4 Green Synthesis of 4-O-aryloxy Carbonates

Phosgene free process

\[
\text{3-aryloxy-1,2-propanediol} \quad \text{Dimethyl carbonate} \quad \text{4-O-(alkyl/aryl)-oxy-1,3-dioxolan-2-one}
\]
4.1 INTRODUCTION

4-O-(Aryl/alkyl)-oxy-1,3-dioxolan-2-one family of chemicals are important building blocks in pharmaceutical industry and can be converted to chiral oxazolidinones. Jegham and coworkers have used them for the synthesis chiral inhibitor analogs of monoamine oxidase, which is used in the degradation of various amine neurotransmitters (Jegham et al., 1998). They are used as important precursors for the preparation of moamine oxidase inhibitors and for synthesis of oxazolidinones.

4-O-(Alkyl/aryl)-oxy-1,3-dioxolane-2-one have wide applications such as additives/solvent in lithium ion batteries to improve their power characteristic. They are also useful in synthesis of chiral oxazolidinones which are used as antidepressants, mood disorders, psychopharmacologic drugs, smoking cessation agent, aid for treatment of poisoning, drug abuse and dependency, MaO-A inhibitors (Chem et al., 2006; Jegham et al., 1997 and 2000; Yaegashi et al., 2001; Lee et al., 2003). Also they are important intermediates in the synthesis of carbamates which show anticonvulsant activity. Some derivatives have been used as muscle relaxant and have widely used as insecticides (Masumi et al., 2004).

Traditional processes to synthesize 4-O-(alkyl/aryl)-oxy-1,3-dioxolan-2-one include a two-step reaction between 3-aryloxy-1,2-propanediol with isocynate, which is highly hazardous and requires longer reaction time (Ludwing et al., 1951). Some of the other processes use phosgene or tri phosgene as carboxylating agent which are again highly toxic (Zappia et al., 2007; Kazutsugu et al., 1996). It is also prepared by using basic condensation homogeneous catalysts like alkali metal salt of weak acid such as sodium bicarbonate, sodium and potassium acetate, potassium bicarbonate, and carbonate, etc. and alkali metal alcohohates such as sodium methylate, sodium ethylate, potassium methylate or alkali metal bases such as sodium hydroxide, potassium hydroxide, etc., which suffer from tedious handling and separation processes (Baizer et al., 1957; Beasley et al., 1957; McDowell et al., 1957; Mitsuru et al., 1999). Ming-Shiu et al., 1996 synthesized 4-phenoxymethyl-1,3-dioxolane-2-one by reacting phenyl glycidyl ether and diphenyl carbonate using quaternary ammonium salt as catalyst. It was also prepared by reacting epoxides or glycidyl ether with CO$_2$ in the presence of hydrotalcite catalyst having Al:Mg catalyst composition (Mineko et al., 2001). All the above processes for production of 4-O-(aryl/alkyl)-oxy 1,3-
dioxolane-2-one suffer from the use of hazardous reactants, harsh reaction conditions and require additional purification steps thereby increasing the cost of production.

Several methods have been developed to convert diols to their carbonate derivatives by reacting with dialkyl carbonates using heterogeneous base catalysts (Takagaki et al., 2010, Ochoa-Gomez et al., 2009; Malyaadri et al., 2011). From the green and sustainable chemistry point of view, it is desirable to develop a neat process using a heterogeneous catalyst with lesser number of steps, easier separation, reusability, high selectivity and yield, milder reaction conditions and use of less hazardous, non toxic reagents. The current work is in that direction where catalyst synthesis using a novel method and its application in developing a green route is discussed.

Combustion synthesis (CS) leads to very interesting characteristics to inorganic oxides, which could be further modified to render them interesting catalytic properties. It is a self propagating high temperature synthesis and is an effective and low cost method for synthesis of materials (Patil et al., 2008; Civera et al., 2003). In combustion synthesis, a thermally induced redox reaction takes place between an oxidant and a fuel (Wang et al., 2008). The combustion characteristics are closely related to the selection of fuel. A good fuel should react non-violently and act as a complexant for metal cations (Yadav et al., 2012(a)). In our laboratory, both strongly acidic and basic catalysts have been prepared recently using combustion synthesis (Yadav and Gawade, 2012; Yadav and Fernandes, 2012).

In the present work, 4-O-(aryl/alkyl)-oxy-1,3-dioxolan-2-one was synthesized by reacting 3-(aryl/alkyl)-oxy-1,2-propanediol with dimethyl carbonate using lithium promoted MgO catalyst prepared by CS method. Catalytic activity of MgO was found to be increased by promoting with alkali metal salt and can be used for several reactions such as condensation, oxidative coupling, O-alkylation, etc (Cosimo et al., 1996; Jose et al., 2010; Leveles et al., 2003; Trionfetti et al., 2009; Diez et al., 2006; Vijayaraj et al., 2006). Alkali metal ion promoted MgO catalyst is conventionally prepared by co-precipitation method, which is tedious and low yield process. Self propagating combustion synthesis offers the best method to prepare highly active oxide nano-particles with low cost and ease in of synthesis (Nagappa et al., 2007; Reddy et al., 2010; Maliyekkal et al., 2010). A series of alkali promoted
MgO with different alkali promoters were prepared using CS method. Lithium promoted MgO with different amount of Li loading was also prepared. The resulting catalysts were characterized by CO$_2$-TPD (Temperature programmed desorption), FTIR, XRD, BET etc. Their catalytic activity was tested in synthesis of 4-O-(aryl/alkyl)-oxy-1,3-dioxolan-2-one. The overall process is clean and green.

