liquid phase (involving Green solvents) and Micro-wave assisted organic synthesis. Solid – phase synthesis has been widely used\(^{29}\) for the synthesis of organic molecules and has dramatically improved yield, purity and reaction time over conventional methodologies. Solid – phase approaches have evolved\(^ {30}\) exponentially in recent decades because they provide a means to develop Green syntheses of organic molecules. Apart from this, Green
solvents, such as polyethylene glycol-600 and ethanol, were also used\textsuperscript{31} for the synthesis of organic molecules. Liquid polymers\textsuperscript{32} have been used as green reaction media with unique properties such as thermal stability with organic solvents and recyclability. Polyethylene glycol (PEG) and its aqueous solutions are interesting solvent systems for solvent replacement.

Micro-wave assisted organic synthesis is a non-conventional synthetic method\textsuperscript{33} which has broad applications as a very efficient way to accelerate the course of many organic reactions, producing high yields and higher sensitivity, lowers side products, easier work up and less or no purification of the products. Therefore, it is considered as a Green-methodology, since many organic reactions can be carried out in solvent-free conditions. Moreover, these procedures allow the parallel synthesis of analogue families with high purity\textsuperscript{34}.

All the three methods of Green synthesis were used in the present work to prepare 15 from 4 and the results are shown in table – 2.2

\begin{center}
\includegraphics[width=0.7\textwidth]{scheme212.png}
\end{center}

Scheme – 2.12
Table-2.2

Alkylation of 2-acetylbenzimidazole under different green condition

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Substrate</th>
<th>Reagent</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>DMS</td>
<td>Physical grinding</td>
<td>15a</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DES</td>
<td>/K₂CO₃/RT /10mins</td>
<td>15b</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph-CH₂-Cl</td>
<td></td>
<td>15c</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>DMS</td>
<td>PEG-600 / Heating / 3hrs</td>
<td>15a</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DES</td>
<td></td>
<td>15b</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph-CH₂-Cl</td>
<td></td>
<td>15c</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>DMS</td>
<td>EtOH / K₂CO₃ / Heating / 3hrs</td>
<td>15a</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DES</td>
<td></td>
<td>15b</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph-CH₂-Cl</td>
<td></td>
<td>15c</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>DMS</td>
<td>Micro wave Irradiation / 5mins</td>
<td>15a</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DES</td>
<td></td>
<td>15b</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph-CH₂-Cl</td>
<td></td>
<td>15c</td>
<td>80</td>
</tr>
</tbody>
</table>

It is obvious from the results of Table – 2.2 that Green conditions can be used very advantageously to prepare 15 from 4.

2A. 2.4 Reduction of the acetyl group of 15

The keto groups of both 4 and 15 could be very efficiently reduced to the corresponding hydroxyl groups with sodium boro hydrate in methanol at room temperature under very simple & mild conditions.

![Scheme 2.13](image)

Scheme – 2.13
SECTION – B

2B. Reactions of 2-(α-hydroxyethyl)benzimidazol.

2B.2.1: Literature:-

Katritzky et. al. studied\(^3\) the condensation of 1 with s-2 resulting in s-3 which on reaction with benzaldehyde dimethyl acetal in the presence of p-toluenesulphonic acid as catalyst gave the cyclic product 17 with retention of charality. 17 on alkylation with EtBr in the presence of n-butyl lithium at (-) 78°C gave optically pure R-alkylated product 18.

Using the above strategy, Katritzky et al also demonstrated the advantageous chiral synthesis of 20 as given in scheme – 2.14.
2B.2.1: Reactions of 3 with benzoyl chloride and tosyl chloride:

3, on reaction with benzoyl chloride (21) in the presence of a base like potassium carbonate and tetra-n-butylammonium bromide as phase transfer catalyst in acetonitrile at room temperature for about 3 hrs gave a product. Its spectral and analytical data indicated it to be either of the two chemoselective products, (22) or (23). Thus, its Infrared spectroscopy showed signals 3340 (-NH), 1732 (-CO-). Its Proton NMR showed signals at 1.98 (s, 3H, -CH), 6.48 (q, 1H, CH₃), 7.26 – 8.82 (m, 9H, protons), 11.98 (s, 1H, NH) and Its CI mass spectrum showed peak at 267 (M⁺+1) corresponding to 266.
At this stage, it could not be decided, unambiguously, whether the product has structure 22 or 23 since the spectral and analytical data is compatible with both the structures. Hence, the following series of reactions were carried out:

