Synthesis of Five-Membered Cyclic Ethers by Reaction of 1,4-Diols with Dimethyl Carbonate

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5-Membered cyclic ethers by reaction of 1,4-diols with dimethyl carbonate

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The reaction of 1,4-diols with dimethyl carbonate in the presence of a base led to the selective and high yielding synthesis of the related 5-membered cyclic ethers. This synthetic pathway resulted of wide application; distinctive cyclic ethers, as well as, industrially relevant compounds were synthesized in quantitative yield. The reaction mechanism for the cyclisation was investigated. Noteworthy it did not affect the chiral centers eventually present in the substrate. The Density Functional Theory (DFT) free energy barriers indicated that the formation of 5-membered cyclic ethers was the most energetically pathway. Usually a rationale for the selectivity exhibited by these systems would be based upon the Hard-Soft Acid-Base theory applied to DMC chemistry. These concepts were applicable here as far as computed energy barriers are considered, but the experimental outcome was shown to be the consequence of a dominant role of the entropic term in the reaction ΔG.

Introduction

Many natural, as well as, synthetic compounds incorporate as structural subunits tetrahydrofuran rings. Some examples of interesting natural products that include these cyclics in their backbones are forskolin,[1] manoyl oxide derivatives,[2] which have significant biological activity, polyether antibiotics,[3] inostamycins,[4] isosorbide[5] to mention but a few. Besides, some cyclic ethers have distinctive aromas and are useful as fragrances. An example is (-)-norlabdane oxide; a compound widely used for providing ambergris-type odours to perfumes as natural ambergris itself is no longer available for this purpose.[6]

Amongst the commonly used synthetic approaches for the formation of cyclic ethers (*via* cyclisation and/or cycloaddition) many involve heavy metals[7] or chlorine chemistry at different levels e.g. activated chlorine-based leaving groups, or leaving groups created through the use of chlorine (e.g. tosylate – through the chlorosulphonation of toluene, mesylate etc.).[8] Cyclisation reactions are also conducted very often in acidic conditions; many patents reports the synthesis of tetrahydrofuran starting from the corresponding 1,4-butane diol by acid catalyzed cyclodehydration.[9,10] However, in this conditions, common cyclodehydration reactions are not very effective when tertiary alcohols are involved affording lower yields due to a mixture of elimination and/or rearrangement products. Recent advances in the synthesis of substituted tetrahydrofuran rings have been achieved by using different approaches with alternative starting materials and novel catalysts:[11] the reaction of 1,4- and 1,5-diols with cerium ammonium nitrate (CAN)[12] proved to be very effective and use mild condition although its application is limited by the presence of at least one tertiary alcohol in the starting diols.

Short chain dialkyl carbonates such as dimethyl carbonate (DMC), produced nowadays by clean processes,[13] are renowned for possessing properties of low toxicity and high biodegradability, which make them true green solvents and reagents.[14] DMC has been widely used as efficient eco-sustainable substitute of phosgene, methyl halides or methylsulfate that are toxic and highly corrosive.[15] In fact, dialkyl carbonates and in particular DMC have shown high selectivity with different monodentate and bidentate nucleophiles acting as methylating and/or carboxymethylating agent.[16] The reactivity of the two electrophilic centers of DMC can be selectively tuned, temperature being the key factor. In particular, at reflux temperature (T = 90 °C) DMC acts as methoxycarbonylation agent by $B_{Ac}2$ mechanism while at higher temperature (T>150 °C) the methylation reaction occurs *via* the $B_{Al}2$ mechanism. Both reactions produce as by-product only methanol and eventually CO_2.[14-16]

We have previously reported the synthesis of industrial relevant 5-membered cyclic ethers by DMC chemistry in mild conditions by reaction of 1,4-diols with DMC in the presence of a base.[17] In this work we applied this new synthetic pathway to several five-member cycles optimizing the reaction conditions. The mechanism of the *intramolecular* cyclisation was investigated by ^{1}H NMR spectroscopy and the reaction intermediates were isolated and fully characterized.

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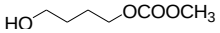
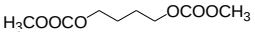
Furthermore the energy barriers associated with the cyclisation and with all the possible concurrent pathways were explored by Density Functional Theory.

Table 1. Cyclisation of 1,4-butane diol with DMC

#	Solvent	DMC[b]	NaOMe[c]	Time	Cyclic (GC-MS %)	Other products (GC-MS %)	
	(ml)	(eq. mol.)	(eq. mol)	(h)			
1	None	20	1.5	2	12	0	88 (75)[a]
2	CH_3CN[b]	4	1.5	3	70 (82)[b]	11 (0)c	19 (17)[c]
3	CH_3CN[b]	4	2	4	100	0	0

[a] Isolated yield by column chromatography; [b] 2.0 g of 1,4-butane diol in 30 mL of CH_3CN at 60 °C; c GC-MS % after 8h.

The assessment of the relevant free energy barriers in DMC solution indicated that the cyclisation pathway is the most energetically favoured in comparison with the methylation, carboxymethylation of the diol or the formation of a 7-membered cyclic carbonate. In the case of soft/hard nucleophiles the ambiphilic character of DMC can be usually explained according to the Hard-Soft Acid-Base (HSAB) theory introduced by Pearson.[18] However, in the present case, this conceptual framework is consistent with the gas-phase energies pertinent to the reaction channels open to the reacting system, but the experimental outcome is ultimately determined by the entropy factor (included in the free energy differences), reinforced by solvent effects.

Results and Discussion

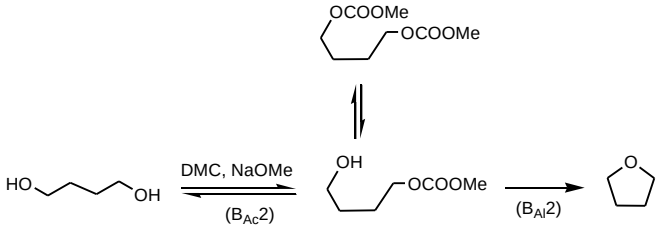
Tetrahydrofuran from 1,4-butane diol

In a first set of experiments 1,4-butane diol was reacted with an excess of DMC, used as solvent and reagent, in the presence of sodium methoxide at reflux temperature (entry 1, Table 1). As expected the dicarboxymethyl derivative of the 1,4-butane diol was the main product observed, whilst tetrahydrofuran formed only in small yield. However, when the reaction was conducted in acetonitrile with 4 molar equivalent of DMC, tetrahydrofuran was identified as the main product (70 % yield) (entry 2, Table 1). Quantitative conversion of the 1,4-butane diol into tetrahydrofuran was achieved by increasing the amount of base (entry 3, Table 1).

