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An innovative synthesis pathway to benzodioxanes: the peculiar reactivity of glycerol carbonate and catechol†

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A peculiar reactivity of glycerol carbonate (GlyC) as an innovative and highly reactive alkylating agent for phenolic compounds is investigated in this article. In particular, 2-hydroxymethyl-1,4-benzodioxane (HMB), a key intermediate for the pharmaceutical industry, has been selectively synthesized by the reaction of a slight excess of GlyC with catechol in the presence of a basic catalyst ($NaOCH_3$, Na-mordenite, MgO), without requiring a reaction solvent. Both reagents have been quantitatively converted in just one hour at 170 °C with a HMB yield, up to 88%, in the presence of a homogeneous basic catalyst ($NaOCH_3$). Notably, the main side product, the HMB isomer, may be an interesting intermediate for the synthesis of calone analogues, which are important scaffolds used in fragrances. A detailed mechanistic study, supported by kinetics, GC-MS, and HMBC NMR characterization, is also reported. Accordingly, this paper describes a completely innovative and greener synthesis pathway to benzodioxanes.

Introduction

Organic carbonates (OCs) are among the most promising green candidates for the replacement of conventional noxious aprotic polar solvents because of their high boiling point and great solvency and also due to their non-toxicity and good biodegradability.

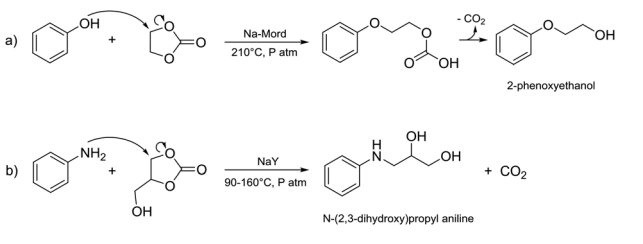
For the same reasons, they are widely used in the manufacture of lithium batteries, as fuel additives, and as innovative reactive chemicals for the development of important intermediates in the pharmaceutical, lubricant, and polymer industries.[1]

In particular, OCs are successfully used as alkylating agents for aromatic compounds, replacing more traditional, harmful, and undesirable compounds. For example, alkyl iodides are known carcinogens, while dimethyl sulphate is an extremely hazardous liquid and vapour (which may be fatal if inhaled).[2–4]

However, only the lightest members of the OC family, namely dimethyl carbonate (DMC) and diethyl carbonate (DEC),[5,6] have been investigated for these kinds of reactions. In more detail, DMC is capable of reacting with a number of nucleophilic substrates, such as phenols, amines, sulphones, thiols, and methylene-active derivatives of aryl and aryloxy-acetic acids, under both batch and continuous flow conditions.[7–13] Scheme S1 in the ESI† comprehensively summarizes the reactivity of DMC and aromatic substrates.

On the other hand, cyclic carbonates can also be successfully used as alkylating agents. Of particular interest is the reaction between ethylene carbonate (EC) and phenol with heterogeneous catalytic systems (such as basic zeolites, *e.g.* Na-mordenites). This pathway makes possible a more selective synthesis of 2-phenoxyethanol than does industrial production from ethylene oxide feedstock (Scheme 1a).[14]

Among the cyclic OCs, glycerol carbonate (4-hydroxymethyl-2-oxo-1,3-dioxolane, GlyC) is a polyfunctional carbonate, bearing both a carbonate moiety and a hydroxyl group representing electrophilic and nucleophilic sites, respectively (Fig. 1).



Scheme 1 Alkylation of aromatic substrates with cyclic carbonates: (a) synthesis of 2-phenoxyethanol through phenol alkylation with EC; (b) aniline alkylation with GlyC with the formation of *N*-(2,3-dihydroxy) propyl aniline as the main product.

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†Electronic supplementary information (ESI) available: Reaction schemes, supplementary catalytic results, ^{1}H- and ^{13}C-NMR characterization of substrates, available pure products and reaction mixtures, and GC-MS of pure compounds and reaction mixtures. See DOI: 10.1039/c8gc02811g

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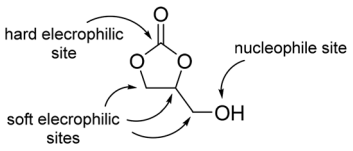


Fig. 1 GlyC structure and polyfunctional reactive sites.

The combination of its bio-based origin and peculiar characteristics and reactivity makes GlyC a versatile and renewable building block for a more sustainable chemistry. Because of its high boiling point (110°–115 °C at 0.1 mmHg), high flash point (190 °C), and low volatility (8 mbar vapour pressure at 177 °C), GlyC and its esters are bio-based alternative solvents with a lower vapour pressure than volatile organic compounds (VOC).[15] Moreover, GlyC has been investigated for use as a component in gas separation membranes, polyurethane foams and surfactants, and coatings, and as a source of new hyperbranched polymers.[16]

Lastly, GlyC has the possibility to become a major chemical intermediate: for instance, it can be converted into either glycidol (by decarboxylation) or epichlorohydrin, a product widely applied in industry, under mild conditions.[17,18]

Nevertheless, only a few studies in the literature have investigated the possibility of using GlyC as an alkylating agent for the derivatization of aromatic compounds. For example, Selva *et al.* reported on the alkylation of aromatic amines (aniline) with GlyC, using a series of different faujasites (*e.g.* NaY) as the catalyst. The reaction (performed in a 90°–160 °C temperature range) leads to a mixture of compounds in which *N*-(2,3-dihydroxy)-propyl aniline is the main product (Scheme 1b).[19]

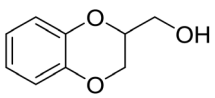


Fig. 2 2-Hydroxymethyl-1,4-benzodioxane (HMB) structure.