Treatment of 4 with benzoyl chloride under a variety of conditions (Table – 2.3) and subsequent processing led to the recovery of 4 and no product corresponding to the structure, 24 could ever be isolated from the reaction mixture. The different reaction conditions used are summarised in Table – 2.3.
Table-2.3

Reaction of 4 with benzoyl chloride 21 under different conditions:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Reaction conditions</th>
<th>Product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aq.NaOH (5%)</td>
<td>None (S.M.was recovered)</td>
</tr>
<tr>
<td>2</td>
<td>DMF,K$_2$CO$_3$/TBAB RT/12hrs</td>
<td>None (S.M.was recovered)</td>
</tr>
<tr>
<td>3</td>
<td>Pyridine / RT/12hrs</td>
<td>None (S.M.was recovered)</td>
</tr>
<tr>
<td>4</td>
<td>DMSO/K$_2$CO$_3$/TBAB/RT/12hrs</td>
<td>None (S.M.was recovered)</td>
</tr>
<tr>
<td>5</td>
<td>CH$_3$CN/K$_2$CO$_3$/TBAB/RT/12hrs</td>
<td>None (S.M.was recovered)</td>
</tr>
</tbody>
</table>

It thus appears that the –NH- benzimidazoles are extremely resistant to benzoylation reaction. This is, probably, due to two reasons:-

1) The hydrogen attached to nitrogen is in tautomerism (25a, 25b) with the other nitrogen in an intermolecular mechanistic exchange process. The hydrogen is thus labile but less available for exchange with electrophillic carbon of benzoyl chloride (21)

![Image](25a, 25b)

2) The lone pair of electrons on the pyrrole nitrogen (i.e., on –NH-) is in resonance with the imidazole ring and is responsible for generating aromaticity thereby conferring considerable stability on the
molecule by way of aromatic resonance energy as shown by the structures given below:

\[
\begin{align*}
\text{H} & \quad \text{N} \quad \text{R} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{N} \quad \text{R} \\
\text{H} & \quad \text{N} \quad \text{R} \\
\text{N} & \quad \text{N} \\
\text{R} & \quad \text{H}
\end{align*}
\]

In a situation, hypothetically, if the \(-\text{NH}\) of imidazole were to undergo benzoylation giving the N-benzyol derivative, then the resonance of the original imidazole ring (as shown above) would be greatly reduced since the carbonyl group of benzoyl moiety is a strongly electron withdrawing group competing for lone pair of electrons on the nitrogen of imidazole---a situation generally found in the case of amides and commonly known as amide resonance (as given below)---which would be greatly resisted by the imidazole ring.

Furthermore, it can be seen from the structure of 3 that there are two basic centres, i.e., \(-\text{OH}\) and \(-\text{NH}\), in the molecule. In the event of reaction with the acid chloride, the hard acidic carbon (or electrophillic carbon) would preferentially be attacked by the electron
rich oxygen rather than by the electron rich nitrogen since, hard–hard interaction is generally favoured over hard–soft interaction (and so is soft–soft interaction or over soft–hard interaction). The alkyl halides have a tendency to readily attack the –NH- in 2-acetylbenzimidazoles due to the fact that the electrophillic carbon of alkyl halides is a soft acidic centre and so would be preferentially attacked by the soft basic centre i.e., the –NH- of imidazoles as was readily found to be the situation even in our case as described in various studies in Section – A involving alkylation of 4 under different conditions including Green conditions.

However, all the above stated experiments and arguments /facts do not conclusively prove that the structure of the product obtained by reaction between 3 and 21 is 22 alone and not 23 although preferentially 22 would be formed. Negative evidence cannot be taken as positive proof of structure and so, yet another series of experiments were carried out which are described below:-

Treatment of the product (either 22 or 23) with dimethyl sulphate in the presence of potassium carbonate and TBAB in acetonitrile solution at room temperature for 3 hrs gave another product, homogeneous on TLC, which could have the structure either 26a or 27a based on spectral data.
To decide between the structures 24a and 25a, the following series of reactions were done:

Thus, treatment of 4 with dimethyl sulphate in the presence of potassium carbonate and TBAB at room temperature for 3 hrs in acetonitrile gave 15a. The latter, on treatment with reducing agent in methanol for 3 hrs, gave 16a.