The synthesis of THF as model reaction for the cyclisation of 1,4-diols via DMC, is not the more convenient reaction as the target molecule is very volatile in batch conditions. However, it was possible to overcome this issue performing the reaction in a continuous-flow apparatus.[19]

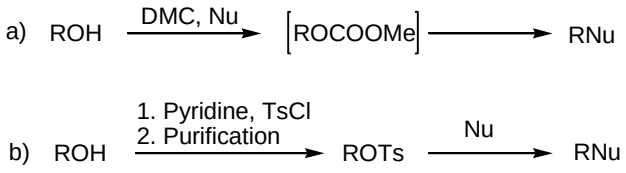
In all the above-mentioned experiments, the dicarboxymethyl derivate was the main by-product observed. This compound was isolated as pure and fully characterized. As expected, the dicarboxymethyl derivate was formed mostly in the presence of an excess of DMC, whilst the cyclic ether was obtained in high yield when DMC was used in smaller amount (entry 2-3, Table 1).

The cyclisation of 1,4-butane diol can be ascribed to the versatility of the DMC as reagent.[16] In particular, the mechanism of the cyclisation herein observed comprises first of the carboxymethylation of the 1,4-diol by a $B_{Ac}2$ mechanism followed by an *intramolecular* cyclisation thorough a $B_{Al}2$ mechanism where a methylcarbonate anion is released as leaving group (Scheme 1).



Scheme 1. Mechanism of the cyclisation of 1,4-diols

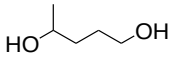
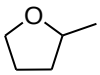
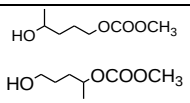
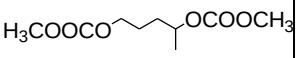
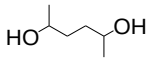
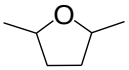
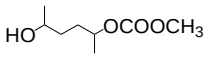
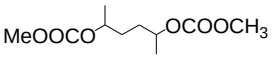
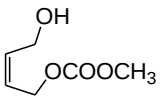
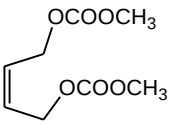
The formation of the (di)carboxymethyl derivatives of the starting diol is a thermodynamically controlled equilibrium reaction whilst the *intramolecular* $B_{Al}2$ cyclisation allows the formation of the kinetically stable cyclic ether. This reaction mechanism ultimately leads to the formation of the cyclic compound in a quantitative yield.



Scheme 2. a) S_N2 *via* DMC chemistry; b) S_N2 *via* chlorine based chemistry

Noteworthy, the direct conversion of the diol into the cyclic ethers *via* DMC chemistry has the advantage to be a single step S_N2 reaction where the leaving group is formed *in situ*.

Table 2. Cyclisation of aliphatic 1,4-diols with DMC to yield THF derivatives

#	Diol	Solvent	DMC[b]	NaOMe[c]	Time	Cyclic (GC-MS %)	Other products (GC-MS %)	
		(ml)	(eq. mol.)	(eq. mol)	(h)			
1		None	20	1.5	2	2	0	73 (60)[a]
2		CH_3CN[b]	4	1.5	4	40	29	26
3		CH_3CN[b]	4	2	6	64	20	15
4		CH_3CN[b]	4	3	6	100	0	0
								
5		None	20	1.5	5	0	4	72 (64)[a]
6		CH_3CN	4	3	6	3 (8)[c]	10 (0)[c]	38 (43)[c]
								
7		None	4	0.05	2	28	33 (24)[a]	38 (31)[a]
8		None	20	1	2	98	0	2
9		CH_3CN[d]	4	2	4	100	0	0

[a] Isolated yield by column chromatography; [b] 0.5 g of diol in 15 ml of CH_3CN at 70 °C; [c] after 24h conversion 52 %; [d] 2 g of diol in 30 ml of CH_3CN.

Scheme 2 shows a comparison between S_N2 reaction involving *in situ* formation of the intermediate [ROCOOMe] entailing the leaving group (path a) and S_N2 reaction by commonly used chemistry (path b).
The latter pathway, an example of chlorine chemistry, is a two step reaction involving tosylation of the substrate and consequent S_N2 on the purified tosyl derivative in basic conditions. Both steps involve the formation of large amounts of waste to be disposed of and time consuming purification of the products.

Synthesis and reaction mechanism of cyclic ethers from 1,4-diols by DMC chemistry

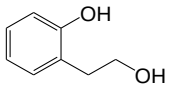
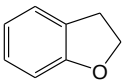
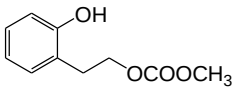
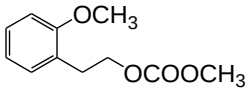
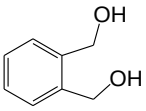
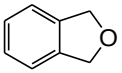
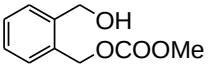
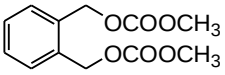
A range of aliphatic and aromatic 1,4-diols were selected, each bearing differently substituted alcohols (primary, secondary, tertiary, allyl, phenyl and benzyl) and reacted with DMC. Table 2 reports the results obtained for aliphatic diols. In particular, 1,4-pentane diol showed to form its related cyclic ether in quantitative yield under similar conditions to those used for 1,4-butane diol (entry 4, Table 2). Results collected showed that quantitative conversion into 2-methyl tetrahydrofuran required 3 molar equivalent of NaOMe (2 mol. eq. used for 1,4-butane diol; entry 3 Table 1). This might be ascribed to the lower reactivity of secondary alcohols.

