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Synthesis of 6-membered cyclic carbonates from 1,3-diols and low CO_2 pressure: a novel mild strategy to replace phosgene reagents†

Georgina L. Gregory, Marion Ulmann and Antoine Buchard*

Low pressure carbon dioxide is used as the carbonation agent in a simple, safe and efficient procedure for the synthesis of 6-membered cyclic carbonates from 1,3-diols. Using readily available reagents and proceeding at room temperature, this route offers a novel mild alternative to phosgene derivatives.

Unlike aromatic polycarbonates, aliphatic polycarbonates (APCs) have been little explored commercially. However, their low toxicity and biodegradability make them excellent candidates for biomedical applications.[1] Recently, they have also been investigated as thermoplastics,[2] binders for photovoltaics,[3] polymer electrolytes[4] and adhesives.[5]

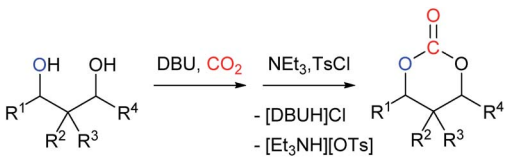
Part of this renewed attention stems from the possibility to obtain APCs *via* the copolymerisation of CO_2 and epoxides,[6] an attractive reaction which uses an abundant and virtually free source of carbon, but is limited by the scope of usable epoxides. APCs can also be synthesised by polycondensation of diols with phosgene derivatives or dialkyl carbonates,[7] but the control of the polymer molecular weight is highly sensitive to the reaction conditions. Hence, Ring-Opening Polymerisation (ROP) of cyclic carbonates has become the method of choice for APC synthesis,[1b,8] as the development of ROP catalysts[9] has enabled controlled polymerisation of highly functionalised monomers[10] under mild conditions (usually 6-, 7-,[11] or strained 5-membered rings[12]).

A common preparation of cyclic carbonate monomers involves the transesterification of diols with phosgene,[8,13] a toxic reagent synthesised from CO and Cl_2 in an energy intensive process. Nevertheless, phosgene is still widely employed due to its efficiency and the lack of a more versatile and sustainable alternative. Safer phosgene derivatives[14] include di-*tert*-butyl dicarbonate,[15] 1,1′-carbonyldiimidazole,[16] and aromatic carbonates,[17] but these reagents all derive from phosgene, and can lead to unwanted side reactions, low reactivity and difficult workups.

Alternative methods, such as the Pd-catalysed oxidative carbonylation of diols using CO pressure,[18] or the catalytic coupling of CO_2 with oxetanes,[19] have also been reported. The latter however, is limited by the availability of oxetanes.[20] Transesterification of diols with urea, industrially produced from CO_2, is also described but with moderate success.[21]

Using CO_2 as a C1-carbonation agent is an attractive goal for phosgene related emissions mitigation and direct CO_2 utilisation. The direct coupling of CO_2 with diols, where water is the sole by-product, would be an attractive process. However, the reaction is generally not kinetically and thermodynamically favoured. Therefore, a catalyst and an efficient stoichiometric dehydrating strategy (*e.g.* nitriles, zeolites, orthoesters, or Mitsunobu reagents) are necessary for the reaction to proceed.[22] Despite recent advances, such as the use of CeO_2 catalyst in tandem with a large excess of 2-cyanopyridine as a dehydrating agent,[23] or the *in situ* introduction of a leaving group based on dibromomethane,[24] high CO_2 pressures (10–50 bar) and high temperatures (70–140 °C) are still required, particularly for the synthesis of 6-membered rings.

Herein, we report a safe and efficient one-pot procedure for the synthesis of 6-membered cyclic carbonates directly from 1,3-diols, which uses CO_2 as the carbonation agent instead of phosgene derivatives. This methodology proceeds at room



Scheme 1 Strategy for the synthesis of cyclic carbonate from 1,3-diols and CO_2 (R^1–R^4 are the various substituents of 1,3-diols used, see Table 2).