Reaction of 16a with 21 in the presence of potassium carbonate and tetrabutylammonium bromide at room temperature for 3 hrs gave a product. The melting point, mixed melting point and co-TLC of the product were found to be identical with those of the product obtained earlier in

S – 2.16, i.e., 26a.
In conclusion, it can be said that the reaction of 21 with 3 results, chemoselectively, in the formation of o-aryl derivatives.

**2B.2.2: Further reactions of 3:**

3 on treatment with 28 in the presence of triethylamine in dichloro methane at room temperature for 3 hrs gave a product which could be either 29 or 30 based on the spectral data. Thus, its Infrared spectroscopy showed absorption 3340 (NH), 1340 (SO₂). Its Proton NMR showed signals at 2.57 (s, 3H₃), 6.58 (q, 1H₃), 7.26 – 8.23 (m, 9H₃), 11.98 (s, 1H, NH) and Its CI mass spectrum showed peak at 303 (M⁺+1) corresponding to the 302.

Scheme – 2.20
At this stage, it could not be decided, unambiguously, whether the product has structure 29 or 30.

Treatment of the product (either 29 or 30) with dimethyl sulphate in the presence of potassium carbonate and TBAB in acetonitrile at room temperature for 3 hrs yielded a product which could have the structure either 31a or 32a based on spectral data.

\[
\begin{align*}
(29) & \quad \text{or} \quad (30) \\
\text{DMS} / \text{CH}_3\text{CN} / \text{K}_2\text{CO}_3 / \text{TBAB} / \text{RT} / 3 \text{ hrs} \\
(31) & \quad \text{or} \quad (32) \\
R = \text{CH}_3
\end{align*}
\]

Scheme – 2.21

15 prepared earlier in an authentic manner on reaction with 28 in the presence of potassium carbonate and TBAB at room temperature for 3 hrs yielded a product whose melting point, mixed melting point and co-TLC were found to be identical with those of the product obtained earlier in S– 2.18 i.e., 3→29→31.
Based on the above results, it may be concluded that the reaction of 3 with 28, also like the case of benzoylation results, chemoselectively, in the o-benzenesulphonation rather than in the N-benzenesulphonylation.

**Section – C**

### 2C: Reactions of 2-(a-chloroethyl)benzimidazole with anilines

#### 2C.2.1: Literature:

Day et al reported the reaction of 1 with 33 in refluxing 5N HCl for 3 hrs, resulting in the formation of 34 in 60% yield.

\[
\begin{align*}
\text{Scheme – 2.23} \\
\end{align*}
\]

34, was also prepared by Heisey et al. in an yield of \( \approx 83\% \) by condensation of 1 with 2 in 4N hydrochloric acid resulting 3, followed by treatment with thionylchloride.

\[
\begin{align*}
\text{Scheme – 2.24} \\
\end{align*}
\]
Day et al studied\textsuperscript{39} the reactivity of chlorine towards nucleophiles. Thus, reaction of \textsuperscript{35} with water under reflux for 30 – 60 mins resulted in the formation of \textsuperscript{36} in 70% yield.

![Scheme 2.25](image)

When the same reaction was done\textsuperscript{39} with \textsuperscript{34}, it also yielded \textsuperscript{3}.

![Scheme 2.26](image)

Further, it was reported that \textsuperscript{37} gave the corresponding hydroxyl compound \textsuperscript{38} in about 60 mins on treatment with water at room temperature alone.

![Scheme 2.27](image)

Day et. al. also reported\textsuperscript{40} that treatment of \textsuperscript{34} with different primary and secondary amines, such as ethylamine, n-butylamine, dimethylamine, benzylamine, diethylamine, dibenzylamine, marpholine, piperidine..etc., in cold dry alcohol for 3 hrs gave the \textsuperscript{39}. 
Siegart and Day reported\textsuperscript{41} the reaction of 34 with diethyl p-aminobenzoyl glutamate in dry dioxane as solvent and triethylamine as a catalyst yielding benzimidazole – glutamate derivative 40.

Tajika et al reported\textsuperscript{42} the reaction of 34 with thiourea forming an intermediate 41, (i.e., thiouronium salt) which on hydrolysis yielded 42.
Rao and Ahmed studied\textsuperscript{43} that when 34 was treated with benzhydroximic acid chloride, 43 was formed as a product. Further, this was treated with aq. Sodium hydroxide solution to yield a tricyclicbenzimidazole derivative 44.