Scheme 1 shows a concise overview of the cited alkylation reactions between aromatic and cyclic OCs.

Another functionalized phenolic derivative of great importance is 2-hydroxymethyl-1,4-benzodioxane (Fig. 2), henceforward referred to as "HMB". HMB is an important intermediate for the pharmaceutical industry, because its moiety is present in many active components of antidepressant, antihypertensive, anxiolytic, and antithrombotic drugs, in addition to cardiovascular agents, to name a few (see Scheme S2 in the ESI†).[20]

The main problems related to the HMB production concern its synthesis, which usually requires a multistep sequence of reactions and the use of toxic solvents and reagents. The traditional synthesis pathways may be divided into three main classes:

(a) glycidol derivative-based synthesis;

(b) "chiral pool" derivative-based synthesis;

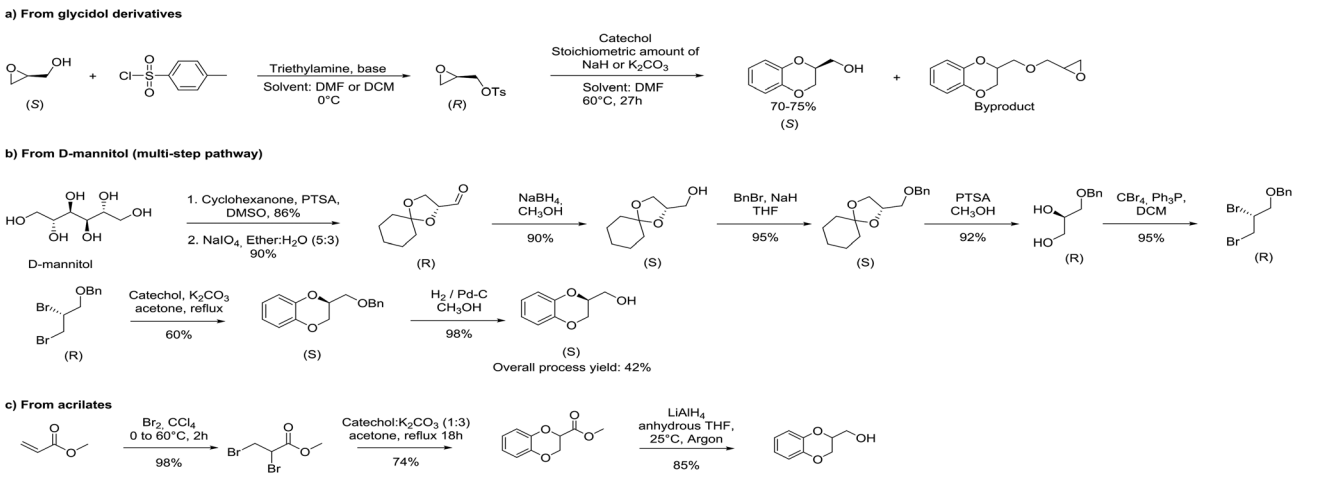
(c) acrylate-based synthesis.

In the first class, glycidol must be tosylated to prevent undesired side reactions. Tosylation is usually performed with 4-toluenesulfonyl chloride in the presence of a base (triethylamine or/and 4-dimethylamino pyridine) at a low temperature (0 °C) in dichloromethane (DCM) or dimethylformamide (DMF) as a solvent.[21] Subsequently, the isolated tosylated glycidol is exploited as an alkylating agent for catechol (as well as nitro-substituted or halogenated catechols), for the formation of HMB (or substituted HMB).

This reaction is performed in DMF at 60 °C for a certain length of time (*e.g.* 27 hours) in the presence of a stoichiometric amount of a base (K_2CO_3 or NaOH), leading to a variable 70–75% HMB yield with the formation of a heavier by-product, derived from the reaction of HMB with another moiety of glycidol (Scheme 2a).[22]

The second synthesis strategy involves the use of chiral building blocks from the "chiral pool", such as D-mannitol, and a multistep sequence of reactions, in order to obtain the halogenated compound ((2,3-dibromopropoxy)methyl) benzene.

This compound subsequently undergoes a reaction with catechol to yield the HMB intermediate (2-benzyloxymethyl-



Scheme 2 Traditional synthetic pathways to HMB.

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1,4-benzodioxane). In the final step, this intermediate is hydrogenated in the presence of a noble metal catalyst (Pd/C), thus leading to the formation of HMB with an overall process yield of 42% (Scheme 2b).[23]

Lastly, HMB analogues (HMB methyl esters) can be obtained *via* the bromination of methyl acrylate or other analogous unsaturated esters (usually in CCl_4 as the solvent), to obtain a halogenated compound which is able to react with catechol in the presence of an excess of a base (*e.g.* K_2CO_3) for 18 hours in refluxing dry acetone (T = approx. 56 °C). This route leads to the formation of methyl 1,4-benzodioxan-2-carboxylate with an isolated yield of 74% (Scheme 2c).[24]

All these synthesis pathways suffer from similar drawbacks: (i) the use of toxic and dangerous reagents (glycidol or halogenated analogues), in order to enhance the condensation step with catechol; (ii) the use of a stoichiometric amount of base with the co-production of an equimolar amount of inorganic waste; (iii) the use of toxic solvents (CCl_4, DMSO, DMF, DCM and anhydrous THF); and (iv) the multistep approach which, in the end, is detrimental to the maximum yield obtainable.