4.2 EXPERIMENTAL

4.2.1 Chemicals and Catalysts
All chemicals were procured from reputed firms: Magnesium nitrate hexahydrate, lithium nitrate, glycine, dimethyl carbonate, n-decane (M/s. s.d. Fine Chemicals Pvt. Ltd., Mumbai, India). 3-Aryloxy-1,2-propanediols were synthesized by procedure reported by Egri et al., 1998 and purified by recrystallization to achieve 98% purity.

4.2.2 Synthesis of catalyst
The lithium promoted magnesium oxide catalyst was synthesized by a process as discussed in Section 3.2.2. All the catalysts were activated in nitrogen atmosphere in oven at 110 °C for 2 h before use.

4.2.3 Catalyst characterization
The lithium promoted magnesium oxide catalyst was fully characterized by a various methods as discussed in Section 3.2.5.

4.2.4 Reaction procedure
Reactions were carried out in an autoclave having 100 cm$^3$ capacity (M/s. Amar Equipments, Mumbai, India), equipped with a four-bladed pitched-turbine impeller along with temperature controller, speed controller and pressure indicator. In typical experiment (Scheme 4.1) autoclave was charged with reaction mixture consisted of 0.02 mol 3-(2-methylphenoxy)-1,2-propanediol, 0.3 mol dimethyl carbonate, internal standard (n-decane) and a catalyst loading 0.03 g/cm$^3$ of total reaction volume. The catalyst was activated at 573 K under nitrogen flow for 4 h prior to use. The temperature was raised and maintained at (±1 °C of the set value with the help of an in-built proportional integral derivative (PID) controller. Once the temperature reached the desired value, agitation was started. Then, an initial sample was withdrawn and further samples were drawn at periodic intervals up to 1 h. The
temperature was maintained at 140 °C and the speed of agitation at 1000 rpm. The reaction was carried out without using any solvent. The total volume of liquid phase was 30 cm$^3$.

**Scheme 4.1: Synthesis of 4-O-aryloxy carbonates**

4.2.5 Analysis of reaction mixture

The samples were analyzed using GC (Chemito Ceres800 Model) equipped with a 30 m x 0.25 mm i.d. BPX-5 capillary column and flame ionization detector (FID). Reaction products were confirmed by GC-MS (PerkinElmer Clarus 500).

4.3 RESULTS AND DISCUSSION

4.3.1 Catalyst characterization

Study of effect of different alkali promoter showed the highest catalytic activity was obtained when lithium was used as promoter, which is in complete agreement with the reported results (Diez et al., 2006). Detailed catalyst characterization was carried out for lithium promoted magnesium oxide as discussed in Section 3.2.5.

4.3.2 Effect of different alkali metal promoter

Effect of various alkali ion promoters on conversion of 3-(2-methylphenoxy)-1,2-propanediol to its cyclic carbonates derivatives was studied. The catalyst prepared by CS method as described above with alkali metal ion to MgO mole ratio of 0.027. The results obtained are as shown in Table 4.1. Alkali promoted MgO is found to be superior with respect to pure MgO. Within different promoters, Li$^+$ ion promoter gives complete conversion of 3-(2-Methylphenoxy)-1,2-propanediol. Whereas going down the group from lithium to cesium, a slight decrease in conversion was observed. No difference in selectivity was found. This can be explained as basicity increases from Li$_2$O to Cs$_2$O, because the size of atom also increases which forms the bulky species such as K$_2$O, Cs$_2$O and block the pores resulting in decrease in surface area.
and conversion (Diez et al., 2006). Hence lithium was used as promoter for further studies.

**Table 4.1:** Effect of different alkali metal ion promoter on particle size and surface area

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Alkali promoter</th>
<th>Particle size</th>
<th>Surface area</th>
<th>Conversion</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pure MgO</td>
<td>9</td>
<td>205</td>
<td>49</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Li$^+$</td>
<td>9.03</td>
<td>181</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Na$^+$</td>
<td>15.84</td>
<td>115</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>K$^+$</td>
<td>10.58</td>
<td>146</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Cs$^+$</td>
<td>13.66</td>
<td>85</td>
<td>89</td>
<td>100</td>
</tr>
</tbody>
</table>

Effect of different alkali metal ion promoter; 3-(o-Methylphenoxy)-1,2-propanediol, 3.6 g (0.02 mol), dimethyl carbonate, 27.04 g (0.3 mol), reaction temperature, 140 °C, catalyst loading, 0.03 g/cc, speed of agitation, 1000 rpm

### 4.3.3 Effect of lithium loading

Catalytic activity of lithium promoted MgO with different Lithium loadings was tested in synthesis of 4-[(2-methylphenoxy)methyl]-1,3-dioxolan-2-one to understand the surface base properties. The results shown in Table 4.2 indicate that rate of reaction increased by promoting MgO with Li. This is due to localization of Li$_2$O species on surface in the form of Li$_2$O$^-$ groups which increases local electronegativity, which increases the ability of the catalyst to abstract proton from 3-(2-methylphenoxy)-1,2-propanediol followed by bond formation with the carbonyl group of dimethyl carbonate. The highest catalytic activity was obtained with 0.1% lithium promoted MgO, where as above 0.1 wt %, catalytic activity decreases which may be due to decrease in surface area and increase in crystalline size as described above. Hence further experiments were conducted with 0.1% lithium promoted MgO catalyst.
Table 4.2: Effect of lithium loading particle size and surface area

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Li(^+) loadings Wt%</th>
<th>Particle Size*</th>
<th>Surface area</th>
<th>Conversion</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>9</td>
<td>205</td>
<td>49</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>9.03</td>
<td>181</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>11.71</td>
<td>117</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>20.93</td>
<td>95.25</td>
<td>76</td>
<td>100</td>
</tr>
</tbody>
</table>