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{C} - \text{Cl} \\
\text{H} \\
\text{Cl} \\
\text{H} \\
\text{N} \\
\text{C} - \text{H} \\
\text{34}
\end{array} 
\xrightarrow{\text{Ar} \text{C} = \text{N} \text{OH}} 
\begin{array}{c}
\text{N} \\
\text{C} - \text{N} - \text{OH} \\
\text{C} - \text{Cl} \\
\text{H} \\
\text{Cl} \\
\text{H} \\
\text{N} \\
\text{C} - \text{H} \\
\text{34}
\end{array} 
\xrightarrow{\text{Hydrolysis}} 
\begin{array}{c}
\text{N} \\
\text{C} - \text{N} \\
\text{O} \\
\text{H} \\
\text{C} - \text{H} \\
\text{34}
\end{array}
\]

Scheme – 2.31

2C.2: Present work:

2C.2.2: Reactions of 2-([alpha]-chloroethyl)benzimidazole with anilines:

3, on reaction with thionylchloride in carbon tetrachloride under refluxing conditions for 3 hrs resulted in the formation of 34 previously reported in literature.

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{C} - \text{OH} \\
\text{H} \\
\text{3}
\end{array} 
\xrightarrow{\text{CCl}_4 \text{/ SOCl}_2 \text{ / Reflux / 4hrs}} 
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{C} - \text{Cl} \\
\text{34}
\end{array}
\]

Scheme – 2.32

34, on reaction with aniline 45a (i.e., 45, R = H) in the presence of potassium carbonate and TBAB in dimethyl formamide at room temperature for 3 hrs gave 46a (i.e., 46, R = H). The structure of 46a has been established on the basis of its spectral & analytical data. Thus, its Infrared spectroscopy showed signals at 3340 (NH), 1250 (C-N). Its Proton-NMR showed signals at 1.98 (s, 3H\textsubscript{3}), 4.60 (q, 1H\textsubscript{1}), 7.26 – 8.83 (m, 9H), 11.67 (s, 1H, phenyl), 13.22 (s, 1H, aryl) and Its CI
mass spectrum showed peak at 238 (M+1) corresponding to mass of 237.

![Chemical structure](image)

Scheme – 2.33

46a on reaction with dimethyl sulphate, in the presence of potassium carbonate and TBAB in acetonitrile at room temperature for 3 hrs, followed by processing gave a product which could be 47a or 48a.

![Chemical structure](image)

Scheme – 2.34

At this stage, it could not be decided, unambiguously, whether the product has structure 47 or 48. Hence, the following series of reactions were carried out:-

Reaction of 15a, with thionylchloride in carbon tetra chloride for 4 hrs resulted in the formation of 49a. Thus, 49a was confirmed by its spectral data. Its Proton-NMR showed signals at 1.97 (s, 3H,), 3.98 (s, 3H,), 5.25 (q, 1H,), 7.26 – 7.93 (m, 4H, four aryl protons), and Its CI
mass spectrum showed ion peak at 195 (M+1) corresponding to the mass of 194.

Scheme – 2.35.

49a on reaction with 45a in the presence of potassium carbonate and tetrabutylammonium bromide in dimethyl formamide at room temperature for 3 hrs gave a product, identical with that obtained earlier by the alkylation / methylation of 46.

Scheme – 2.36

It thus appears that in the alkylation of 46a leading to 47a, the reaction occurs chemoselectively on the imidazole –NH- rather than on the arylamino –NH- grouping. The is probably due to the following reasons: - (i) The imidazole ring is more basic and so probably, more nucleophilic in character compared to arylamino –NH-. This is supported by the fact that the pka of imidazole ring is 6.95 and that of arylamino –NH- is 4.63. (ii) The alternative explanation is that the imidazole nitrogen is in a less sterically crowded position compared to the arylamino –NH-. The second explanation or line of reasoning is considered to be less acceptable due to the following reasons: - A
careful construction of the frame-work molecular model of 47a shows very little steric crowding around the –NH- of arylamino group.

This view is further supported by the conformational pictures of 47a drawn using a computer programme with the commercially available software from ACDlabs Chem sketch, which are shown below: -
Fig-1: Computer drawn molecular model of 46a

Fig-2: Computer drawn molecular model of 47a

It thus appears that chemoselective and first alkylation of –NH- of imidazole ring over that of the –NH- of arylamino group is a case of reactivity effect rather than any other effect (i.e., stereo or electronic). The reactivity effect can be carefully punctuated by proper choice of conditions. The following experiments will demonstrate this fact:
Treatment of 47a with dimethyl sulphate in dimethyl formamide in the presence of potassium carbonate and TBAB at room temperature for 3 hrs and subsequent simple processing gave a product 50a on the basis of its spectral and analytical data. Thus, its Infrared spectroscopy showed peaks at 1230 (C-N). Its proton-NMR showed signals at 1.89 (s, 3H), 3.26 (s, 3H), 3.98 (s, 3H), 4.90 (q, 1H), 6.70 – 7.65 (m), and Its CI mass spectrum showed ion peak at 266 (M+1) corresponding to the mass of 265 when recorded in Q+1 mode.