In our work, we sought an innovative synthesis procedure, which could avoid the solvent while making use of the base-catalysed alkylation of catechol with GlyC, followed by intramolecular cyclization, thus enabling us to obtain HMB in a single step. In this way, the use of GlyC as an innovative, reactive, and selective alkylating agent for catechol is a completely pioneering synthetic pathway to HMB, which is capable of overcoming all the limitations previously reported.

Experimental

Catalyst preparation and characterization

Sodium methoxide. Sodium methoxide was prepared by reacting Na(s) with an ice-cold solution of MeOH. The solvent was removed under vacuum, while the resulting solid was stored under nitrogen before use.

Magnesium oxide (MgO). Magnesium oxide was synthesized by a precipitation technique. A solution of $Mg(NO_3)_2{\cdot}6H_2O$ in distilled water (1 mol L^{-1}) was added dropwise to a second aq. solution of $Na_2CO_3{\cdot}10H_2O$ (1 mol L^{-1} in distilled water) which was kept, under magnetic stirring, at 60 °C. The pH was maintained between 9.8 and 10.2 during the reaction. The obtained magnesium hydroxide was filtered, washed with distilled water, and dried overnight at 110 °C. The material was then crushed and calcined at 450 °C for 5 hours.

MgO powder was characterized by X-ray diffraction, using Ni-filtered Cu Kα radiation (λ = 1.54178 Å) on a Philips X'Pert vertical diffractometer equipped with a pulse height analyser and a secondary curved graphite-crystal monochromator.

The BET surface area of MgO was determined by N_2 absorption–desorption at the temperature of liquid N_2 using a Sorpty 1750 Fison instrument. A sample of 0.2 g was first outgassed at 150 °C before N_2 absorption. The surface area of MgO was found to be equal to 170 ± 5 m^2 g^{-1}.

The leaching of Mg into the reaction mixture at 200 °C was evaluated using microwave plasma atomic emission spectroscopy (Agilent Technologies MP-EAS 4210) calibrated for the determination of Mg (in the range 0, 1–100 ppm). In particular, after the reaction, the mixture was cooled at room temperature and the organic compounds were dissolved using 10 mL of acetone. The mixture was filtered using a syringe equipped with a PTFE filter (0, 20 μm) in order to remove all the heterogeneous catalyst. The mixture was diluted 10 times in water (no precipitation occurs during the dilution). To all the solutions (standards and samples) 100 μL of a solution of Cs_2CO_3 (100 g L^{-1}) were added as the ionization buffer in order to avoid ionisation interference for Mg. The results are shown in Table S2† demonstrating that the leaching of Mg was negligible.

Sodium mordenite (Na-Mord). The zeolite used for heterogeneous catalytic tests was Zeocat FM-8, provided by Zeochem, which was characterized by a SiO_2/Al_2O_3 molar ratio (SAR) of 12, a surface area of 350 m^2 g^{-1} (pore size 6.5 × 7.0/2.6 × 5.7 Å), and a sodium content expressed as Na_2O wt% equal to 6.8.[25] The zeolite was dried at 120 °C overnight before each test.

Reaction procedure and product analysis

Catalytic tests were conducted in a round-bottom Pyrex glass flask equipped with a magnetic stirrer and fitted with a condenser.

In a typical experiment, the flask was charged with the aromatic alcohol (usually catechol from 1 to 3 mmol), catalyst ($NaOCH_3$ from 0.066 to 0.2 mmol or MgO/Na-Mord 5 wt% with respect to the limiting reagent), and GlyC (from 2 to 6 mmol), purged with a nitrogen atmosphere, and then closed. The mixture was heated rapidly to the desired temperature (*e.g.* 170 °C) and stirred for 1 h, and then cooled to RT. Afterwards, the mixture was recovered with acetone (10 mL, HPLC grade, Sigma-Aldrich). The solution was further diluted with acetone (ten volumes) and added together with *n*-octane (20 μL), which served as an external standard. If needed (when a heterogeneous catalyst was used), the resulting mixture was filtered and then analysed with a Thermo Focus gas-chromatograph equipped with a HP-5 capillary column (25 m × 320 μm × 1.05 μm; $T_{injector}$: 280 °C; split ratio: 30 : 1, nitrogen flow: 1.2 mL min^{-1}). The temperature ramp was 50 °C for 2 min, with subsequent heating up to 280 °C at 10 °C min^{-1}, 280 °C for 5 min. Each compound was calibrated with respect to *n*-octane (the standard), to obtain the corresponding response factor in the appropriate range of concentration. The structure of the products was determined by ESI-MS and GC-MS, and whenever possible, by comparison with pure commercial samples.

Most of the catalytic tests were triplicated to verify their reproducibility. In the repeated runs carried out under the same conditions, the values of conversion and product yields (determined by GC/MS) differed by less than 5% from one reaction to another.

The spectroscopic properties of the products corresponded to those reported in the literature.