When 2,5-hexan diol, as mixture of isomers, was used as substrate, the cyclisation did not occur even using an excess of base (entry 6, Table 2). The fact that, even after 24 hours of reaction the substrate was still not fully converted (50%) and the cyclic ether was present only in traces (8%), demonstrates that secondary functionality are less reactive either in the carboxymethylation step[14] and in the nucleophilic substitution reaction.

A detailed mechanistic investigation was carried out using *cis*-1,4-but-2-ene diol. This compound showed to undergo a very fast and quantitative cyclisation reaction (entry 9, Table 2), even using an excess of DMC (entry 8, Table 2). Most probably the formation of the 2,5-dihydro furan is aided by the favourable *cis* position of the alcohol moieties; even when the reaction was repeated using a catalytic amount of base (0.05 mol. eq.) the cyclic was formed in appreciable yield i.e. 30% (entry 7, Table 2).

Table 3. Cyclisation of 1,4 diols bearing aromatic moiety with DMC

#	Diol	Solvent	DMC[b]	NaOMe[c]	Time	Cyclic	Other products

					(GC-MS %)	(GC-MS %)	
		(ml)	(eq. mol.)	(eq. mol)	(h)			
1		None	10	0.5	7	62.5[a] (55)[b]	37.5 (31)[b]	0
2		None	10	1	5	85[a] (76)[b]	15	0
3		None	10	2	5	100[a] (93)[b]	0	0
4		CH_3CN[c]	4	2	2	100[a] (95)[b]	0	0
								
5		None	10	0.5	7	45 (30)[b]	33 (24)[a]	53 (41)[b]
6		None	10	2	4	74	0	26
7		CH_3CN[d]	4	2	4	100 (95)[b]	0	0

[a] Yield calculated by ^{1}H NMR spectra; [b] Isolated yield by column chromatography; [c] 1g of 2-hydroxyphenethyl alcohol in 20 mL of CH_3CN at 90 °C; [d] 1.0 g of 1,2-benzene dimethanol in 20 mL of CH_3CN

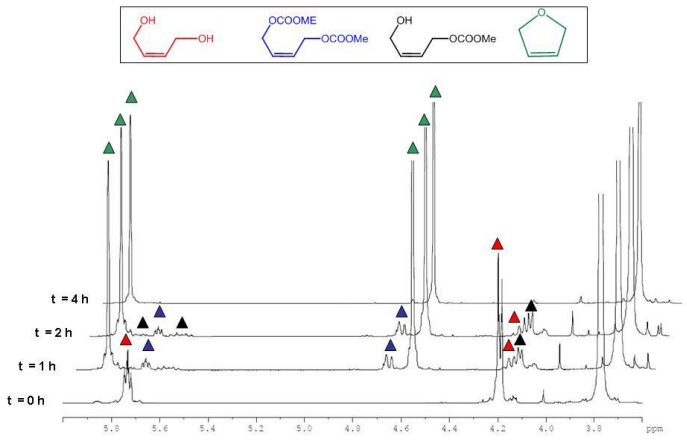


Figure 1. ^{1}H NMR spectra showing the formation of 2,5-dihydrofuran over time.

In all cases, the main by-products formed were the mono and the dicarboxymethyl derivates; these compound were isolated as pure and fully characterized. Performing the cyclisation of *cis*-1,4-but-2-ene diol in deuterated acetonitrile it was possible to follow the formation of the cyclic ether by proton NMR. Figure 1 reports the ^{1}H NMR data collected at time intervals according to the conditions depicted in entry 9, Table 2. The spectra showed that, already after one hour, the cyclic ether is the main product; small amount of the mono and dicarboxymethyl derivatives together with traces of the starting diol are also present. After four hours the 2,5-dihydrofuran was the only product present in the solution.

The reactivity of 1,4-diols bearing aromatic moieties was also investigated (Table 3). 1,2-Dihydroxymethyl benzene and 2-hydroxyethyl phenol were selected as substrates. 2-Hydroxyethyl phenol resulted to be one of the most reactive substrates as 2,3-dihydro benzofuran, was the major product of the reaction (65% yield) already using 0.05 mol. eq. of base (entry 1, Table 3). Quantitative formation of the cyclic ether was achieved using 2 molar equivalent of base (entries 2-3 Table 2). The reaction resulted effective even using a lower amount of DMC i.e. 4 molar equivalent (entry 4, Table 3). The pure cyclic can be recovered after filtration of the base and evaporation of the solvent without any further purification (entry 3-4, Table 3). In any case the formation of the methoxy derivatives of the 2- hydroxyethyl phenol was not observed. The monocarboxymethyl derivative of the starting diol was the only intermediate observed. This compound was isolated as pure and fully characterized.

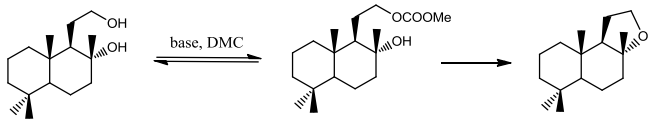
1,2-Dihydroxymethyl benzene led to the quantitative formation of the related cyclic ether, phthalan (entry 7, Table 3) using similar reaction condition to the 2-hydroxyethyl phenol. The dicarboxymethyl derivative of the aromatic 1,4-diol, the only intermediate formed, was isolated and characterized (entry 5, Table 3). The monocarboxymethyl derivatives was probably present only in traces as its presence in the reaction mixture was not detected. In any case, the phthalan resulted the main products in all the reactions. Possibly, the rigid structure of the substrate aided the formation of the cyclic ether. Noteworthy in all the cases studied the reaction solution is crystal clear; this confirmed the absence of any decomposition products (Tables 1-3).