*From XRD, Effect of lithium loading; 3-(o-Methylphenoxy)-1, 2-propanediol, 3.6 g (0.02 mol), dimethyl carbonate, 27.04 g (0.3 mol), reaction temperature, 140 °C, catalyst loading, 0.03 g/cc, speed of agitation, 1000 rpm

4.3.4 Effect of speed of agitation

Effect of speed of agitation was studied in the range of 800-1200 rpm with 0.03 g/cm\(^3\) catalyst loading at 140 °C (Figure 4.1). There was no significant change in the rate and conversion patterns, which indicates the absence of any resistance to external mass transfer of reactants to the external surface of the catalysts. All further reactions were carried out at 1100 rpm. A theoretical analysis was also done as per our previous work to conclude that there was no external mass transfer resistance (Yadav and Kumbhar 1989; Yadav and Mehta 1994; Yadav and Krishnan, 1998; Yadav and Krishnan, 2004; Yadav and Doshi, 2000).

4.3.5 Effect of catalyst loading

Effect of catalyst loading was studied over range of 0.01-0.03 g/cm\(^3\) (Figure 4.2). In the absence of external mass transfer resistance, the rate of reaction was directly proportional to catalyst loading based on the entire liquid phase volume. This indicated that as the catalyst loading increased the conversion of 3-aryloxy-1,2-propanediol increases, which was due to proportionate increase in the number of active sites on the catalyst surface. All further experiments were carried out at 0.03 g/cm\(^3\) catalyst loading.
Figure 4.1: Effect of speed of agitation
3-(o-Methylphenoxy)-1, 2-propanediol, 3.6 g (0.02 mol), dimethyl carbonate, 27.04 g (0.3 mol), reaction temperature, 140 ºC, catalyst loading, 0.03 g/cc. ▲ 600 rpm, ● 800 rpm; ◆ 1000 rpm

4.3.6 Effect of mole ratio
Effect of mole ratio of 3-(2-methylphenoxy)-1,2-propanediol to dimethyl carbonate was studied from 1:6 to 1:15 under otherwise similar conditions. As the concentration of dimethyl carbonate increased, the conversion as well as rate of reaction increased (Figure 4.3). Considering solubility of reactants and products formed in the reaction to have a homogeneous liquid phase, further studies were carried out at 1:15 mole ratio.

4.3.7 Effect of temperature
Effect of temperature on conversion was studied in the range of 120–140 ºC under otherwise similar conditions (Figure 4.4). It was observed that the conversion increased with temperature. This would suggest a kinetically controlled mechanism. This is discussed again.
Figure 4.2: Effect of catalyst loading
3-(o-Methylphenoxy)-1, 2-propanediol, 3.6 g (0.02 mol), dimethyl carbonate, 27.04 g (0.3 mol), reaction temperature, 140 °C, speed of agitation, 1000 rpm, ▲ 0.01 g/cc; ■ 0.02 g/cc; ● 0.03 g/cc

Figure 4.3: Effect of mole ratio
temperature, 140 °C, catalyst loading, 0.03 g/cc, speed of agitation, 1000 rpm, (3-(o-Methylphenoxy)-1, 2-propanediol: dimethyl carbonate) ▲ 1:6; ■ 1:10; ● 1:15.
3-(o-Methylphenoxy)-1, 2-propanediol, 3.6 g (0.02 mol), dimethyl carbonate, 27.04 g (0.3 mol), speed of agitation, 1000 rpm, catalyst loading, 0.03 g/cc. 120 ºC; 130 ºC; 140 ºC

4.3.8 Reaction mechanism and kinetics

From the observed initial rate, it is evident that the rate is independent of the external mass transfer effects. Thus, the reaction could be controlled by one of the following steps, namely: (a) adsorption, (b) surface reaction or (c) desorption. Therefore, actual reaction mechanism was undertaken for the further development of model.

The initial rate data can be analysed on the basis of Langmuir-Hinshelwood-Hougen-Watson (LHHW) or Eley-Rideal mechanism. From the initial rate, the following analysis was found to be the most appropriate in Scheme 4.2 was used to arrive at the LHHW type of mechanism with bifunctional sites $S_1$ and $S_2$. The preliminary analysis suggested that the reaction followed zero order kinetics.

1. Adsorption of 3-aryloxy-1,2-propanediol (A) on the vacant site $S_1$ is given by:

$$A + S_1 \xrightarrow{k_r} AS_1$$

Similarly adsorption of dimethyl carbonate (B) on the vacant site $S_2$ is presented by:

$$B + S_2 \xrightarrow{k_d} BS_2$$
Scheme 4.2: Proposed reaction mechanism

\[ B + S_2 \xrightleftharpoons[K_d]{K_a} BS_2 \]  \tag{2}

2. Surface reaction of AS with BS (dimethyl carbonate), in the vicinity of the site, leading to formation of 4-O-aryloxy-1,3-dioxolan-2-one (DS) and methanol (MS) on the site.

\[ AS_1 + BS_2 \xrightleftharpoons[K_d]{K_a} DS_1 + MS_2 \]  \tag{3}

Desorption of 4-O-aryloxy-1,3-dioxolan-2-one (DS\(_1\)) and methanol (MS\(_2\))

\[ DS_1 \xrightarrow{1/K_d} D + S_1 \]  \tag{4}

\[ DS_2 \xrightarrow{1/K_d} M + S_2 \]  \tag{5}

The total concentration of the sites, \( C_t = C_{t_1} + C_{t_2} \) expressed as,

\[ C_{t_1} = C_{S_1} + C_{AS_1} + C_{BS_1} \]  \tag{6}

\[ C_{t_2} = C_{S_2} + C_{BS_2} + C_{MS_2} \]  \tag{7}

By substituting for the concentrations of surface species, the following is obtained.
\[ C_{S_i} = \frac{C_i}{1 + K_iC_iK_DC_D} \]  

\[ C_{S_2} = \frac{C_{i_2}}{1 + K_iC_{i_2} + K_mC_M} \]  