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Product separation

The reaction mixture, obtained after one hour of reaction at 170 °C with a ratio of catechol : GlyC : $NaOCH_3$ = 1 : 2 : 0.066, was rapidly cooled down to RT with an ice bath and then solubilized and transferred into a separating funnel using 10 mL of ethyl acetate. In this way, the heavier oligomeric hydrophilic compounds remained in the reaction batch.

Afterwards, the products dissolved in the organic phase were washed twice with 5 mL of slightly acidified water (*e.g.* solution of diluted HCl, pH = 4): the residual unreacted catechol and glycerol could thus be selectively extracted from the aqueous solution. The organic solution was then dried with sodium sulphate, filtered, and lastly the solvent (ethyl acetate) was removed under vacuum, obtaining a solid in an overall isolated yield of 85% (77% HMB and 8% isomer). HMB was further purified by column chromatography on silica gel (dichloromethane/diethyl ether 100 : 1) with an isolated yield of 68% (see the ^{1}H-NMR spectrum in Fig. S22†).

NMR experiments

In a typical experiment, glycerol carbonate (40 mg) and phenol (15 mg) or catechol (15 mg) were dissolved in 0.6 mL DMSO-d_6 in a J Young valve NMR tube. Reactions were performed at the desired temperature for 1–3.5 h without stirring. The reaction was monitored by ^{1}H-, ^{13}C- and HMBC NMR using a Varian Inova 600 (^{1}H, 599.7; ^{13}C, 150.8 MHz) instrument.

Results and discussion

Background of this work and the "one-pot" synthesis approach

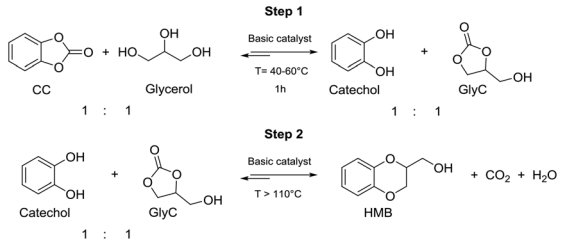
In a recent patent, we outlined the outstanding performance of catechol carbonate (CC) as a novel carbonate source in the carbonate interchange reaction (CIR) with both aliphatic alcohols and polyols such as glycerol.[26]

In particular, CC is a highly reactive compound. It is able to react with glycerol in the presence of a basic catalyst, under mild conditions (40° to 60 °C, atmospheric pressure, 1 hour reaction time), leading to the selective formation of a mixture of GlyC, with up to 96% yield, and catechol (the leaving group of CC and the co-product of the CIR), with a molar ratio between the two compounds equal to 1.

The separation of these two compounds, however, is not a simple matter; the purification of the product was possible only by means of flash chromatography. Thus GlyC was isolated in a 77% yield with a purity grade >99%.[27]

Therefore, we decided to investigate the reactivity of GlyC and catechol in the presence of a sodium methoxide catalyst, using the "one-pot" synthesis strategy shown in Scheme 3: Step 1, allow CC and glycerol to react, in order to form GlyC and catechol *in situ* (Step 1 in Scheme 3), and then Step 2, change the reaction conditions (higher temperature than in Step 1), thus avoiding the isolation of intermediates GlyC and catechol.

It is important to note that this approach made it possible for us to avoid the use of toxic and halogenated compounds. The two reactions were performed without any reaction solvent



Scheme 3 The "one-pot" synthetic approach.

(glycerol and GlyC themselves act as solvents, and HMB has a mp of 90 °C). The atom economy of the overall process is very high (AE_{Step1} = 100%; AE_{Step2} = 72.8%) and the only co-products of the reaction (Step 2) are water and carbon dioxide.

Since the first step of this procedure was investigated in our previous work,[26,27] which enabled us to obtain a mixture characterized by a molar ratio of catechol : GlyC equal to 1, after 1 hour of reaction at 60 °C, in the presence of a catalytic amount of $NaOCH_3$ (1/15 mol with respect to CC, approx. 6.6% mol), we will focus here on the results of the second step of the process.

Screening of the best reaction temperatures and the role of water

We first investigated the effect of temperature, in the 110°–170 °C range, by performing Step 2 for 4 hours. The results obtained are shown in Fig. 3.

These results clearly show the importance of temperature in speeding up the reaction rate. HMB was the main reaction product, obtained with a yield similar to that of glycerol. This unexpected by-product was formed by the hydrolysis of GlyC, thanks to the water coproduced during the main reaction. The hydrolysis also contributed to increasing GlyC conversion, which was higher than that expected based on HMB formation. On the other hand, the only other by-product of the reaction was the HMB isomer, 3,4-dihydro-2*H*-benzo[*b*][1,4]

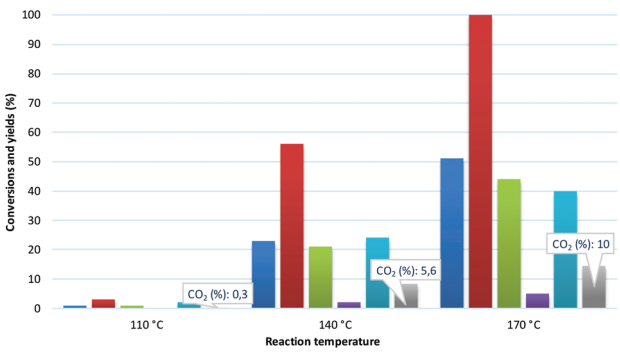


Fig. 3 Catalytic results obtained with a catechol : GlyC : $NaOCH_3$ molar ratio of 1 : 1 : 0.066, N_2 atmosphere, 4 hours at the desired temperature. Product yields refer to catechol. C-loss is comprehensive of the CO_2 released (specified in the caption). Catechol conversion (blue bar), GlyC conversion (red bar), HMB yield (green), HMB isomer (purple), glycerol (light blue), and atomic C-loss (grey).