One-pot synthesis of ambroxan and isosorbide

(-)-Norlabdane oxide represents one of the preferred synthetic compounds with desirable ambergris-type odour and is commercially available under various trade names (notably as

amberlyn, ambroxan, ambrofix, ambrox or amberoxide).[20,21] (-)-Norlabdane oxide is industrially synthesized by cyclisation of the related diol, amberlyn diol, in acidic condition.[21]

This reaction leads to a mixture of ambroxan (ca 60%) and by–products deriving from the concurrent elimination reaction. Table 4 reports the results obtained by reacting amberlyn diol[22] with DMC in the presence of a base.[17] In a first set of experiment potassium *tert*-butoxide was used in a presence of an excess of DMC (entries 1-3, Table 4). Results showed that, using 2 molar equivalents of base in an excess of DMC (used as reagent and solvent), amberlyn diol cyclised quantitatively to ambroxan in only 3 hours (entry 1, Table 4). Decreasing the amount of base resulted in a lower yield of the cyclic ether (entry 2, Table 4).



Scheme 3. Synthesis of Ambroxan

Table 4. Synthesis of Ambroxan by DMC chemistry[a]

#	Base (eq. mol)	DMC (eq. mol)	Ambroxan (% isolated)	Carboxymethyl derivative (% isolated)
1	*t*-BuOK (2)	30	95	0
2	*t*-BuOK (1)	30	66	23
3	*t*-BuOK (2)	10	75	0
4	*t*-BuOK (2)	5	91	0
5	NaOMe (2)	5	86	0
6[b]	*t*-BuOK (2)	3	90	0
7	K_2CO_3 (2)	30	0	90

[a] Reaction Conditions: Amberlyn Diol 1.0 gr (1 mol. ratio); Temperature 90° C; Reaction time 3 h; conversion of starting material 100%.; [b] THF used as solvent

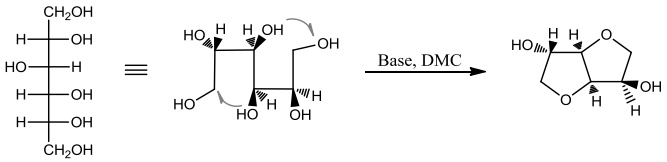
The amount of DMC used can be reduced without affecting the outcome of the cyclisation reaction (entries 3-4 Table 4). Besides, when sodium methoxide was employed instead of potassium *tert*-butoxide, the cyclisation reaction resulted equally efficient (entry 5, Table 4).

The cyclisation reaction was also performed using THF as solvent as this can aid reducing the amount of DMC up to 3 molar equivalents (entry 6, Table 4) without affecting the quantitative formation of ambroxan. Most importantly, the novel synthetic methodology, showed not only high selectivity and high yield, but both proton NMR and optical measurements of the compound demonstrated that the reaction maintains the chiral integrity of the starting material.

The mechanism of the amberlyn diol cyclisation most probably follows two-step reaction. First, the monocarboxy methyl derivative of the starting diol is formed (Scheme 3), thus the tertiary alcohol functionality undergoes an *intramolecular* nucleophilic attack leading to ambroxan. This was confirmed by the fact that the monocarboxy methyl derivative was the only by-product observed in all the above-mentioned reactions. This compound was synthesized in quantitative yield using potassium carbonate as a base in the presence of an excess of DMC (entry 7, Table 4).

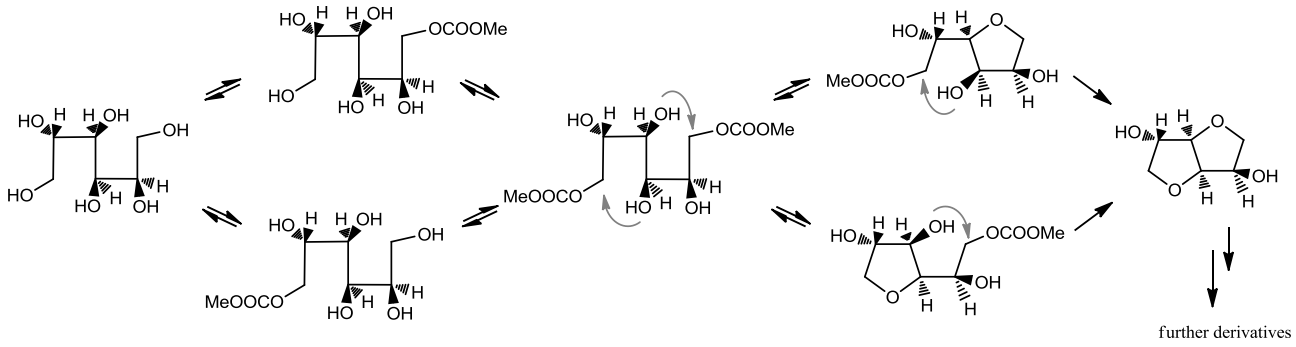
Cyclic ethers in the form of anhydro sugar alcohols have also many applications in industry, in particular in food industry and in the pharmaceutical field and they are also employed as monomers for polymers and copolymers. Such anhydro sugar alcohols are derivatives of mannitol, iditol, and sorbitol. In particular, isosorbide, the anhydro sugar alcohol derived from sorbitol, is useful as a monomer in the manufacture of many derivatives as polymers and copolymers, especially polyester polymers and copolymers.

Isosorbide is industrially synthesized by dehydration of sorbitol by an acid-catalyzed reaction that leads to different anhydro-compounds, but also to polymer-like products.[23] Noteworthy, D-sorbitol is a more complex starting material to be used in cyclisation reaction *via* DMC chemistry, since the mechanism leading to the formation of this anhydro sugar trough *intramolecular* reaction requires a one-pot double-cyclisation without affecting the numerous chiral centres of the molecules (Scheme 4).



Scheme 4. Synthesis of isosorbide.

Table 5 shows the results obtained. In particular, when D-sorbitol was reacted with 2 molar equivalent of base and an excess of DMC, isosorbide was isolated in relatively low yield (entry 1, Table 5). In reality isosorbide, formed readily, but once formed, it reacts with the excess of DMC leading to the formation of its mono and dicarboxymethyl and methyl derivatives.[24]



Scheme 5. Possible reaction mechanism for isosorbide synthesis by DMC chemistry; primary alcohol functionalities react first.

