This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Zinc monoglycerolate as a catalyst for the conversion of 1,3- and higher diols to diurethanes

Sanjitha Kulasegaram¹, Uzma Shaheen¹, Terence W. Turney¹,², Will Gates³ and Antonio F. Patti¹

¹. School of Chemistry  Monash University, Victoria 3800, Australia 2. Department of Materials Engineering, 3. Department of Civil Engineering, Monash University, Victoria 3800, Australia.

Key words: zinc monoglycerolate, diurethane, diols, urea
Abstract
A green methodology exploring the scope of diurethane synthesis from diols and urea in the presence of a homogeneous catalyst is described. Past reactions of diurethanes have relied heavily on environmentally corrosive reagents such as phosgene. Prior to this work, we have utilized metal glycerolates as homogeneous catalysts in the glycerolysis of urea. Here we explore the synthetic scope of this system with a variety of diols. The conversion to diurethanes is proposed to proceed via an intermediate zinc bound isocyanate ligand, which rearranges to form the terminal urethane in the case of 1,3- and higher diols in good selectivity and yields. With butane 1,2,4-triol the selectivity is exclusively for the 5-membered carbonate, suggesting that the proximity of the second hydroxyl group is critical in forming the ring.
**Introduction**

Sustainable development is vital in today's over-polluted world. Hence the need for green chemical methods outweighs traditional reaction pathways. There is a drive to develop cheap eco-friendly solvent-free processes to synthesise fine chemicals.\(^1\) In reactions that are initiated by a catalyst the ideal is to sustain the atom economy, which will in turn lead to ease of isolation of product and cost effectiveness of the process. Our previous work\(^2\) utilized glycerol as a cheaply available starting material in the glycerolysis of urea (also a low cost and readily available reactant) to form glycerol carbonate in the presence of a metal glycerolate catalyst.

There are a number of reports on the reaction of glycerol with urea using various zinc containing catalysts\(^3-5\). Here we report the extension of our previous work\(^2\) to other 1,2 diols as well as the preferential formation of diurethanes from 1,3- and higher diols via a green chemical process. There has been a growing market for diurethane derivatives in medicinal use since the 1950's. Past synthesis of diols to diurethanes have looked at the anticonvulsant properties of 1,3-propanediol derivatives.\(^6\) This was followed in the 1960's by an extensive review of a series of carbamates that were tested in anticonvulsant animal models.\(^7\) One of the more successful candidates to emerge in the 1990’s as an antiepileptic was felbamate, a 1,3-dicarbamate, however it does cause aplastic anemia and is hepatotoxic.\(^8\) Other popular 1,3-dicarbamate derivatives sold as anxiolytic drugs today are meprobamate and mebutamate, but these too possess unfavourable side effects.\(^9\) Hence the arena is open to explore new carbamate candidates that are potential anti-epileptics and CNS drugs via a synthetic strategy that does not involve toxic reagents. This need gave purpose to our current methodology that yields dicarbamates from diols in the absence of an external isocyanate reagent.
In moving to 1, 3- and higher terminal diols, we observed that cyclization to larger ring carbonates did not occur and instead the process stopped once the diurethane was formed. Previous syntheses of diurethanes have proceeded via reacting diols with phosgene to give the chlorocarbonate which then reacts with ammonia to form the urethane (Scheme 1). An early approach in the 1950’s utilized sub-atmospheric pressures, where a series of 1-3, 1-4 and 1-5 diols were reacted with alkyl urethanes at 140-180°C at pressures of 20-300 mbar. The catalyst employed was aluminium alkoxide and the mixture was kept vigorously boiling in the absence of extraneous solvent. The resultant alcohol from this reaction was continuously removed, in order to enhance the process (Scheme 3).}

Analogous to the O-bonded diurethanes which are derived from diols, the N-bonded diurethanes are accessed from diamines and the relevant carbonate. Zinc based catalysts are known to effect this transformation either via a heterogeneous or homogeneous mechanism (Scheme 2). These monomers undergo subsequent polymerization reactions, unlike their O-bonded counterparts.

Instead of utilising urethanes, we directly employed urea with zinc monoglycerolate as a catalyst in a solvent free environment, yielding good conversions and selectivities. (Scheme 4).
Results and Discussion