If surface reaction controls the rate of reaction, then the rate of reaction of A is given by

\[ -r_A = \frac{-dC_A}{dt} = k_2C_{A_S}C_{BS} - k_2C_{DS}C_{MS} \]  

\[ \frac{-dC_A}{dt} = \frac{k_2(k_AK_BC_AK_C - (K_BK_MC_D)/k_{i_2}=C_{i_2})}{(1+K_iC_A+K_DC_D)(1+K_BC_B+K_mC_M)} \]  

When the reaction is far away from the equilibrium

\[ \frac{-dC_A}{dt} = \frac{k_2(k_AK_BC_AK_C)C_{i_2}C_{i_2}}{(1+K_iC_A+K_DC_D)(1+K_BC_B+K_mC_M)} \]  

\[ \frac{-dC_A}{dt} = \frac{k_{3w}K_AK_BC_AK_C}{(1+K_iC_A+K_DC_D)(1+K_BC_B+K_mC_M)} \]  

Where, \( k_{3w} = k_2C_{i_2} \)

When the reactants are strongly adsorbed,

When \( K_iC_A >> (1+K_DC_D) \) \& \( K_BC_B >> (1+K_mC_M) \)

And \( w \) is catalyst loading, then the above equation reduces to

\[ \frac{-dC_A}{dt} = k_{3w} \]  

Integration of the above equation leads to the following:

\[ C_{A_i} - C_A = k_{3w}t \]  

Which in terms of fractional conversion becomes:

\[ X_A = \frac{k_{3w}t}{C_{A_i}} = k_4t \]  

Where \( k_4 = \frac{k_{3w}}{C_{A_i}} \)

Thus, plots of \( X_A \) versus time were made for a fixed value of \( w \) and \( C_{A0} \) to show a linear relation, where \( X_A \) is the fractional conversion of 3-ary/alkyl-oxy-1,2-propanediol. Thus plots were made, for instance, for different temperatures (Figure
The slopes of these lines are equal to $k_i$ from which Arrhenius plots were made to determine the apparent energy of activation (Figure 4.6). It was found to be 20.36 kcal/mol, which indicates that the reaction rate is intrinsically kinetically controlled.

**Figure 4.5:** Plots of $X_A$ vs time

- ▲ 120 °C; ■ 130 °C; ● 140 °C
4.3.9 Catalyst reusability

After the completion of the reaction, the catalyst was filtered and washed with dry methanol (50 cm$^3$) in order to remove adsorbed material from catalyst surface and pores. It was then dried at 120 °C and calcined at 500 °C for 4 h. Catalyst lost during filtration was made up with fresh catalyst, activated and the activity was tested. The same conversion and selectivity was observed with reused catalyst. This demonstrates that the catalyst was stable and retained its catalytic activity. The same procedure was followed thrice. The catalyst was found to be stable and reusable three times without any loss in activity. There was no change in selectivity. Leaching of base sites in the liquid phase was tested by stopping the reaction after 30 min and immediately quenching the reaction mixture to arrest the reaction progress followed by centrifuging reaction mixture. The separated clear supernatant reaction mixture was then charged in to the reactor and continued reaction under same condition. There was practically no conversion during next two hours which suggests that catalyst is stable and there is no leaching of alkali metal in to the reaction mass (Figure 4.7).
4.3.10 Substrate study

To explore the generality and scope of the catalyst for 4-O-aryl/alkyl-oxy-1,3-dioxolan-2-one synthesis, the reaction was examined with structurally diverse 3-aryl/alkyl-oxy-1,2-propanediol as shown in Table 4. In all cases, the reaction proceeds cleanly and desired 4-O-aryl/alkyl-oxy-1,3-dioxolan-2-one were obtained with high selectivity. (Table 4.3) In case of some substrates solvent was required so as to dissolve the reactants.

4.3.11 Green chemistry aspects

Considering 90% recovery of the excess reactant, calculated E-factor is 0.3 which is much less, which is the proof of less waste product formation. Also methanol is recycled and thus there is no waste and hence for practical purposes the E factor is zero. Table 4.4 shows different green chemistry factors, which proves greenness of the reaction. It was found that 0.1% lithium ion promoted MgO is highly active, cleaner and green catalyst. Considering corrosive nature, toxicity and handling problems of reagent reported in prior art such as phosgene, triphosgene, isocynate as carboxylating agent and high temperature and pressure conditions required, dimethyl carbonate offers cleaner, greener method of carboxylation in the synthesis of 4-O-aryl/alkyl-oxy-1,3-dioxolan-2-one.
### Table 4.3: Substrate study

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substrate (R)</th>
<th>Reaction time (h)</th>
<th>Product</th>
<th>Conversion (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-methylphenyl</td>
<td>1</td>
<td><img src="product1.png" alt="Product" /></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>3-methylphenyl</td>
<td>1</td>
<td><img src="product2.png" alt="Product" /></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>4-methylphenyl</td>
<td>1</td>
<td><img src="product3.png" alt="Product" /></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>4-methoxyphenyl</td>
<td>1</td>
<td><img src="product4.png" alt="Product" /></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Allyl</td>
<td>1.5</td>
<td><img src="product5.png" alt="Product" /></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>2,5-dichlorophenyl</td>
<td>3</td>
<td><img src="product6.png" alt="Product" /></td>
<td>99*</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>2,6-dichlorophenyl</td>
<td>3</td>
<td><img src="product7.png" alt="Product" /></td>
<td>98*</td>
<td>100</td>
</tr>
</tbody>
</table>

3-(o-aryl/alkyl oxy)-1, 2-propanediol, 3.6 g (0.02 mol), dimethyl carbonate, 27.04 g (0.3 mol), reaction temperature, 140 °C, catalyst loading, 0.03 g/cc, speed of agitation, 1000rpm. * Solvent- MeOH.