![Scheme](image)

The structure of 50 has also been confirmed by its alternative synthesis. Thus,

Treatment of 34 with 51 in the presence of potassium carbonate and tetrabutylammonium bromide in dimethyl formamide at room temperature for 3 hrs gave a product 52a and not 47a. The structure of this product was decided based on spectral data. Thus, its Infrared spectroscopy showed peaks at 3400 (very strong). Its Proton-NMR showed signals at 1.68 (s, 3H), 3.98 (s), 5.25 (q, 1H), 6.59 – 7.98 (m, 4H), and Its CI mass spectrum showed ion peak at 252 (M+1) corresponding to the mass of 251.
Treatment of 52a with dimethyl sulphate, in the presence of potassium carbonate and TBAB in acetonitrile at room temperature for 3 hrs, followed by processing, gave a product 50a.

Scheme – 2.39
Scheme – 2.40

(3) \[ \text{N-N-C-CH}_3 \] + (21) \[ \text{Cl-C-} \]

\[ \text{K}_2\text{Cr}_2\text{O}_7 / \text{dil H}_2\text{SO}_4 \]

\[ \text{RT / 10 mins} \]

(4) \[ \text{N-N-C-CH}_3 \]

\[ \text{CH}_3\text{CN} \]

\[ \text{K}_2\text{CO}_3 / \text{TBAB} \]

\[ \text{RT / 3 hrs} \]

(22)

(23)

\[ \text{CH}_3\text{CN} \]

\[ \text{K}_2\text{CO}_3 / \text{TBAB} \]

\[ \text{Alkylation agent} \]

\[ \text{RT / 3 hrs} \]

(24)

(25)

(26)

(27)

\[ \text{R=CH}_3 \]

(15)

\[ \text{MeOH} \]

\[ \text{NABH}_4 \]

\[ \text{RT / 3 hrs} \]

(16)
Scheme – 2.41

(3) K$_2$Cr$_2$O$_7$ / H$_2$SO$_4$

(4) Alkylation agent / CH$_3$CN / K$_2$CO$_3$ / TBAB / RT / 3 hrs

(15) MeOH / NaBH$_4$ / RT / 3 hrs

(16) Alkylation agent / CH$_3$CN / K$_2$CO$_3$ / TBAB / RT / 3 hrs

(28) Alkylation agent / CH$_3$CN / K$_2$CO$_3$ / TBAB / RT / 3 hrs

(29)

(30)

(31) R=CH$_3$

(32) 

R=CH$_3$
Scheme – 2.42

(3) \[ \text{H} \quad \text{N} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{H} \]

K\(_2\)Cr\(_2\)O\(_7\)
H\(_2\)SO\(_4\)

\[ \text{H} \quad \text{N} \quad \text{O} \quad \text{C} \quad \text{H} \quad \text{H} \quad \text{N} \quad \text{O} \quad \text{C} \quad \text{H} \quad \text{H} \]

CH\(_3\)CN
K\(_2\)CO\(_3\) / TBAB
Alkylation agent
RT / 3 hrs

(4)

\[ \text{R} \quad \text{N} \quad \text{O} \quad \text{C} \quad \text{H} \quad \text{R} \]

MeOH
NaBH\(_4\)
RT / 3 hrs

(15)

\[ \text{R} \quad \text{N} \quad \text{C} \quad \text{H} \quad \text{R} \]

CH\(_3\)CN
K\(_2\)CO\(_3\) / TBAB
Alkylation agent
RT / 3 hrs

(16)

\[ \text{H} \quad \text{N} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{H} \]

Refluxing
4 hrs

\[ \text{H} \quad \text{N} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{C} \quad \text{Cl} \quad \text{H} \]

CH\(_3\)CN
K\(_2\)CO\(_3\) / TBAB
Alkylation agent
RT / 3 hrs

(34)

(45)

(49)

CH\(_3\)CN
K\(_2\)CO\(_3\) / TBAB
Alkylation agent
RT / 3 hrs

(47a), i.e., 47, R\(^1\)=H, R=CH\(_3\)

CH\(_3\)CN
K\(_2\)CO\(_3\) / TBAB
RT / 3 hrs
Experimental Section:-

1. Preparation of 22 from 3 (General Procedure): A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20 mM), tetrabutyl ammonium bromide, 3 (1.80 gms, 10 mM) and 21 (1.16 ml, 10 mM) was stirred at room temperature for 3 hrs. At the end of this period, the mixture was poured into ice-cold water. The solid was filtered.