We have shown that reacting glycerol with urea in the presence of zinc monoglycerolate at a temperature of 140°C and a pressure of 40 mbar gives glycerol carbonate in high conversion and yield. When the scope of this methodology was explored with a series of diols and polyols we observed that with 1,2-diols, the preferred selectivity was to form the cyclic carbonate with the terminal urethane intermediate as a side product[2]. With the polyols listed in Table 1, it was essential to apply reduced pressure to the system, thereby removing ammonia, in order to promote all the conversions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Time/h</th>
<th>Conversion (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>Glycerol carbonate[^a^]</td>
<td>7</td>
<td>98</td>
<td>85</td>
</tr>
<tr>
<td>Ethane-1,2 diol[^b^]</td>
<td>Ethylene carbonate[^c^]</td>
<td>24</td>
<td>71</td>
<td>43[^d^]</td>
</tr>
<tr>
<td>Propane-1,2-diol[^c^]</td>
<td>Propylene carbonate[^c^]</td>
<td>24</td>
<td>99</td>
<td>80</td>
</tr>
<tr>
<td>Butane-1,2,4-triol</td>
<td>4-(2-Hydroxyethyl)-1,3-dioxolan-2-one[^c^]</td>
<td>7</td>
<td>73</td>
<td>91</td>
</tr>
<tr>
<td>Cis-cyclohexane-1,2-diol</td>
<td>Hexahydrobenzoi d[1,3]dioxol-2-one[^c^]</td>
<td>7</td>
<td>87</td>
<td>86</td>
</tr>
<tr>
<td>Trans-cyclohexane-1,2-diol</td>
<td>Cyclohexane-1,2-diyd dicarbamate</td>
<td>7</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>1,2-Dihydroxy benzene</td>
<td>2-Hydroxyphenyl carbamate[^c^]</td>
<td>7</td>
<td>58</td>
<td>76</td>
</tr>
</tbody>
</table>

[^a^] Unless otherwise stated all reactions were performed at 140°C/40 mbar, with 1.5 mole equivalents of urea to glycerol and 5% wt. zinc monoglycerolate to alcohol.  
[^b^] Performed at standard pressure.  
[^c^] Selectivity for terminal mono-carbamate intermediate was 37%.  
[^d^] Pressure was 400 mbar.  
Analytical data for these compounds is provided in the Supplementary information.
In the case of ethylene glycol and propylene glycol, as these are more volatile, the reactions were carried out at atmospheric pressure and 400 mbar, respectively. The two reactions were monitored over 24 h compared to the usual 7 h. In the case of ethylene glycol the final yield of the cyclic carbonate was low, in spite of the conversion being quite high. We attribute this to the two-step reaction in forming the cyclic carbonate, where the first step proceeds with ease to form the terminal urethane, but once formed, the cyclization to form the carbonate requires a catalyst, as well as heat and reduced pressure, to eliminate ammonia. Details of the mechanism for this reaction have been described by Turney et al. In a previous study, it was shown that the polymeric glycerolate complexes of Zn or Co form a homogeneous catalyst, containing a coordinated isocyanate ligand. This complex subsequently reacts with a hydroxyl group of the diol to give a zinc coordinated urethane intermediate. The proximity of a second hydroxyl group in the 2-position favours cyclic carbonate formation, as was previously shown. However in diols or other alcohol systems where the hydroxyl group is not in a 1,2 relationship, linear urethane products are favoured. This requires further reaction of the free hydroxyl of the monourethane with the catalyst, to form the diurethane.

With ethylene glycol we were unable to exert reduced pressure on the system and maintain the temperature at 140°C without also losing the starting material and products (despite the use of a water condenser), which resulted in poorer selectivity. In the reaction of 1,2-propylene glycol, which was less volatile than ethylene glycol, a reduced pressure of 400 mbar was applied over 24 h, in order to maximize conversion and selectivity. The higher selectivity for the cyclic carbonate in this instance is a direct effect of the applied reduced pressure, which promotes the cyclization with the removal of ammonia. In the case of the cis and trans 1,2-diols of cyclohexane, the expected carbonate was obtained with the cis-isomer. The trans-isomer of the mono-urethane intermediate however is stereochemically too rigid to successfully undergo an intra-molecular nucleophilic substitution, instead the diurethane is formed in preference (Table 1, 67% selectivity) along with minor amounts of the mono-urethane (9%) and cyclic carbonate (6%). On applying this methodology to an aryl 1,2-diol
such as catechol, we obtained the mono-urethane intermediate with poor conversion and
yield; none of the cyclized product was observed over 7 h. This mixture blackens within 1 h
of heating under our standard conditions. Similarly with 2-(hydroxymethyl) phenol, the major
product was the mono-urethane with preference for carbamoylation taking place on the aryl
rather than the benzylic oxygen (Table 2).

When we proceeded to look at higher diols (>1, 3-), with 2 equivalents of urea and 5%
wt. catalyst at a temperature of 140°C and a pressure of 40 mbar, we observed the
predominant formation of diurethanes rather than cyclic carbonates (Table 2).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Conversion (%)</th>
<th>Selectivity (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3-Propane diol</td>
<td>Propane-1,3-diyl dicarbamate</td>
<td>75</td>
<td>75</td>
<td>56</td>
</tr>
<tr>
<td>1,4-Butane diol</td>
<td>Butane-1,4-diyl dicarbamate</td>
<td>71</td>
<td>76</td>
<td>54</td>
</tr>
<tr>
<td>1,6-Hexane diol</td>
<td>Hexane-1,6-diyl dicarbamate</td>
<td>84</td>
<td>94</td>
<td>79</td>
</tr>
<tr>
<td>1,8-Octane diol</td>
<td>Octane-1,8-diyl dicarbamate</td>
<td>82</td>
<td>87</td>
<td>71</td>
</tr>
<tr>
<td>1,10-Decane diol</td>
<td>Decane-1,10-diyl dicarbamate</td>
<td>66</td>
<td>86</td>
<td>57</td>
</tr>
<tr>
<td>Diethylene glycol</td>
<td>Oxybis(ethane-2,1-diyl) dicarbamate</td>
<td>86</td>
<td>84</td>
<td>72</td>
</tr>
<tr>
<td>Triethylene glycol</td>
<td>(Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) dicarbamate</td>
<td>68</td>
<td>80</td>
<td>54</td>
</tr>
<tr>
<td>Pentaerythritol</td>
<td>Tetra carbamate of pentaerythritol</td>
<td>74</td>
<td>93</td>
<td>69</td>
</tr>
<tr>
<td>2-(Hydroxymethyl) phenol</td>
<td>2-(Hydroxymethyl)phenyl carbamate</td>
<td>86</td>
<td>93</td>
<td>80</td>
</tr>
</tbody>
</table>