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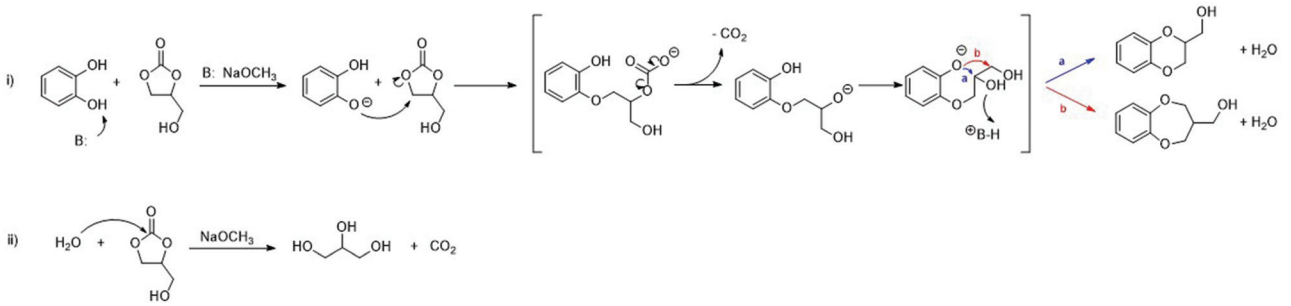

Scheme 4 (i) Initially proposed reaction pathway for the alkylation and condensation reactions of catechol and GlyC; (ii) GlyC hydrolysis to yield glycerol.

dioxepin-3-ol. This compound, however, is a valuable product because it is a reactive intermediate in the synthesis of methylbenzodioxepinone-based compounds (trade name "calone" or "calone 1951"): molecules that are known in the fragrance industry for their distinct marine scent.[28]

The suggested reaction mechanism is shown in Scheme 4. One of the catechol acidic hydroxyl groups is deprotonated by the basic catalyst; the catecholate anion (a "softer" nucleophile than aliphatic analogues due to the resonance of the negative charge on the aromatic ring) is able to perform the nucleophilic attack on the more available "soft" electrophilic site of GlyC, leading to the formation of an unstable intermediate, which rapidly undergoes decarboxylation followed by an intramolecular condensation which, in the end, leads either to the desired HMB (Scheme 4, pathway i, a) or to its isomer (pathway i, b), and water as the co-product. The latter is responsible for GlyC hydrolysis back to glycerol and carbon dioxide (Scheme 4, pathway ii).

These reactions are characterized by a non-negligible carbon loss (Fig. 3, grey columns), which is mainly due to substrate decarboxylation and, to a minor extent, to some heavier hydrophilic by-products, such as polyol oligomers, which are easily solubilized in water.

The mechanisms plausibly responsible for the formation of these by-products are summarized in Scheme S3 in the ESI.†

Surprisingly, none of the reaction intermediates suggested in Scheme 4 has ever been observed, not even in reactions performed at relatively low temperatures (110° and 140 °C) and for short reaction times (for example, see the kinetic study at 140 °C, Fig. S1 in the ESI†). This suggests that decarboxylation and intramolecular condensation are very fast reactions.

The reaction mechanism has been thoroughly investigated and described in a dedicated section (see below).

Synthesis optimization

Because of the formation of an equimolar amount of water, which is responsible for GlyC hydrolysis, a small excess of carbonate was necessary in order to increase the HMB yield. Moreover, 170 °C was chosen as the best reaction temperature, while the reaction time was decreased from 4 h to 1 h, in order to better highlight the effect of both the reagents' molar ratio and the catalyst loading on HMB formation.

The results of the catalytic experiments are shown in Fig. 4 and 5.

Surprisingly, GlyC conversion was completed after 1 h reaction at 170 °C (irrespective of its molar excess), while the reaction required only a small excess of GlyC to enhance the HMB

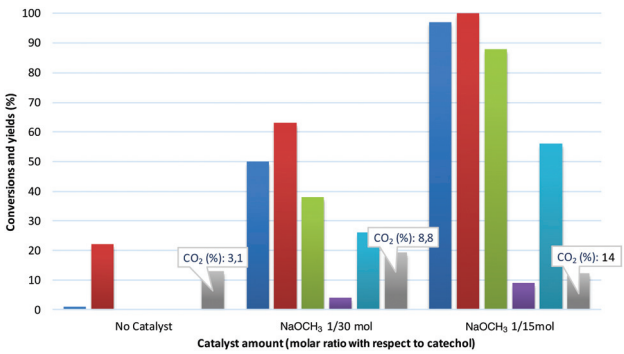

Fig. 4 Catalytic results obtained with a catechol : GlyC : $NaOCH_3$ molar ratio of 1 : 2 : *X*, N_2 atmosphere, 1 hour at 170 °C. Product yields refer to catechol. C-loss is comprehensive of the CO_2 released (specified in the caption). Catechol conversion (blue bar), GlyC conversion (red bar), HMB yield (green), HMB isomer (purple), glycerol (light blue), and atomic C-loss (grey).