### Table 4.4: Green chemistry aspects

![Chemical Structures](chemical_structures.png)
<table>
<thead>
<tr>
<th>Carboxylating agent</th>
<th>E-factor</th>
<th>Mass intensity</th>
<th>Atom economy</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosgene</td>
<td>7.1</td>
<td>18.04</td>
<td>74.04</td>
<td>60</td>
</tr>
<tr>
<td>Dialkyl carbonate+</td>
<td>0.3</td>
<td>7.52</td>
<td>86.66</td>
<td>98.52</td>
</tr>
</tbody>
</table>

+ Methanol as co-product is recycled on plant scale. Hence, there is no waste and E can be viewed as zero.

### 4.4 CONCLUSION

A green process for synthesis of 4-O-aryl/alkyl-oxy-1,3-dioxolan-2-one was developed using highly active alkali promoted alkaline earth metal oxide catalyst which was prepared by combustion synthesis method. Effect of different promoters on conversion of aryl/alkyl-oxy-1,2-propanediol to its carbonate derivative was studied and lithium was found to be the best among other alkali metal promoters. It was found that as Li$^+$ loading increases the crystalline size increases and surface area decreases. The maximum surface area obtained was 145 $m^2/g$ for 0.1% wt CS-Li/MgO. The catalytic activity was found maximum with 0.1% wt of Li$^+$ metal loading. The catalyst is nanocrystalline with crystalline size of 9 nm. The catalyst so prepared was reusable for several times. The green aspects of this process appeared to be more promising green alternative over the conventional processes. A variety of substrates were also studied.
5 Synthesis of Oxazolidinones Over Combustion

Synthesized 0.1% Li/MgO as Catalyst

2-[(2-hydroxyethyl)amino]ethanol + diethyl carbonate

Nano crystalline

Combustion synthesis

Alkali/MgO

3-(2-hydroxyethyl)-1,3-oxazolidin-2-one
5.1 INTRODUCTION

Oxazolidinone and its derivatives have been incorporated into a variety of therapeutically interesting compounds having antibacterial, antifungal, antiallergy, psychotropics and immunomodulatory activity (Bhattacharya et al., 1991; Grabley et al., 1987; Kakeya et al., 1998; Danielmeier et al., 1995). Oxazolidin-2-ones, in particular enantiomerically pure 4-substituted compounds, have been used as chiral auxiliaries in asymmetric synthesis of a wide range of compounds (Zappia et al., 2007). They have been also used in oxygen scavengers in energy curable compositions, such as inks (Schwarz et al., 1997), coatings and adhesives (Green et al., 1987); they have been extensively used in cosmetics (Philippe et al., 1997), pesticides, mosquito repellents (Elbe et al., 1992), additives to prevent overcharging of batteries (Nanbu et al., 2010) etc. Conventionally, 2-oxazolidinones are synthesized by phosgenation of the corresponding 1,2-aminoalcohols with toxic phosgene or its derivative, which may cause serious environmental pollution and equipment corrosion (Nobuyuki et al., 1992). Therefore, a number of non-toxic procedures have been suggested,

1. Oxidative carbonylation using CO/O₂ and β-aminoalcohols (Zerella et al., 2006)
2. From dialkyl carbonates and β-aminoalcohols (Xiao et al., 2007)
3. Direct synthesis of 2-oxazolidinones and cyclic ureas from carbon dioxide and 1,2-aminoalcohols (Fujita et al., 2006).

The intramolecular oxidative cyclocarbonylation of β-aminoalcohols catalyzed by transition metals is a way to produce these heterocyclic compounds, but the oxidative carbonylation is expensive in using carbon monoxide and it has potential of explosion hazards (Bacchi et al., 1997; Gabriele et al., 2003; Li and Xia et al., 2004). As an alternative, dialkyl carbonates and urea were used for the synthesis of 2-oxazolidinones (Fu et al., 2001; Vani et al., 2001). There are several reports on direct synthesis of 2-oxazolidinones by carbon dioxide and β-aminoalcohols; however, toxic catalysts and high pressure and/or high temperature have been used in most of these reports. Development of a simple, highly efficient and environmentally benign method for synthesis of 2-oxazolidinone derivatives is still highly desired. Herein, we report a novel method for synthesis of 2-oxazolidinones from alkyl carbonates.
In the present work, 2-oxazolidinones were synthesized by reacting 2-aminoalcohols with dimethyl carbonate using lithium promoted MgO catalyst prepared by combustion synthesis (CS) method. Effect of various parameters such as alkali promoter, lithium loading on MgO, speed of agitation, mole ratio, catalyst loading, and temperature has been studied. Different amino alcohol substrates were used to synthesize corresponding oxazolidinones.

5.2 EXPERIMENTAL

5.2.1 Chemicals and catalysts
All chemicals were procured from reputed firms: magnesium nitrate hexahydrate, lithium nitrate, sodium nitrate, potassium nitrate, cesium nitrate, glycine, starch, sucrose, citric acid, diethyl carbonate, n-decane, diethanolamine, ethanol (M/s. s.d. Fine Chemicals Pvt. Ltd., Mumbai), hydroxypropl acetate (Aldrich, USA).

5.2.2 Synthesis of catalyst
The lithium promoted magnesium oxide catalyst was synthesized by a process as discussed in Section 3.2.2. All the catalysts were activated in nitrogen atmosphere in oven at 110 °C for 2 h before use.