2. Preparation of 26 from 22: A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20 mM), tetrabutyl ammonium bromide, 22 (2.50 gms, 10 mM) and alkylating agent (0.95 ml, 10 ml) was stirred at room temperature for 3 hrs. At the end of this period, the mixture was poured into ice-cold water. The solid was filtered.

3. Preparation of 26 from 16: A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20 mM), tetrabutyl ammonium bromide, 16 (1.76 gms, 10 mM) and 21 (1.76 gms, 10 mM) was stirred at room temperature for 3 hrs. The solid was filtered.

4. Preparation of 29 from 3: A mixture of dichloromethane (20 ml), triethylamine, 3 (1.62 gms, 10 mM) and 28 (1.27 ml, 10 mM) was stirred at room temperature for 3 hrs. The solid was filtered and dried.

5. Preparation of 31 from 29: A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20 mM), tetrabutyl ammonium bromide, 29 (3.02 gms, 10 mM) and dimethyl sulphate (0.95 ml, 10 mM) was stirred at room temperature for 3 hrs. The solid was filtered and dried.
6. **Preparation of 31 from 16:** A mixture of dichloromethane (20 ml), triethylamine, 16 (1.76 gms, 10 mM) and 28 (1.27 ml, 10 mM) was stirred at room temperature for 3 hrs. The separated solid was filtered and dried.

7. **Preparation of 34 from 3:** To a solution of 3 (1.62 gms, 10 mM) in carbon tetra chloride was added thionyl chloride (1.44 ml, 20 mM) slowly over a period of 30 mins. The mixture was heated under reflux for 4 hrs. At the end of this period, the reaction mixture was cooled to room temperature, treated with aqueous sodium bicarbonate solution (5%, 20 ml). The separated solid was filtered and dried.

8. **Preparation of 46 from 34:** A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20mM), tetrabutyl ammonium bromide, 34 (1.80 gms, 10mM) and 45 (0.73 ml, 10ml) was stirred at room temperature for 3 hrs. The separated solid was filtered and dried.

9. **Preparation of 47 from 46:** A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20 mM), tetrabutyl ammonium bromide, 46 (2.36 gms, 10 mM) and dimethyl sulphate (0.95 ml, 10 mM) was stirred at room temperature for 3 hrs. The separated solid was filtered and dried.

10. **Preparation of 15 from 4:** A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20 mM), tetrabutyl ammonium bromide, 4 (1.60 gms, 10 mM) and dimethyl sulphate (0.95 ml, 10 mM) was stirred at room temperature for 3 hrs. The separated solid was filtered and dried.
11. **Preparation of 16 from 15 (General Procedure):** A mixture of 15 (1.74 gms, 10 mM), methanol (20 ml) and reducing agent (0.37 gms, 10 mM) was stirred at room temperature for 3 hrs. The separated solid was filtered, and dried.

12. **Preparation of 49 from 16:** To a solution of 16 (1.76 gms, 10 mM) in carbon tetra chloride was added thionyl chloride (1.44 ml, 20mM) slowly over a period of 30 min. The mixture was heated under reflux for 4 hrs. At the end of this period, the reaction mixture was cooled to room temperature, treated with aqueous sodium bicarbonate (5% 20 ml). The separated solid was filtered, and dried.

13. **Preparation of 47 from 49:** A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20 mM), tetrabutyl ammonium bromide, 49 (1.94 gms, 10 mM) and 45 (0.73 ml, 10mM) was stirred at room temperature for 3 hrs. The separated solid was filtered, and dried.