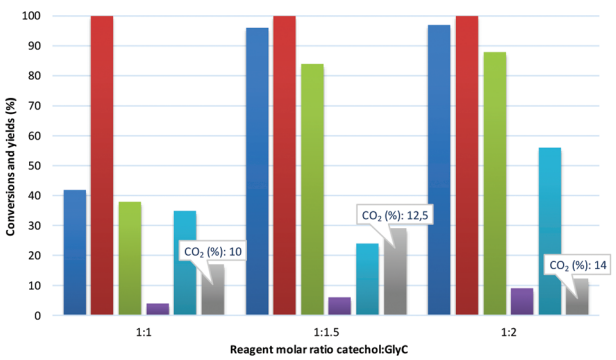

Fig. 5 Catalytic results obtained with a catechol : GlyC : $NaOCH_3$ molar ratio of 1 : *X* : 0.066, N_2 atmosphere, 1 hour at 170 °C. Product yields refer to catechol. C-loss is comprehensive of the CO_2 released (specified in the caption). Catechol conversion (blue bar), GlyC conversion (red bar), HMB yield (green), HMB isomer (purple), glycerol (light blue), and atomic C-loss (grey).

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yield, as shown in Fig. 4. The effect of the catechol : GlyC molar ratio can be summarized as follows:

(i) A slight excess of GlyC made it possible for us to obtain a HMB yield higher than 80% in a one-hour reaction at 170 °C; (ii) with a GlyC : catechol ratio of 1.5, however, the theoretical HMB maximum yield, in consideration of the concomitant stoichiometric GlyC hydrolysis, should be equal to 75%, suggesting an accelerating effect of GlyC also on the main reaction, compared to the parasitic ones: the hydrolysis and the formation of heavier hydrophilic compounds. This trend was also confirmed in the experiment with a GlyC : catechol molar ratio of 2, which showed that a greater GlyC excess led to a further increase in the HMB yield (approx. 88% after 1 h) but also to a lower selectivity to heavier by-products (with a lower C loss), in favour of the formation of glycerol.

On the other hand, some experiments showed that the use of a large excess of GlyC made it possible to obtain a complete catechol conversion that, however, turned out to be detrimental to the carbon balance, with a C loss higher than 50%. This was probably due to the higher acidity of catechol hydroxyl groups compared to the GlyC and glycerol aliphatic hydroxyl moieties; in this way, the presence of catechol in the batch prevents the basic catalyst deprotonating aliphatic –OH groups, thus limiting the parasite reactions.

Further evidence of the importance of adjusting reaction conditions in order to achieve a high, albeit incomplete, catechol conversion, limited carbon loss, and high HMB yield was obtained by conducting a GlyC decomposition test. In this test, GlyC was charged with the basic catalyst (with a molar ratio $NaOCH_3$: GlyC = 0.066) and heated to 170 °C.

After 10 minutes, dark, heavy, polymer-like compounds were formed, while the complete GlyC conversion was observed after 30 minutes, without the formation of either glycerol or glycidol, and with a C-loss of 100%.

The best reaction conditions (catechol : GlyC : $NaOCH_3$ = 1 : 2 : 0.066, 170 °C, 1 h) were then chosen to further investigate the effect of the basic catalyst loading; the results are shown in Fig. 5. It is worth noting that without the catalyst, no HMB was formed, while part of the GlyC was thermally decomposed into heavier by-products. An increase in the amount of Na methoxide led to an increase in both catechol conversion and HMB yield, while GlyC conversion became more similar to catechol conversion, *i.e.* with less GlyC decomposition.

Interestingly, in all the tests conducted so far, the HMB : isomer molar ratio was close to 10, regardless of parameters such as temperature.

Performance of heterogeneous catalysts

An initial screening of heterogeneous basic catalysts was performed; this means the recovery of the used catalyst will be easier, thus facilitating both product purification and catalyst recycling. In particular, we studied the catalytic activity of sodium mordenite (Na-Mord) characterized by a silica-to-alumina ratio (SAR) of 12, and of a synthesized "high area" magnesium oxide (MgO); in fact, both catalysts proved to be active in other reactions between carbonates and alcohols or phenolics.[14,25]

At first, the effect of the reaction temperature was studied. The results, summarized in Fig. S2,† underscore the need to work at a higher temperature, *e.g.* at 170 °C instead of 140 °C, and for a longer reaction time than those used in the homogeneous system. In particular, using a Na-Mord : catechol wt ratio of 5% : 95%, a HMB yield higher than 80% was achieved by performing the reaction at 200 °C for 6 hours. The conversion and yield profiles based on the reaction time at 200 °C are shown in Fig. 6.

Interestingly, when performing the reaction at a lower temperature (140 °C and 170 °C, Fig. S2†) or at 200 °C for shorter reaction times (1 and 2 hours), catechol conversion was higher than GlyC conversion. This may seem meaningless considering the results obtained with a homogeneous catalyst; however, it was due to the strong interaction of catechol with the basic sites of the catalyst (almost irreversible at low temperature), which, in the end, is responsible for the increase of both the catechol loss and overall C-loss.