Department of Chemistry, Centre for Sustainable Chemical Technologies, University of Bath, Claverton Down, Bath BA2 7AY, UK. E-mail: a.buchard@bath.ac.uk; Tel: +44 (0) 1225 386122

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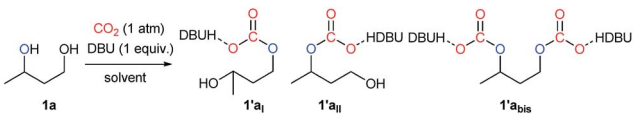
temperature, needs only 1 atm. of CO_2 and common lab reagents (Scheme 1), and does not require the preliminary preparation of oxetanes or chloroalcohols.[25]

In 2005, Jessop and coworkers reported the reversible carbonation of alcohols with CO_2 promoted by 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU).[26] The conversion was later found to depend on the choice of solvent with almost full conversion of 1-hexanol being achieved in $CDCl_3$.[27] Inspired by these reports, we investigated the selective mono-insertion of CO_2 into one alcohol moiety of 1,3-diols in various solvents. The slow addition of DBU under 1 atm of CO_2 to solutions of (±)-1,3-butanediol (**1a**) was monitored and the conversion to alkyl carbonate species assessed by ^{1}H NMR (Table 1). Regardless of the solvent used, the carbonation of **1a** by CO_2 proceeded quickly at low pressure and room temperature, with good selectivity towards the mono-insertion products (*ca.* 90% of products). A slight preference for the primary alcohol moiety was also observed, in agreement with DFT calculations (see ESI Fig. S4†). In neat diol, the conversion was limited by the increased viscosity upon CO_2 insertion (Table 1, Entry 1), but even in solution and with the addition of ionic liquid $bmimPF_6$, as used by Lim *et al.* (Table 1, Entry 5),[24] full conversion of **1a** was not observed with only one DBU equivalent. Apolar toluene-d_8 gave less conversion than more polar solvents, whereas more dicarbonated product was obtained in acetonitrile-d_3 (Table 1, Entry 2 and 4). Overall, optimal results were obtained in $CDCl_3$, and despite it not being a desirable solvent which should be replaced in the future, chloroform was used in the rest of our study. Addition of DBU at low temperature resulted in no further improvement in mono-insertion selectivity (Table 1, Entry 7), while increasing the temperature promoted decarboxylation. A lower concentration of diol slightly decreased the amount of disubstituted product (Table 1, Entry 6) but did not affect the global conversion. The use of stronger base 1,5,7-diazabicyclo[4.3.0]-undec-7ene (TBD) in place of DBU resulted in less conversion, which is attributed to an increased sensitivity to moisture (Table 1, Entry 8). The use of triethylamine resulted in no carbonation of **1a**.

Table 1 Reaction of 1,3-butanediol **1a** with DBU under 1 atm of CO_2[a]



Entry	Solvent	T (°C)	[**1a**] (M)	Conv. into carbonated products[b] (%) Total	**1′a$_{I+II}$**	**1′a$_I$**	**1′a$_{II}$**	**1′a$_{bis}$**
1	Neat	25	n/a	47	44	30	14	3
2	C_7D_8	25	1.7	60	56	37	19	4
3	$CDCl_3$	25	1.7	78	69	46	23	9
4	CD_3CN	25	1.7	73	58	40	18	15
5[c]	$CDCl_3$	25	1.7	69	52	35	17	17
6	$CDCl_3$	25	0.1	78	73	49	24	5
7[d]	$CDCl_3$	−78	1.7	77	68	45	23	9
8[e]	$CDCl_3$	25	1.7	62	56	37	19	6
9[f]	$CDCl_3$	25	1.7	>99	57	40	17	43

[a] Reactions conditions: diol (5.6 mmol, 1.7 M), DBU (5.6 mmol), room temperature, CO_2 (1 atm), 2 h (saturation). [b] Based on diol conversion and determined by relative integration of methine signals in ^{1}H NMR (*e.g.* 4.64 ppm for **1′a$_{II}$**/see ESI Fig. S1–S3). [c] Addition of 1-butyl-3-methylimidazolium hexafluorophosphate ($bmimPF_6$, 5.6 mmol); [diol] = 0.4 M. [d] Addition of DBU at $T = -78$ °C then rt. [e] 1 equiv. of TBD was used instead of DBU. [f] 3 equiv. of DBU were used.