Table 5. Synthesis of isosorbide by DMC chemistry[a]

#	Solv.	NaOMe	DMC (eq. mol)	Time (h)	Isosorbide (% isolated)
1	None	2	20	8	16
2	MeOH	2	4	4	58 (46)
3	MeOH	2	4	8	80 (64)
4	MeOH	4	8	8	98 (76)

[a] Reaction Conditions: D-Sorbitol 2 grams (1 mol ratio); reflux temperature; Conversion of the starting material 100%; [b] isolated

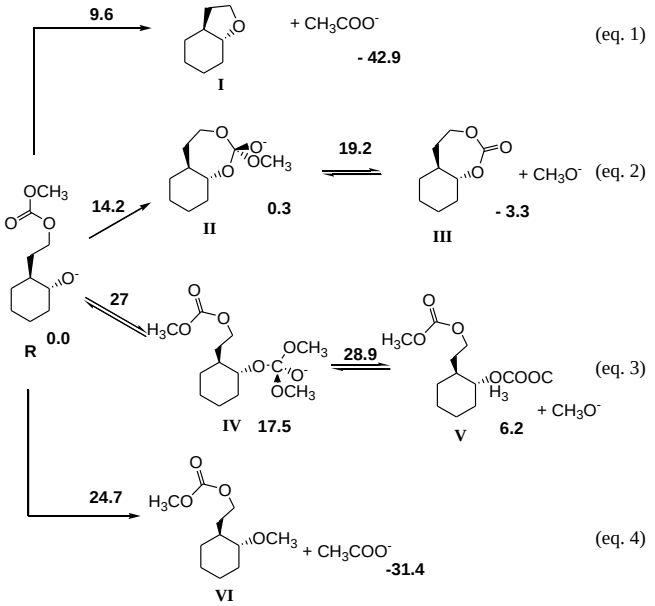
However, when methanol was used as a solvent (entries 2-4, Table 5), the reaction equilibrium is shifted towards isosorbide preventing the formation of carboxymethyl and derivatives. Besides, using DMC only as reagent and not as solvent should also reduce the formation of methyl derivatives. Thus, D-sorbitol was reacted with DMC (4 molar equivalent) in the presence of an excess of methanol; the results obtained are reported in entries 2-4 (Table 5). In these conditions, isosorbide showed to form in high yield (76% isolated). The excess of NaOMe required (entry 4, Table 5) is justified by the fact that the formation of isosorbide requires a one-pot double ciclysation (2 molar equivalent of base for each ether cylic formed). Most probably the mechanism of the reaction involves first the carboxymethylation of the primary alcohol of D-sorbitol, which is more reactive than secondary alcohol, and then an *intramolecular* cyclisation (Scheme 5). Although most probably the reaction proceeds trough the formation of a monocyclic derivative of D-sorbitol (Scheme 5), this compounds was never isolated due to the fast conversion into isosorbide. Noteworthy, comparing the NMR spectra of the synthesized isosorbide and of the commercially available compound confirmed that the chiral centres were not affected by the reaction.

Ab-initio Calculations

In all the investigated reactions DMC acts as ambident elecrophile. First one alcoholic functionality of the substrate reacts with the carbonyl group of the DMC (Hard-Hard interaction)[16] forming the carboxymethyl derivative; thus, the second alcoholic functionality attacks the alkyl chain of the so-formed alkyl carbonate. According to the HSAB theory of Pearson the latter should be a Soft-Soft interaction.[17]

However, the results herein reported show that this interpretation is not well appropriate for the proposed case study as the alcohol moiety is an hard nucleophile.

This discrepancy with the expected results clearly indicates that in this case the hard/soft character of the nucleophile does not have a decisive influence on the reaction outcome. Thus, computational calculations are required in order to have a better insight in terms of the energy barriers involved in the cyclisation reaction.



Scheme 6. Competing reaction pathways and related energy barriers. Free energy differences (ΔG) in Kcal mol-1 at T=388 K in the solvent DMC are reported. All energy values are refereed to the model compound R.

In this prospect, the computational investigation took into account the competition between four processes, namely two cyclisation reactions and two bimolecular reactions involving DMC (Scheme 6). Free energies were assessed in the gas phase and in DMC solution. In detail, the molecule (1*R*, 2*S*)-2-hydroxyethyl cyclohexanol **R**, selected as representative model for this investigation, can undergo two competitive cyclisations to form either a 5-membered ring *via* an *intramolecular* "S_N2-like" reaction (eq. 1, Scheme 6), or a 7-membered ring *via*

intramolecular S_NAc reaction (eq. 2, Scheme 6). On the other hand, two *intermolecular* nucleophilic substitutions can also take place: an acylic one (S_NAc, eq. 3) and an aliphatic one (S_N2, eq. 4), due to the attack of the alcoholate **R** on a DMC molecule.

Figure 2. Free Energy profile in DMC solution, at 388 K.

Free energy data obtained in solution at T=388 K (ΔG_{sol}) demonstrated that methylation of the substrate leads to derivative **VI** (eq. 4), a quite stable product. However, the free energy G barrier associated to the methylation reaction is rather high (Scheme 6 and Table 1 in Supporting Information).

The carboxymethylation of the substrate (eq. 3), on the other hand, leads to a high energy tetrahedral intermediate (**IV**) through a high free energy barrier. The subsequent elimination of a methoxyl group to form V has a modest G barrier, while the dissociation limit is slightly above the reactants. Because its initial high free energy barrier (transition structure, TS **R-IV**), this channel is not discussed afterward.

On the other hand, the cyclisation reactions require a lower free energy barriers. In particular, the energy barrier leading to **I** (S_N2), is quite low and the reaction is very exoergic. The other possible cyclisation reaction (S_NAc) forms a tetrahedral intermediate **II**, almost isoergic with the reactant. However, this pathway is overall energetically more demanding. Moreover, the formation of the 7-membered ring **II** is reversible, and the back reaction (TS **II-R**) has lower barrier than the reaction leading to the cyclic **III** (TS II-III).

By comparing the four relevant transition structures (TS **R-VI**, TS **R-IV**, TS **R-I** and TS **R-II**), it was possible to investigate which effect contributes more to the barrier heights. Considering only the potential energy E+zpe (Supporting Information), TS **R-IV** (carboxymethylation) would have the lowest barrier compared to the other pathways. However, in solution TS **R-IV** has the highest G barrier.