14. **Preparation of 49 from 34 (General Procedure):** A mixture of acetonitrile (20 ml), potassium carbonate (2.76 gms, 20 mM), tetrabutyl ammonium bromide, 34 (1.80 gms, 10 mM) and dimethyl sulphahte (0.95 ml, 10mM), was stirred at room temperature for 3 hrs. The separated solid was filtered and dried.
### TABLE-2.4

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Starting material</th>
<th>Reagent</th>
<th>Product obtained</th>
<th>Yield (%)</th>
<th>M.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46a (R=H)</td>
<td>DMS</td>
<td>47a (R=CH₃)</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>46a (R=H)</td>
<td>DES</td>
<td>47b (R=C₂H₅)</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46a (R=H)</td>
<td>PH-CH₂-Cl</td>
<td>47c (R=Ph-CH₂)</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE-2.5

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Starting material</th>
<th>Reagent</th>
<th>Product obtained</th>
<th>Yield (%)</th>
<th>M.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 (R=C₆H₅ or CH₃)</td>
<td>28</td>
<td>29 (R=C₆H₅ or CH₃)</td>
<td>Semi Solid</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>DMS</td>
<td>31a (R¹=CH₃, R=C₆H₅ or CH₃)</td>
<td>Semi Solid</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>DES</td>
<td>31b (R¹=C₂H₅, R=C₆H₅ or CH₃)</td>
<td>Semi Solid</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>Ph-CH₂-Cl</td>
<td>31c (R¹=Ph-CH₂-Cl, R=C₆H₅ or CH₃)</td>
<td>Semi Solid</td>
<td>Nil</td>
</tr>
<tr>
<td>5</td>
<td>16a (R¹=CH₃)</td>
<td>28</td>
<td>31a (R¹=CH₃, R=C₆H₅ or CH₃)</td>
<td>Semi Solid</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>16b (R¹=C₂H₅)</td>
<td>28</td>
<td>31b (R¹=C₂H₅, R=C₆H₅ or CH₃)</td>
<td>Semi Solid</td>
<td>Nil</td>
</tr>
<tr>
<td>7</td>
<td>16c (R¹=Ph-CH₂-Cl)</td>
<td>28</td>
<td>31c (R¹=Ph-CH₂-Cl, R=C₆H₅ or CH₃)</td>
<td>Semi Solid</td>
<td>Nil</td>
</tr>
</tbody>
</table>
TABLE-2.6: Characterization data for derivatives 46

<table>
<thead>
<tr>
<th>S.No</th>
<th>Starting material</th>
<th>Reagent used</th>
<th>Product obtained</th>
<th>Yield (%)</th>
<th>M.P.°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34a (R^3=H)</td>
<td>45a (R^1=H, R^2=H)</td>
<td>46a (R^1=H, R^2=H, R^3=H)</td>
<td>80</td>
<td>140 – 42</td>
</tr>
<tr>
<td>2</td>
<td>34a (R^3=H)</td>
<td>45b (R^1=CH_3, R^2=H)</td>
<td>46b (R^1=CH_3, R^2=H, R^3=H)</td>
<td>75</td>
<td>138 – 40</td>
</tr>
<tr>
<td>3</td>
<td>34a (R^3=H)</td>
<td>45c (R^1=H, R^2=OCH_3)</td>
<td>46c (R^1=H, R^2=OCH_3, R^3=H)</td>
<td>82</td>
<td>192 – 94</td>
</tr>
<tr>
<td>4</td>
<td>34a (R^3=H)</td>
<td>45d (R^1=H, R^2=CH_3)</td>
<td>46d (R^1=H, R^2=CH_3, R^3=H)</td>
<td>82</td>
<td>180 – 84</td>
</tr>
<tr>
<td>5</td>
<td>34a (R^3=H)</td>
<td>45e (R^1=H, R^2=Cl)</td>
<td>46e (R^1=H, R^2=Cl, R^3=H)</td>
<td>82</td>
<td>170 – 72</td>
</tr>
<tr>
<td>6</td>
<td>34a (R^3=H)</td>
<td>45f (R^1=H, R^2=OH)</td>
<td>46f (R^1=H, R^2=OH, R^3=H)</td>
<td>80</td>
<td>194 - 96</td>
</tr>
<tr>
<td>7</td>
<td>34a (R^3=H)</td>
<td>45g (R^1=H, R^2=NO_2)</td>
<td>46g (R^1=H, R^2=NO_2, R^3=H)</td>
<td>80</td>
<td>186 - 88</td>
</tr>
</tbody>
</table>
### TABLE-2.7: Characterization data for derivatives 47