5.2.3 Catalyst Characterization
The lithium promoted magnesium oxide catalyst was fully characterized by a process as discussed in Section 3.2.5.

5.2.4 Catalyst activity (reaction procedure)
Oxazolidinone synthesis reactions were carried out in an autoclave having 100 cm$^3$ capacity (M/s. Amar Equipments, Mumbai, India), equipped with a four-bladed pitched-turbine impeller along with temperature controller, speed controller and pressure indicator. In a standard experiment, the autoclave was charged with 0.04 moldiethanolamine, 0.08 mol diethyl carbonate and internal standard (n-decane) and the reaction volume made to 30 cm$^3$ with methanol. A catalyst loading was 0.03 g/cm$^3$ of total volume of reaction mixture. The temperature was raised and maintained at ±1°C of the set value with the help of an in-built proportional integral derivative (PID) controller. Once the temperature reached the desired value, agitation was started. Then, an initial sample was withdrawn. Further samples were drawn at
periodic intervals up to 1 h. A. The temperature was maintained at 140°C and the speed of agitation at 1000 rpm. The total volume of liquid phase was 30 cm$^3$. The reaction is given by Scheme 5.1.

\[
\begin{align*}
\text{HO} & \quad \text{NH} \quad \text{OH} \quad \text{O} \quad \text{CH}_3 \quad \text{O} \\
& \quad + \quad \text{O} \quad \text{N} \quad \text{OH} \quad \text{O} \quad \text{Et OH} \quad 3\text{-}(2\text{-hydroxyethyl})\text{-1,3-oxazolidin-2-one}
\end{align*}
\]

\[2\text{-}(2\text{-hydroxyethyl})\text{amino}]\text{ethanol} \quad \text{diethyl carbonate} \quad 3\text{-}(2\text{-hydroxyethyl})\text{-1,3-oxazolidin-2-one}

**Scheme 5.1:** Reaction scheme

5.2.5 **Analysis of reaction mixture**

The samples were analyzed by using GC (ChemitoModelCeres800) equipped with a 30 m x 0.25 mm i.d. BPX-5 capillary column and flame ionization detector (FID). n-decane was used as internal standard in the reaction. Reaction products were confirmed by GC-MS (PerkinElmer clarus 500).

5.3 **RESULTS AND DISCUSSION**

5.3.1 **Catalytic activity in oxazolidinone synthesis**

Experiments were conducted to measure activity of alkali promoted magnesium oxide catalyst prepared by CS method. Activity of the catalyst with different alkali promoters, different loadings of selected promoter was examined to achieve maximum conversion and selectivity towards desired product.

5.3.2 **Effect of different alkali metal promoter**

Preliminary experiments were conducted to find out activity of different alkali metal promoters in oxazolidinone synthesis (Table 5.1). Loading of alkali metal on MgO increased catalytic activity of catalyst with respect to pure MgO. In agreement with the previous findings although basicity of alkali earth metal oxides increases down the group [Cosimo et al., 1996], Li was superior alkali promoter amongst all, giving complete conversion of diethanolamine. There was a slight decrease in conversion of diethanolamine going down the group from Na to K. This is because decrease in surface area leading to correspondingly reducing total active sites. Hence further studies were conducted using Li as promoter.
Table 5.1: Effect of different alkali promoter

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Alkali promoter (Loadings 0.1%)</th>
<th>Particle size (nm)</th>
<th>Surface area (m²/g)</th>
<th>Total Pore volume Cm³/g</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>9</td>
<td>205</td>
<td>0.44</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>Li⁺</td>
<td>9.03</td>
<td>181</td>
<td>0.68</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>Na⁺</td>
<td>15.84</td>
<td>115</td>
<td>0.82</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>K⁺</td>
<td>10.58</td>
<td>146</td>
<td>0.31</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>Cs⁺</td>
<td>13.66</td>
<td>85</td>
<td>0.54</td>
<td>83</td>
</tr>
</tbody>
</table>

5.3.3 Effect of lithium loading

Different lithium ion loadings were used to study the effect of surface basic properties on conversion of diethanolamine (Table 5.2). The rate of reaction was increased by promoting MgO with Li. This was due to localization of Li₂O species on surface in the form of Li₂⁺O⁻ groups which increase local electronegativity. Thus increases ability of the catalyst to abstract proton from diethanolamine followed by bond formation with the carbonyl carbon of diethyl carbonate.

0.1 wt % lithium ion loading was found to be the optimum loading with complete conversion of diethanolamine. As the loading was increased above 0.1 wt %, the conversion was decreased. This may be due to decrease in surface area and increase in particle size, thereby decreasing total concentration of accessible active sites. This is also in the agreement with previous work wherein lithium loading of 0.5 wt % shows formation of less reactive lithium carbonate species on the surface and hence less activity (Diez et al., 2006). This was also confirmed by the XRD studies.

Table 5.2: Effect of lithium loadings
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Li⁺ (Loadings wt %)</th>
<th>Particle size (nm) By Sherrer's formulae</th>
<th>Surface area (m²/g)</th>
<th>Total Pore volume</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>9</td>
<td>205</td>
<td>0.44</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>9.03</td>
<td>181</td>
<td>0.68</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>11.71</td>
<td>117</td>
<td>0.63</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>20.93</td>
<td>95.25</td>
<td>0.3</td>
<td>85</td>
</tr>
</tbody>
</table>

5.3.4 Effect of speed of agitation

The reaction was carried out at three different speeds of agitation from 800 to 1000 rpm with 0.1% Li/MgO catalyst. There was a slight increase in conversion from 800 to 900 rpm (Figure 5.1). The initial rate of reaction was the same at 900 and 1000 rpm. This indicated that external mass transfer resistance was eliminated beyond 900 rpm. To be on a safer side, all subsequent reactions were carried out with 1000 rpm while assessing the effect of other variables on the rate of reaction. Further, it was also confirmed by studying the effect of temperature which will be discussed later.