This is due to the combination of two factors: entropic effect and solvation. Thus, TS **R-IV** is characterized by a large entropy decrease $\Delta S^{\neq}$ = -44.2 cal mol^{-1} K^{-1}, because is a bimolecular reaction, and as result, the free energy barrier in the gas phase rises significantly respect to the potential energy E+zpe.

Moreover, the solvation free energy is also unfavorable (see Table 1 in the Supporting Information). In the gas phase, according to the hard-soft acid base theory, TS **R-IV** would have a lower energy barrier (hard-hard interaction) than TS **R-VI** (hard-soft interaction). However, since the entropy and solvation effects dominate, in solution the free energy barrier of TS **R-IV** becomes higher than that of TS **R-VI**.

The cyclisation reactions show very similar solvation effects, but the activation entropy for TS **R-I** is only $\Delta S^{\neq}$ = -2.1 cal mol^{-1} K^{-1}. For TS **R-II**, it is larger, $\Delta S^{\neq}$ = -13.1 cal mol^{-1} K^{-1}, probably due to a higher ring strain in the 7-member ring, and the release of the carboxymethyl moiety.

In conclusion, the entropic effect is the main responsible for the lower barrier of TS **R-I** compared with the others, and solvation effect contributes to accentuate the barrier differences. Temperature effects were also taken into account, by performing free energy calculations at higher temperature (458 K). However, only small changes in the relative energies (at most 2 kcal mol^{-1}) were observed, and they do not affect the mechanistic picture discussed above (Supporting Information).

Conclusion

The reaction of 1,4-diols with DMC in the presence of a base and in mild condition led to the corresponding cyclic ethers in high yield and short reaction time. It was possible to synthesize distinctive cyclic ethers and industrially relevant compounds such as (-)-norlabdane oxide and isosorbide from their related 1,4-diols in quantitative yield.

Comparing this reaction with a chlorine based procedure (path a) and b), Scheme 2), the DMC-mediated pathway is quantitative, occurs in one step, do not require any chlorine-based chemical or strong acid and do not produce any chlorinated waste material. The synthesis herein proposed is of general application, as resulted effective for aliphatic and aromatic diols incorporating several functionalities (primary, secondary, tertiary, allylic, phenolic). However, this procedure requires that at least a primary alcohol functionality is present in the starting diol for the cyclisation to take place. Most importantly, this synthesis demonstrated to maintain the chiral integrity of the substrate.

A computational investigation confirmed that cyclisation to form the 5-member ring is indeed the preferred pathway over 7-member ring closure and, even more sharply, over two different alcoholate attacks onto DMC. Indeed, the fact that the last two reactions are unfavourable can be traced back to a larger entropy reduction that occurs at the relevant transition states. Then, solvent effects enhance the differences among the energy barriers with respect to the gas phase. Temperature, on the other hand, has only a small effect on free energy barriers.

Noteworthy, the herein reported synthetic pathway represents a good step forward towards a “no-chlorine-in-the making” one-pot environmental friendly method of synthesizing heterocyclic compounds. In order to pursuit the best modus operandi and to achieve an industrially appealing procedure, these cyclisations reactions are at the moment investigated in continuous flow apparatus.

Experimental Section

Proton Nuclear Magnetic Resonance spectra (^{1}H NMR) were recorded at 300 MHz. The chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm) and regarding the tetramethylsilane (TMS). Data are reported as follows: chemical shift, integration multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, sext = sextet, sept = septet, br = board, m = multiplet) and coupling constants (Hz). Carbon Nuclear Magnetic Resonance spectra (^{13}C NMR) were recorded at 75 MHz . Chemical shift are reported in ppm from the solvent resonance as internal standard ($CDCl_3$: 77 ppm). Analytical chromatography (TLC) was performed on precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on silica gel 60Å grade 9385 (230-400 mesh). GC-MS analysis were performed on a Gas Chromatograph equipped with HP-5MS 30 m x 0.25 mm column and Network Mass selective detector. All the reaction were performed using dimethyl carbonate dried on molecular sieves 4Å. All the bases and catalysts were used without further purification. The other simple chemicals were used as such.

Synthesis of tetrahydrofuran (Example from Table 1, entry 1)

In a round bottom flask equipped with a dephlegmator 1,4-butane diol 2.0 g (22.2 mmol, 1 mol. equiv.), DMC 40 g (44,4 mmol, 20 mol. equiv.) and sodium methoxide 1,8 g (33.3 mmol, 1.5 mol. equiv.) were heated at reflux while stirring continuously under nitrogen atmosphere. The reaction was followed by NMR and GC-MS analysis until complete disappearance of the starting material. According to GS-MS analysis and NMR spectroscopy tetrahydrofuran was formed in 12% yield and the dicarboxymethyl derivative of the 1,4-diols namely butane-1,4-diyl dimethyl dicarbonate in 88% yield . The solution was then filtered and the solvent removed by evaporation to isolate the dimethylcarbonate derivative as pure.

Butane-1,4-diyl dimethyl dicarbonate: as white crystals in 75 % yield; HRMS for $C_8H_{14}O_6$: calculated $[M+Na]^+$ 229.0683 g.mol-1, found $[M+Na]^+$ 229,0685; m.p.: 61-62.3 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ = 4.12-4.20 (m, 4H), 3.81 (s, 6H), 1.74-1.82 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 155.6, 67.2, 54.6, 25.0.

Synthesis of 2-methyl tetrahydrofuran (Example from Table 2, entry 1)

In a round bottom flask equipped with a dephlegmator 1,4-pentadiol 1.0 g (9.6 mmol, 1 mol. equiv.), DMC 17.3 g (192 mmol, 20 mol. equiv.) and sodium methoxide 0,77 g (14.4 mmol, 1.5 mol. equiv.) were heated at reflux while stirring continuously under nitrogen atmosphere. The reaction was followed by NMR and GC-MS until equilibrium was reached (2 hours). The solution was then filtered and the solvent removed by evaporation. Column chromatography using DCM/methanol (95/5) as elution mixture allowed the isolation of the reaction intermediates.