<table>
<thead>
<tr>
<th>S.No</th>
<th>Starting material</th>
<th>Reagent</th>
<th>Product obtained</th>
<th>Yield (%)</th>
<th>M.P.°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46a (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=H, R&lt;sup&gt;3&lt;/sup&gt;=H)</td>
<td>DMS</td>
<td>47a (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=H, R&lt;sup&gt;3&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>82</td>
<td>236 -38</td>
</tr>
<tr>
<td>2</td>
<td>46b (R&lt;sup&gt;1&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;, R&lt;sup&gt;2&lt;/sup&gt;=H, R&lt;sup&gt;3&lt;/sup&gt;=H)</td>
<td>DMS</td>
<td>47b (R&lt;sup&gt;1&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;, R&lt;sup&gt;2&lt;/sup&gt;=H, R&lt;sup&gt;3&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>75</td>
<td>240 -42</td>
</tr>
<tr>
<td>3</td>
<td>46c (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=OCH&lt;sub&gt;3&lt;/sub&gt;, R&lt;sup&gt;3&lt;/sup&gt;=H)</td>
<td>DMS</td>
<td>47c (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=OCH&lt;sub&gt;3&lt;/sub&gt;, R&lt;sup&gt;3&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>75</td>
<td>170 -72</td>
</tr>
<tr>
<td>4</td>
<td>46d (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;, R&lt;sup&gt;3&lt;/sup&gt;=H)</td>
<td>DMS</td>
<td>47d (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;, R&lt;sup&gt;3&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>75</td>
<td>145 -47</td>
</tr>
<tr>
<td>5</td>
<td>46e (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=Cl, R&lt;sup&gt;3&lt;/sup&gt;=H)</td>
<td>DMS</td>
<td>47e (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=Cl, R&lt;sup&gt;3&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>70</td>
<td>180 -82</td>
</tr>
<tr>
<td>6</td>
<td>46f (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=OH, R&lt;sup&gt;3&lt;/sup&gt;=H)</td>
<td>DMS</td>
<td>47f (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=OH, R&lt;sup&gt;3&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>70</td>
<td>230 -32</td>
</tr>
<tr>
<td>7</td>
<td>46g (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=NO&lt;sub&gt;2&lt;/sub&gt;, R&lt;sup&gt;3&lt;/sup&gt;=H)</td>
<td>DMS</td>
<td>47g (R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=NO&lt;sub&gt;2&lt;/sub&gt;, R&lt;sup&gt;3&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>75</td>
<td>228 -30</td>
</tr>
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</table>
### TABLE-2.8: Characterization data of 47

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Starting material</th>
<th>Reagent</th>
<th>Product obtained</th>
<th>Yield (%)</th>
<th>M.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49a (R=CH₃)</td>
<td>45a (R¹=H, R²=H)</td>
<td>47a (R¹=H, R²=H, R³=CH₃)</td>
<td>82%</td>
<td>236-38</td>
</tr>
<tr>
<td>2</td>
<td>49a (R=CH₃)</td>
<td>45b (R¹=CH₃, R²=H)</td>
<td>47b (R¹=CH₃, R²=H, R³=CH₃)</td>
<td>75%</td>
<td>240-42</td>
</tr>
<tr>
<td>3</td>
<td>49a (R=CH₃)</td>
<td>45c (R¹=H, R²=OCH₃)</td>
<td>47c (R¹=H, R²=OCH₃ R³=CH₃)</td>
<td>75%</td>
<td>170-72</td>
</tr>
<tr>
<td>4</td>
<td>49a (R=CH₃)</td>
<td>45d (R¹=H, R²=CH₃)</td>
<td>47d (R¹=H, R²=OCH₃ R³=CH₃)</td>
<td>75%</td>
<td>145-47</td>
</tr>
<tr>
<td>5</td>
<td>49a (R=CH₃)</td>
<td>45e (R¹=H, R²=Cl)</td>
<td>47e (R¹=H, R²=Cl, R³=CH₃)</td>
<td>70%</td>
<td>180-82</td>
</tr>
<tr>
<td>6</td>
<td>49a (R=CH₃)</td>
<td>45f (R¹=H, R²=OH)</td>
<td>47f (R¹=H, R²=OH, R³=CH₃)</td>
<td>70%</td>
<td>230-32</td>
</tr>
<tr>
<td>7</td>
<td>49a (R=CH₃)</td>
<td>45g (R¹=H, R²=NO₂)</td>
<td>47g (R¹=H, R²=NO₂, R³=CH₃)</td>
<td>75%</td>
<td>228-30</td>
</tr>
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</table>