Further DFT calculations showed that the direct coupling of **1a** and CO_2 to form cyclic carbonate **2a** is slightly thermodynamically disfavoured ($\Delta\Delta G = +3.0$ kcal mol^{-1}). Following the DBU-aided insertion of CO_2, the activation barriers are then too high for the cyclisation of **1′a$_I$** (or **1′a$_{II}$**) to proceed under mild conditions (61.1 and 42.2 kcal mol^{-1} *via* an S_N2 or addition/elimination mechanism, respectively) (see Fig. S4†). An *in situ* leaving group strategy was thus applied experimentally to overcome the kinetic as well as the thermodynamic limitation of the reaction. After the selective mono-insertion of CO_2 into **1a** in $CDCl_3$ at low concentration, 1 equivalent of tosyl chloride and triethylamine were added to the reaction mixture and stirred at room temperature overnight. Rapidly, the cyclic carbonate **2a** was detected by ^{1}H NMR (addition of triethylamine alone did not result in any product). The pure product was later isolated by column chromatography in a 44% yield, *i.e.* 60% conversion based on the mono-CO_2 inserted products (Table 2‡, Entry 1). A higher concentration of diol (1.7 M), despite being slightly detrimental to the first step of the procedure, proved to lead to a higher isolated yield of cyclic carbonate (68%, *i.e.* 99% conversion based on CO_2 mono-insertion, Table 2, Entry 2). This compares well with the traditional phosgene-based method (50%)[28] as well as oxidative carbonylation methods (45%).[18a] The procedure was found to be robust: CO_2 from sublimed dry ice could be used and yielded cyclic carbonate **2a**, albeit in lower yield (48%, Table 2, Entry 3). The reaction also proceeded without solvent (30% yield). Investigation into the scope of the procedure was carried out with various 1,3-diols. The cyclisation step proceeded efficiently from the CO_2-mono insertion products and all cyclic carbonates were isolated in moderate yields (Table 2), comparative with phosgene-based and alternative methods. For example, the isolation of **2d** from 2,2-dimethyl-1,3-propanediol (53%, Table 2, Entry 8) was previously reported using phosgene derivatives (60%),[29] oxidative carbonylation (50%),[18b] and metal free cyclisation (50%).[24] *O*-isopropylidene-xylose was also successfully transformed, though isolation proved challenging (11%, Table 2, Entry 12).

As cyclisation happens readily, reaction intermediates could not be isolated, but DFT calculations on model compound (***R***)-**1a** and additional experiments with optically active diols were carried out to investigate the reaction mechanism. After insertion of CO_2, tosylation can occur at the carbonate or at the remaining alcohol group, so that cyclisation proceeds *via* either an addition/elimination or a S_N2 pathway, leading to retention or inversion of stereochemistry (see Scheme 2). However, the exclusive formation and isolation of (*R*,*R*)-cyclic carbonate **2b** from (*R*,*R*)-2,4-pentanediol, as well as the optical activities of the cyclic carbonates obtained from enantiopure (*R*) and (*S*)-1,3-butanediol (Table 2, Entries 4–6),[30] both indicated an addition/

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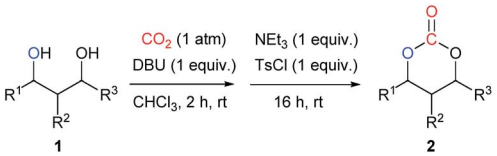
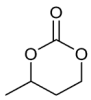
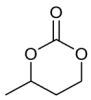
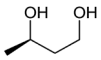
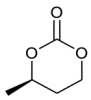
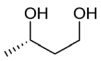
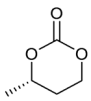
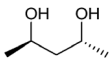
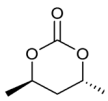
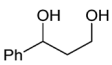
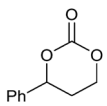
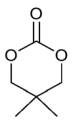
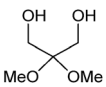
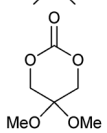
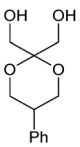
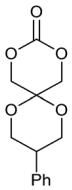
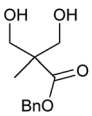
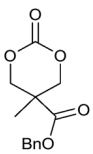
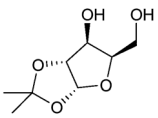
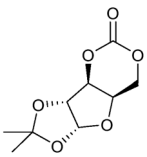
Table 2 Synthesis of various cyclic carbonates from 1,3-diols and CO_2



Entry	Substrate		% Yield[a] [conv.$_{1'\rightarrow 2}$][b]	Product	
1[c]		**1a**	44 [60]		**2a**
2		**1a**	68 [99]		**2a**
3[d]		**1a**	48		**2a**
4		(***R***)-**1a**	68		(***R***)-**2a**
5		(***S***)-**1a**	70		(***S***)-**2a**
6		**1b**	53 [71]		**2b**
7		**1c**	55 [96]		**2c**
8		**1d**	53 [82]		**2d**
9		**1e**	49 [78]		**2e**
10		**1f**	46 [71]		**2f**
11		**1g**	41 [70]		**2g**
12		**1h**	11		**2h**

[a] Isolated yield based on starting diol. [b] Spectroscopic conversion of CO_2 mono-insertion products **1′** into cyclic carbonate **2**. [c] [Diol] = 0.1 M. [d] CO_2 from the sublimation of dry ice was used.