A comparison of the catalytic performances of Na-mordenite and MgO at 200 °C is summarized in Table S1.†

Mechanism investigation

As already mentioned, no reaction intermediates were detected under any of the conditions used. This was probably due to the fast intramolecular reactions involved. Therefore, the reaction mechanism was investigated by means of both NMR (*vide infra*) and a simple, yet effective, strategy: the simplification of functional groups.

We thus decided to investigate the influence of each functional group on the reaction pathway. In particular, the following tests were performed:

- the reaction of catechol (or other aromatics) with glycerol, by removing the carbonate functional group from the aliphatic counterpart (green, Fig. 7);

- the reaction of phenol with GlyC, by removing the second hydroxyl group of the catechol moiety (red, Fig. 7), thus

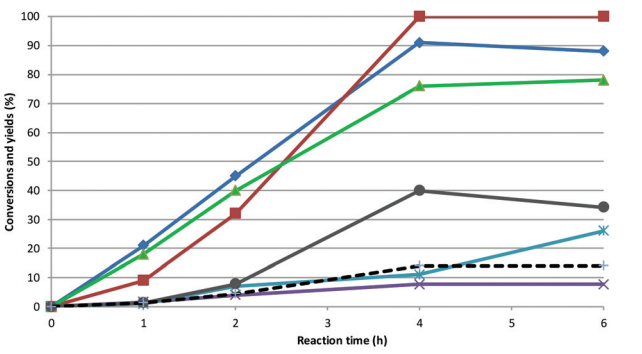

Fig. 6 Catalytic results obtained at 200 °C with a catechol : GlyC molar ratio of 1 : 2, Na-mordenite 5% w/w with respect to catechol, N_2 atmosphere. Product yields refer to catechol. Catechol conversion (blue line), GlyC conversion (red line), HMB yield (green), HMB isomer (purple), glycerol (light blue), and atomic C-loss (grey). The dotted line represents the part of C-loss related to the CO_2 released. The results showed were obtained by feeding new reagents for each reaction time, to collect the mixture after the reaction and correctly calculate the C-loss.

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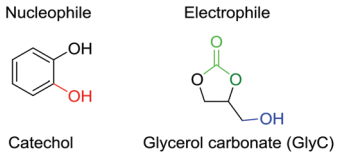


Fig. 7 Catechol and GlyC functional groups selected for the mechanism investigation.

making the rapid intra-molecular cyclization to HMB impossible;

- the reaction of catechol with propylene carbonate (PC), by removing the polyfunctionality provided by the residual hydroxyl group in GlyC (blue, Fig. 7).

- the reaction of catechol and glycidol was investigated by using DMSO-d_6 as the reaction solvent and analysing the reaction mixture by means of NMR, in order to exclude the effect of GlyC decarboxylation (green, Fig. 7).

First, the reaction of glycerol with various aromatic compounds (aniline, phenol, and catechol) was performed at 170 °C in the presence of $NaOCH_3$, to exclude the condensation between the aromatic and the aliphatic –OH groups.

Interestingly, in no case were traces of condensation products found, demonstrating the peculiar reactivity of the organic carbonate involved. Indeed, the reaction mechanism is likely to start from the nucleophilic attack of the catecholate anion on the alkylene carbon in the carbonate ring. Furthermore, tests using the protected form of glycerol ((2,2-dimethyl-1,3-dioxolan-4-yl)methanol, "Solketal"), in order to somehow reproduce the ring strain in GlyC, only led to the formation of the protected form of catechol (2,2-dimethylbenzo[*d*][1,3]dioxole).

Afterwards, we studied the reaction between phenol and GlyC, in order to block the intra-molecular cyclization leading to HMB. The results are shown in Fig. 8.

As expected, the main product was the *O*-alkylated compound: 3-phenoxy-1,2-propandiol.

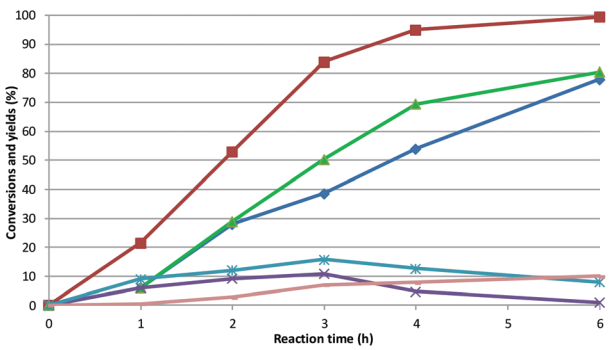
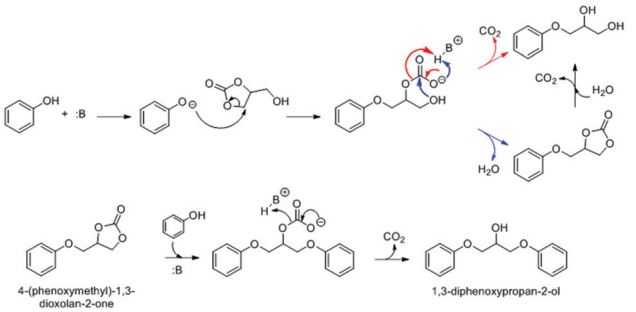


Fig. 8 Catalytic results obtained at 140 °C with a phenol : GlyC : $NaOCH_3$ molar ratio of 2 : 1 : 0.066, N_2 atmosphere. Product yields refer to GlyC. Phenol conversion (blue), GlyC conversion (red), 3-phenoxy-1,2-propandiol (green), 4-(phenoxymethyl)-1,3-dioxolan-2-one (purple), glycerol (light blue) and di-alkylated compounds (pink).