Dimethyl pentane-1,4-diyl dicarbonate: as a light colored oil in 60 % yield; HRMS for $C_9H_{16}O_6$: calculated $[M+Na]^+$ = 243.0845 g.mol-1, found $[M+Na]^+$ = 243.0856 g.mol-1; ^{1}H NMR (300MHz, $CDCl_3$) δ = 4.71-4.9 (m, 1H), 4.28-4.14 (m, 2H), 3.8 (s, 3H), 3.78 (s, 3H), 1.9-1.5 (m, 4H), 1.28 (d, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 155.6, 155.2, 74.5, 67.5, 54.6, 54.4, 31.9, 24.5, 19.7.

Synthesis of 2,5-dimethyl tetrahydrofuran (Example from Table 2, entry 5)

In a round bottom flask equipped with a dephlegmator 2,5-hexandiol (mixture of isomers) 0.5 g (4.2 mmol, 1 mol. equiv.), DMC 7.5 g (83 mmol, 20 mol. equiv.) and sodium methoxide 0,34 g (6.3 mmol, 1.5 mol. equiv.) were heated at reflux while stirring continuously under nitrogen atmosphere. The reaction was followed by NMR and GC-MS until equilibrium was reached (6 hours). The solution was then filtered and the solvent removed by evaporation. Column chromatography using DCM/methanol (99/1) as elution mixture allowed the isolation of the reaction intermediates.

Hexane-2,5-diyl dimethyl dicarbonate (mixture of isomers): as a light colored oil in 64 % yield; HRMS for $C_{10}H_{18}O_6$: calculated $[M+Na]^+$ = 257,1001 g.mol-1; found $[M+Na]^+$ = 257,1035 g.mol-1; ^{1}H NMR (300MHz, $CDCl_3$) δ = 4.6-4.8 (m, 2H), 3.8 (s, 6H), 1.7-1.5 (m, 4H), 1.28 (d, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 155.2, 74.9, 75.6, 54.4, 31.6, 31.2, 19.8, 19.7.

Synthesis of 2,5-dihydrofuran (Example from Table 2, entry 7)

In a round bottom flask equipped with a dephlegmator cis-but-2-ene-1,4-diol 1.0 g (11.3 mmol, 1 mol. equiv.), DMC 4.1 g (45,45 mmol, 4 mol. equiv.) and sodium methoxide 0,03 g (0.56 mmol, 0.05 mol. equiv.) were heated at reflux while stirring continuously under nitrogen atmosphere. The reaction was followed by NMR until complete disappearance of the starting material. The solution was then filtered and the solvent removed by evaporation. Column chromatography using DCM/methanol (98/2) as elution mixture allowed the isolation of the reaction intermediates.

(Z)-4-Hydroxybut-2-enyl methyl carbonate:[25] as transparent oil in 24 % yield; GC-MS for $C_6H_{10}O_4$ M = 146.06 g.mol-1 ^{1}H NMR (300MHz, $CDCl_3$) δ = 5.93-5.50 (m, 2H), 4.67 (d, 2H), 4.21 (d, 2H), 3.69 (s, 3H), 2.88 (bs, 1H,OH); ^{13}C NMR (75MHz, $CDCl_3$) δ = 156.9, 133.9, 124.5, 63.3, 58.0, 54.7. Analysis conducted on the isolated product were consistent with the one conducted reported in the reference.

(Z)-2-Butenylene dimethyl dicarbonate:[26] as light yellow oil in 31 % yield; GC-MS for $C_8H_{12}O_6$; M = 204.06 g.mol-1; ^{1}H NMR (300MHz, $CDCl_3$) δ = 5.83 (t, 2H), 4.73 (d, 2H), 3.81 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 156.7, 127.8, 63.0, 58.0, 54.7. Analysis conducted on the isolated product were consistent with the one conducted reported in the reference.

Synthesis of 2,3-dihydrobenzofuran (Example from Table 3, entry 1)

In a round bottom flask equipped with a dephlegmator and 2-hydroxyethyl phenol 1.0 g (7.24 mmol, 1 mol. equiv.), DMC 6.5 g (72,4 mmol, 10 mol. equiv.) and sodium methoxide 0,19 g (3.6 mmol, 0,5 mol. equiv.) were heated at reflux while stirring continuously under nitrogen atmosphere. After 7 hours the reaction was stopped, cooled at room temperature and diethyl ether was added to the mixture. The reaction mixture was then filtrated over Gooch n°4 and the solvent evaporated. The solvent was distilled under vacuum to recover the crude reaction mixture that was then analyzed by ^{1}H-NMR in order to determine the product ratio. Finally gradient elution chromatography using first DCM/Cyclohexane (9/1) (for the isolation of the cyclic ether) and then DCM/MeOH (97/3) (for the isolation of the carbonate derivative) on silica gel allowed all of the product to be isolated as pure compounds:

2,3-Dihydrobenzofuran: as transparent liquid in 55% yield; C_8H_8O; M = 120,06 g.mol-1; ^{1}H NMR (300MHz, $CDCl_3$) δ = 7.20 (d, 1H), 7.15 (t, 1H), 6.90-6.77 (m, 2H), 4.6 (t, 2H), 3.25 (t, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 159.9, 127.8, 126.7, 124.8, 120.2, 70.9, 29.6.

2-Hydroxyphenethyl methyl carbonate:[27] as light yellow oil in 29 % yield; GC-MS for $C_{10}H_{12}O_4$; M = 196.07 g.mol-1; m.p.: 68.5-68.8 °C ^{1}H NMR (300MHz, $CDCl_3$) δ = 7.20-7.08 (m, 2H), 6.92-6.80 (m, 2H), 5.95 (s, 1H, OH), 4.37 (t, 2H), 3.81 (s, 3H), 3.05 (t, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 156.9, 153.4, 130.9, 128.2, 120.6, 67.6, 54.8, 30.0.