[a] Typical reaction conditions were 5% wt. zinc monoglycerolate to substrate with 2 mole equivalents of urea heated to 140°C under a reduced pressure of 40 mbar over 7h. [b] Pressure used was 400 mbar over 24h. [c] Used a 5 mole excess of urea. [d] Used 1.5 mole equivalents of urea. Analytical data for these compounds is provided in the Supplementary information.

Under these solvent free conditions, once the urea and diol are in a liquid phase and the
catalyst is homogeneous, product formation begins where the long chain diurethanes
deposit as a solid in the reaction mixture even at elevated temperatures. In general this
methodology with terminal diols is robust when zinc monoglycerolate is used as a catalyst,
consistently yielding the diurethane in good yield. It was also possible to recover and reuse the catalyst, in the same way as described in our previous work\textsuperscript{[2]}. In progressing to a C-10 chain there is a slight drop in conversion which affects the yield. Here the long alkyl chains may serve as deterrents towards the approaching metal bound-isocyanate and hinder the conversion. With polyethylene glycol derivatives the transformation was similar to long chain hydrocarbon moieties.

Reaction of thiourea with 1,6-hexanediol under our optimized conditions with ZMG did not yield the desired cyclic carbonate even though there was IR evidence for a thioisocyanate species (2050 cm\textsuperscript{-1}) during the course of the reaction. The unreacted diol was recovered quantitatively. The reaction of this diol with 1.5 mole equivalents of biuret resulted in 75\% conversion, where the exclusive product was the mono-carbamate. The reaction of 1,6-hexanediol with 2 mole equivalents of tetramethyl urea under optimal conditions did not yield any carbamate. When 1,6-hexanediol was reacted with 2 mole equivalents of N,N dimethylurea, 65\% conversion was achieved with the formation of the monocarbamate. A minor byproduct (<12\%) was not fully characterised, however mass spectrometry evidence suggested it may be the disubstituted N,N dimethyl carbamate (Table 3).

<table>
<thead>
<tr>
<th>Table 3. Zinc monoglycerolate catalyzed reactions of 1,6-hexanediol with urea derivatives\textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urea derivative</strong></td>
</tr>
<tr>
<td>Thiourea</td>
</tr>
<tr>
<td>Biuret</td>
</tr>
<tr>
<td>N,N-Dimethyl Urea\textsuperscript{[b]}</td>
</tr>
<tr>
<td>Tetramethyl urea</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Typical reaction conditions were 5\% wt. zinc monoglycerolate to substrate with 2 mole equivalents of the urea derivative heated to 140\textdegree C under a reduced pressure of 40 mbar over 7h.  
\textsuperscript{[b]} 400 mbar. pressure was used.
Experimental

The general method to convert diols to either the cyclic carbonate or the diurethane was as follows: a mixture of diol (0.066 mol), urea (0.132 mol) and 5% wt. zinc monoglycerolate (0.25 g) with respect to the diol, were heated to 140°C at a reduced pressure of 40 mbar in a round bottom flask fitted with a condenser. The reaction was monitored by gas chromatography until product formation was optimum. The crude mixture was taken up in methanol to precipitate out the catalyst, then filtered and concentrated to obtain an oil. With solid diurethanes, the product directly precipitated out in the reaction mixture. Here the solid was recrystallized from ethanol when required. Products that are known in literature are characterized by $^1$H NMR at least. The two new compounds, cyclohexane-1,2-diyl dicarbamate and 2-(hydroxymethyl)phenyl carbamate are identified by $^1$H NMR, $^{13}$C NMR and GC-MS. Details of experimental are in the Supplementary Information.

Conclusions

This paper has highlighted the use of zinc monoglycerolate being used as a homogeneous catalyst in the transformation of 1,2- and higher order diols to yield the cyclic carbonate or the linear diurethane selectively in good yields (54-79%).

Acknowledgements

The authors are grateful to Micronisers Pty Ltd for supply of zinc glycerolate nanoparticles, the Australian Research Council for financial support (Grant No: DP1095129), the Faculty of Science for providing an international PhD fees scholarship (US) and wish to thank Mingdeng Luo and Sally Duck from Monash University for instrumental support.

References