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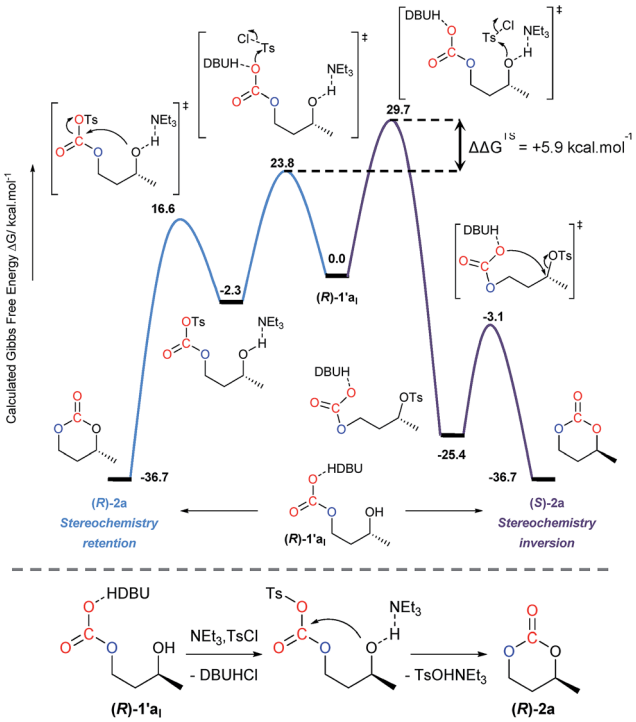

Scheme 2 DFT computed pathways (6-31+G(d)/rωb97xD/cpcm = chloroform/298 K protocol) and mechanism for the cyclisation of **1′a**$_I$ to **2a**, as supported by experiments and calculations (see ESI Fig. S4† for full details of calculations).

elimination pathway, with no racemisation or inversion of stereochemistry being observed.

DFT calculations supported these conclusions and gave supplementary insight into the selectivity. Scheme 2 illustrates the computed pathways for the cyclisation of **1′a**$_I$ to **2a**. As expected with a tosyl leaving group, the formation of the cyclic carbonate is strongly favoured ($\Delta\Delta G = -36.7$ kcal mol^{-1}). Additionally, the activation energy barriers for both the nucleophilic addition/elimination and S_N2 ring-closing mechanisms are similar and low enough to happen at room temperature ($\Delta\Delta G^{TS} = +18.9$ and $+22.3$ kcal mol^{-1} respectively). The tosylation of the second alcohol moiety is however more favoured thermodynamically than that of the carbonate ($\Delta\Delta G = -25.4$ *vs.* $= -2.3$ kcal mol^{-1}). Yet, the activation barrier for the tosylation of the carbonate is lower than that of the alcohol moiety ($\Delta\Delta G^{TS} = +23.8$ and $+29.7$ kcal mol^{-1} respectively). Hence, we believe that the addition/elimination pathway, resulting in stereochemical retention, is kinetically favoured over the S_N2 ($\Delta\Delta G^{TS} = +5.9$ kcal mol^{-1}).

In conclusion, in the wider context of an ever-growing need for innovative materials and CO_2 emissions mitigation and utilisation, a novel one-pot procedure that uses safe and readily available reagents yielded 6-membered cyclic carbonates directly from abundant 1,3-diols and carbon dioxide under mild conditions (room temperature and low pressure), and compared well with toxic or expensive alternative methods. Computational and experimental evidence shows that the reaction proceeds through an addition/elimination pathway. On-going work is now aiming at replacing chloroform for a more environmental benign solvent and making the procedure catalytic in order to reduce the amount of salts produced.

Acknowledgements

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Notes and references

‡ Typical procedure for the synthesis of cyclic carbonate monomers: under a CO_2 atmosphere, DBU (1 equiv.) was added dropwise to a stirring solution/suspension of diol (0.5 g, 1 equiv.) in dry chloroform (1.7 M). After stirring at room temperature for 2 hours, triethylamine (1 equiv.) was added dropwise to the resulting viscous solution. A solution of TsCl in chloroform (1 equiv., 0.5 M) was then added slowly and the mixture stirred overnight. Removal of volatiles *in vacuo* afforded an oily residue, which was purified by column chromatography.

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