Synthesis of phthalan (Example from Table 3, entry 5)

In a round bottom flask equipped with a dephlegmator dihydroxymethyl benzene 1.0 g (7.24 mmol, 1 mol. equiv.), DMC 6.5 g (72,4 mmol, 10 mol. equiv.) and sodium methoxide 0,19 g (3.6 mmol, 0,5 mol. equiv.) were heated at reflux while stirring continuously under nitrogen atmosphere. After 7 hours the reaction was stopped, cooled at room temperature and diethyl ether was added to the mixture. The reaction mixture was then filtrated over Gooch n°4 and the solvent evaporated. The solvent was distilled under vacuum to recover the crude reaction mixture that was then analyzed by ^{1}H-NMR in order to determine the product ratio. Finally gradient elution chromatography using first DCM/Cyclohexane (9/1) (for the isolation of the cyclic ether) and then DCM/MeOH (97/3) (for the isolation of the carbonate derivative) on silica gel allowed all of the product to be isolated as pure compounds:

Phthalan: as transparent liquid in 30% yield; Analysis conducted on the isolated product were consistent with the one obtained by commercially available compound.

1,2-Phenylenebis(methylene) bismethyl dicarbonate: as light yellow liquid in 41% yield; HRMS for $C_{12}H_{14}O_6$: calculated $[M+Na]^+$ = 277,0688 g.mol-1; found $[M+Na]^+$ = 277,0722; m.p.: 51-51.5 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ = 7.48-7.30 (m, 4H), 5.27 (s, 4H), 3.77 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 155.4, 133.8, 129.8, 128.9, 66.9, 54.8.

Synthesis of (-)-norlabdane (ambroxan) (Example from Table 4, entry 1)

In a round bottom flask equipped with a dephlegmator amberlyn diol 1.0 g (3.93 mmol, 1 mol. equiv.), DMC 10.6 g (118,00 mmol, 30 mol. equiv.) and potassium *tert*-butoxide 0,88 g (7.87 mmol, 2 mol. equiv.) were heated at reflux while stirring continuously under nitrogen atmosphere. The reaction was followed by TLC until complete disappearance of the starting material. The solution was then filtered and DMC removed by evaporation to recover the pure ambroxan as a white crystalline powder. Purer samples of ambroxan could be obtained either by crystallization using 2-propanol or by column chromatography (if needed) using DCM/methanol (98/2) as elution mixture.

(-)-Norlabdane:[21] as white crystals in 95 % yield; $C_{16}H_{28}O$; M = 236.21 g.mol-1; m.p.: 69.1-70 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ = 0.84 (s, 3H), 0.85 (s, 3H), 0.89 (s, 3H), 0.91-1.09 (m, 2H), 1.12 (s, 3H), 1.36-1.51 (m, 7H), 6.92-6.80 (m, 2H), 5.95 (s, 1H, OH), 4.37 (t, 2H), 3.81 (s, 3H), 3.05 (t, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 79.8, 64.8, 60.0, 57.1, 42.3, 39.8, 39.6, 36.0, 33.5, 32.9, 22.5, 21.0, 20.5, 18.3, 14.9. Analysis conducted on the isolated product were consistent with the one reported in the literature.[17,21]

Monocarboxymethyl derivative of Amberlyn diol (entry 7, Table 4): This compounds was isolated as pure by column chromatography (DCM:EtOAc 92:8) as yellow oil in 90 % yield. Analysis conducted on the isolated product were consistent with the one reported in the references.[21]

Synthesis of isosorbide (Example from Table 5, entry 4)

In a round bottom flask equipped with a D-sorbitol 2.0 g (10.98 mmol, 1 mol. equiv.), DMC 8 g (87,88 mmol, 8 mol. equiv.), sodium methoxide 2,4 g (43.42 mmol, 4 mol. equiv.) and methanol (30 ml) were heated at reflux while stirring continuously under nitrogen atmosphere. After 8 hours the reaction was stopped, cooled at room temperature and diethyl ether was added to the mixture. The reaction mixture was then filtrated over Gooch n°4 and the solvent evaporated. The solvent was distilled under vacuum to recover the crude reaction mixture. Finally gradient elution chromatography using first DCM/methanol (9/1) on silica gel allowed the product to be isolated as pure:

Isosorbide: as light yellow crystals in 75% yield; Analysis conducted on the isolated product were consistent with the one conducted on a pure sample of the commercially available compound.

Theoretical Calculations

The potential energy surface (PES) was studied by Density Functional Theory (DFT), making use of the B3LYP functional.[28] The 6-311G(d) polarized basis set[29] was used in the geometry optimizations. The nature of each critical point (reactant, product, intermediate, or transition structure) was determined by harmonic vibrational analysis. To assess an estimate of the energy barriers, single-point energy calculations were carried out by using the aug-cc-pVTZ Dunning's correlation consisten basis sets.[30] The final Free Energies were calculated by combining the 6-311G(d) thermochemical corrections with the single-point DFT/aug-cc-pVTZ energies.

Solvent effect was taken into account via the Self Consistent Reaction Field (SCRF) method, using the IEF-PCM model.[31] Single point IEF-PCM energies calculations were carried out at the DFT/aug-cc-pVTZ level. Chemico-physical properties were used to parametrize the solvent dimethyl carbonate (DMC), which is defined as "non-standard" in the Gaussian 03 program, by which all calculations were carried out.[32]

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Keywords: Cyclisation · Dimethyl carbonate · Cyclic ethers · Halogen-free · Ab-initio calculations

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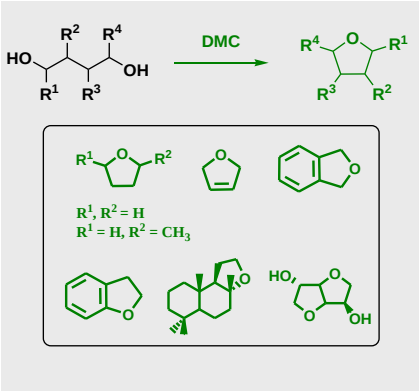
Entry for the Table of Contents

FULL PAPER

The high yielding green synthesis of distinctive and industrially relevant 5-membered cyclic ethers has been achieved starting from 1,4-diols with dimethyl carbonate in the presence of a base. The reaction mechanism was investigated. Computational studies demonstrated that the cyclisation reaction is due to the dominant role of the entropic term in the reaction ΔG.



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5-Membered cyclic ethers by reaction of 1,4-diols with dimethyl carbonate