5.3.5 Effect of catalyst loading

In the absence of external mass transfer resistance, the rate of reaction is directly proportional to catalyst loading based on the entire liquid phase volume. The catalyst loading was varied over a range of 0.01-0.03 g/cm³ on the basis of total volume of the reaction mixture (Figure 5.2). The conversion increases with catalyst loading due to the proportional increase in the number of active sites. All further experiments were carried out at 0.03 g/cm³ of catalyst loading.
**Figure 5.1:** Effect of speed of agitation

Diethanolamine, 4.2 g (0.04 mol), Dimethyl carbonate, 9.45 g (0.08 mol), reaction temperature, 140 ºC, catalyst loading, 0.03 g/cc, △ 800 rpm, ◻ 900 rpm, ◆ 1000 rpm

**Figure 5.2:** Effect of catalyst loading

Diethanolamine, 4.2 g (0.04 moles), Diethyl carbonate, 9.45 g (0.08 moles), reaction temperature, 140 ºC, speed of agitation 1000 rpm, catalyst loading, △ 0.01 g/cm³, ◆ 0.02 g/cm³, △ 0.03 g/cm³.

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5.3.6 Effect of mole ratio

The mole ratio of diethanolamine to diethylcarbonate was varied from 1:1.5 to 1:3 under otherwise similar operating conditions (Figure 5.3). As the concentration of diethyl carbonate was increased with respect to the concentration of diethanolamine, an increase in the conversion of diethanolamine and the rate of reaction was observed. However, there was no significant increase in the conversion of diethanolamine by increasing the mole ratio from 1:2 to 1:3. Therefore, further kinetic parameters studied with the mole ratio of diethanolamine to diethyl carbonate of 1:2.

![Figure 5.3: Effect of mole ratio](image)

Figure 5.3: Effect of mole ratio

reaction temperature, 140 °C, speed of agitation, 1000 rpm, catalyst loading, 0.03 g/cm³, mole ratio (diethanolamine : diethyl carbonate), ♦ 1:1.5, ● 1:2, ▲ 1:3.

5.3.7 Effect of temperature

The effect of temperature on conversion was studied in the range of 120–140 °C under otherwise similar conditions (Figure 5.4). It was observed that the conversion increased with temperature. This would suggest a kinetically controlled mechanism. The initial rates of reaction were calculated at different temperatures and the Arrhenius plots have made to determine the energy of activation.
Figure 5.4: Effect of temperature

Diethanolamine, 4.2 g (0.04 moles), Diethyl carbonate, 9.45 g (0.08 mol), speed of agitation, 1000 rpm, catalyst loading, 0.03 g/cm³, reaction temperature, ◇ 120 ºC, ▲ 130 ºC, ◆ 140 ºC

5.3.8 Reaction mechanism and kinetics

From the calculated values of mass transfer rates of A and B, initial observed rate, it was evident that the rate was independent of the external mass transfer effects. It was also seen from the values of activation energy, that the intra-particles diffusion resistance was absent. Thus, the reaction could be controlled by one of the following steps, namely: (a) adsorption, (b) surface reaction or (c) desorption. Therefore, for the further development of model, the actual reaction mechanism was undertaken.

The initial rate data can be analysed on the basis of Langmuir-Hinshelwood-Hougen-Watson (LHHW) or Eley-Rideal mechanisms. From the initial rate data, the following analysis was found to be the most appropriate. The mechanism shown in scheme 5.2 can be used to arrive at the LHHW type of mechanism.
Scheme 5.2: Plausible reaction mechanism

1. Adsorption of diethanolamine (A) on the vacant site S is given by:

\[ A + S \overset{k_1}{\rightleftharpoons} AS \]  

Similarly adsorption of diethyl carbonate (B) on the vacant site is presented by:

\[ B + S \overset{k_2}{\rightleftharpoons} BS \]  

2. Surface reaction of AS with BS (diethyl carbonate), in the vicinity of the site, leading to formation of 3-(2-hydroxyethyl)-1,3-oxazolidin-2-one (DS) on the site.

\[ AS + BS \overset{k_3}{\rightleftharpoons} DS + MS \]  

Desorption of 3-(2-hydroxyethyl)-1,3-oxazolidin-2-one (DS) and ethanol (MS)

\[ DS \overset{1/k_1}{\rightleftharpoons} D + S \]  

\[ DS \overset{1/k_2}{\rightleftharpoons} M + S \]  

The total concentration of the sites, \( C_t \) expressed as,

\[ C_t = C_S + C_{AS} + C_{BS} + C_{DS} + C_{MS} \]
or, 
\[ C_i = C_s + K_A C_A C_S + K_B C_B C_S + K_D C_D C_S + K_M C_M C_S \]  \hspace{1cm} (2)

or, the concentration of vacant sites,
\[ C_s = \frac{C_i}{1 + K_A C_A + K_B C_B + K_D C_D + K_M C_M} \]  \hspace{1cm} (3)

If surface reaction controls the rate of reaction, then the rate of reaction of A is given by
\[ -r_A = \frac{-dC_A}{dt} = k_2 C_A S C_{BS} - k_2 C_{DS} C_{MS} \]  \hspace{1cm} (4)

When the reaction is far away from the equilibrium
\[ \frac{-dC_A}{dt} = \frac{k_2 C_i^2}{1 + \sum K_i C_i} \]  \hspace{1cm} (6)

Where,
\[ k_{R2} w = k_2 C_i^2 K_A K_B \]

And \( w \) is catalyst loading.

If the adsorption constants are very small, then the above equation reduces to
\[ \frac{dC_A}{dt} = k_{R2} C_A C_B w \]  \hspace{1cm} (8)

Let,
\[ \frac{C_{B0}}{C_{A0}} = M \]  \hspace{1cm} (8a)

The molar ratio of diethyl carbonate to diethanolamine at \( t = 0 \). Then the equation (8) can be written in terms of fractional conversion as
\[ \frac{-dX_A}{dt} = k_{R2} w C_{A0} (1 - X_A) (M - X_A) \]  \hspace{1cm} (9)

This upon integration leads to:
\[ \ln \{ (M - X_A) / M (1 - X_A) \} = k_{R2} w C_{A0} (M - 1)t \hspace{1cm} M \neq 1 \]  \hspace{1cm} (10)

To validate the above mechanism, plots were made in consonance with Eq. (10) (Figure 5.5) It shows four straight lines passing through the origin at catalyst loading.
of 0.01, 0.02 and 0.03 g/cm³ respectively. The slopes of these lines, $k_1 = k_{2wC_0}$ which are functions of $w$. Thus, plots of $k_1$ against $w$ were made showing linear relationship (Figure 5.6). This linear relationship also indicates that the rate is proportional to the number of active sites present on the surface. It would therefore mean that the reaction mechanism is LHHW type with very weak adsorption of both the reactants in the absence of any diffusional resistance.

![Graph showing linear relationship between $k_1$ and $w$.](image)

**Figure 5.5:** Plot of ln\(\{(M-X_A)/(M*(1-X_A))\}\) Vs time at different catalyst loading (w)

- $\Diamond$ 0.01 g/cm³
- $\blacktriangle$ 0.02 g/cm³
- $\blacklozenge$ 0.03 g/cm³

The values of $k_1$ were also found at the different temperatures at the same $w$ and $M$ (Figure 5.7). The Arrhenius plot of ln$k_1$ vs. T$^{-1}$ is shown in Figure 5.8, from which the activation energy was calculated as 23.44 kcal/mol. The high value of activation energy also supported the fact that the overall rate if reaction is not influenced by either external mass transfer or intraparticle diffusion resistance and it is intrinsically kinetically controlled reaction on active sites.
Figure 5.6: Plot of $k$ Vs different catalyst loading ($w$)

Figure 5.7: Plot of $\ln \frac{(M-X_A)}{(M(1-X_A))}$ Vs time at different temperature: 120 ºC, 130 ºC, 140 ºC

- $y = 1.2571x$, $R^2 = 0.9921$
- $y = 0.0396x$, $R^2 = 0.9983$
- $y = 0.0242x$, $R^2 = 0.9973$
- $y = 0.0146x$, $R^2 = 0.9936$

120 ºC, 130 ºC, 140 ºC

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5.3.9 Catalyst reusability

The catalyst reusability was studied four times, including the use of fresh catalyst (Table 5.3). After the experiment was completed, the catalyst was filtered and washed with dry methanol (50 cm$^3$) in order to remove adsorbed material from catalyst surface and pores. The catalyst was then dried at 120°C and calcined at 500°C for 4 h. The catalyst lost during filtration was made up with fresh catalyst, activated and the activity was tested. The same conversion and selectivity was observed with reused catalyst. This demonstrates that the catalyst is stable and retains its catalytic activity. The same procedure was followed thrice. The catalyst was found stable and reusable three times without any loss in activity.

Table 5.3: Reusability study
Cycle | Conversion | selectivity
---|---|---
Fresh | 100 | 100
1<sup>st</sup> reuse | 95 | 100
2<sup>nd</sup> reuse | 90 | 100
3<sup>rd</sup> reuse | 89 | 100

### 5.3.10 Substrate study

Various amino alcohol substrates were used to synthesize corresponding oxazolidinones using 0.1 wt % Li/MgO. All reactions were conducted at optimized reaction parameters. The results were summarized in Table 5.4. In all cases reaction proceeds cleanly and desired oxazolidinones were obtained with high selectivity.

#### Table 5.4: Substrate study

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reactant</th>
<th>Product</th>
<th>Conversion (%)</th>
<th>Time (h)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO NH HO</td>
<td>O</td>
<td>100</td>
<td>1.5</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>H₃C NH HO</td>
<td>O</td>
<td>100</td>
<td>1.5</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>H₃C NH HO</td>
<td>O</td>
<td>100</td>
<td>1.5</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>H₂N HO</td>
<td>O</td>
<td>100</td>
<td>2</td>
<td>88</td>
</tr>
</tbody>
</table>
5.4 CONCLUSION

A novel combustion synthesis method was developed to prepare alkali promoted alkaline earth metal oxide. Various combustion synthesis parameters were studied, in which amongst different combustion fuels glycine was best with optimized fuel to oxidant (F/O) of 2. As F/O was increased beyond 2, it led to decrease in surface area and increase in particle size. Effect of different promoters on conversion of diethanolamine to oxazolidinones derivative was studied and lithium was found to be the best among other alkali metal promoters. It was observed that as Li$^+$ loading increases the crystalline size increases and surface area decreases. Maximum surface area obtained was 181 m$^2$/g for 0.1% wt Li/MgO. Catalytic activity was found maximum with 0.1% wt of Li$^+$ metal loading. The catalyst is nanosrystallinewith size of 9 nm. However, above 0.1 wt% Li on MgO, decrease in catalyst activity was observed due to decrease in surface area and formation of carbonate species. Excellent conversion and selectivity was obtained in oxazolidinones synthesis with different substrates.