However, two other products were spotted. The first was 4-(phenoxymethyl)-1,3-dioxolan-2-one, a phenolic alkylated compound, which maintains the organic carbonate functionality and behaves as a reaction intermediate. Its formation appeared to increase during the first hours of reaction, and then decreased in favour of consecutive products such as 1,3-diphenoxypropan-2-ol. A reaction mechanism is suggested in Scheme 5.

The results obtained with phenol underscored the possibility of the intramolecular rearrangement of the carbonate group over the free –OH group of the GlyC moiety: this behaviour may play a key role in HMB formation. To investigate this possibility, propylene carbonate (PC) was made to react with catechol with the aim of forming a HMB analogue: 2-methyl-1,4-benzodioxane (MB). The results obtained at 170° and 200 °C are shown in Fig. 9.

Interestingly, under the usual conditions required for HMB formation with the homogeneous basic catalyst, no formation of the target product was observed, while the main product was the monoalkylated compound: 2-(2-hydroxypropoxy) phenol and its isomer 2-((1-hydroxypropan-2-yl)oxy)phenol.



Scheme 5 Proposed reaction mechanism for the phenol alkylation with GlyC.

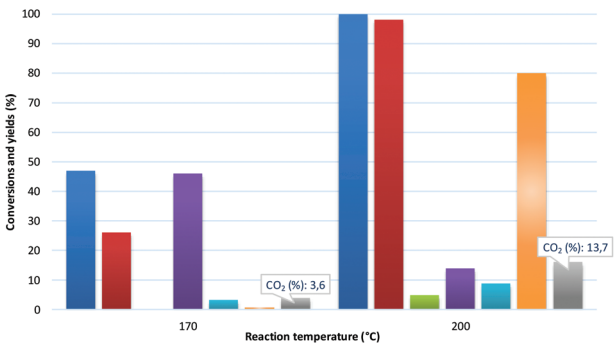


Fig. 9 Catalytic results obtained with a catechol : PC : $NaOCH_3$ molar ratio of 1 : 2 : 0.066, N_2 atmosphere, 1 hour at different reaction temperatures. Product yields refer to catechol. C-loss is comprehensive of the CO_2 released (specified in the caption). Catechol conversion (blue bar), PC conversion (red bar), MB yield (green), monoalkylated (purple), 1,2-propandiol (light blue), di-alkylated (orange), and atomic C-loss (grey).

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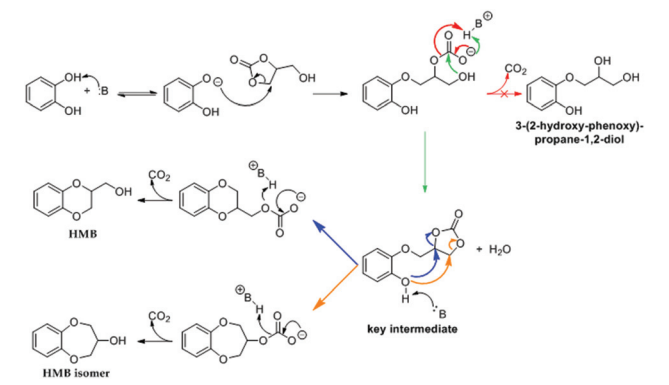
When the reaction temperature was increased to 200 °C, however, MB formed as a minor product (approx. 5% yield), while the increasing temperature led to a greatly enhanced yield of dialkylated compounds.

This behaviour proves that the intramolecular cyclization with the formation of the benzodioxane ring is not facilitated when PC is used instead of GlyC, clearly underscoring the importance of the "free" –OH group of the GlyC moiety in the promotion of a reaction pathway other than the expected condensation with the consequent elimination of water. The reaction mechanism using PC is shown in Scheme S4 of the ESI.†

Lastly, the reaction of catechol and glycidol was investigated. Indeed, glycidol is a highly reactive compound that might be produced by the decarboxylation of GlyC at high temperature (see Scheme S5 in the ESI†). This reaction was performed at 170 °C in DMSO-d_6 in an NMR tube by diluting reagents and the homogeneous basic catalyst, in order to limit the undesirable glycidol oligomerization. The mixture was analysed by ^{1}H- and ^{13}C-NMR (Fig. S3 and S4†) and no traces of HMB (*cf.* with Table S3 and Fig. S8 and S9†) were observed, clearly underpinning the importance of carbonate scaffolds in the formation of benzodioxanes. On the other hand the spectra show the formation of both mono arylglyceryl ethers as the main products of the reaction, and of some aliphatic oligomers of glycidol as expected.[29]

A summary of all the information obtained so far made it possible for us to outline a new reaction mechanism for the innovative HMB synthesis pathway proposed herein (Scheme 6).

First, catechol is activated by the basic catalyst (otherwise no reaction occurs) and forms the alcoholate anion, which is now able to perform a nucleophilic attack on the more feasible and accessible alkylene carbon of the GlyC carbonate ring. The intermediate does not undergo decarboxylation, but an intramolecular closure with the consequent formation of another cyclic carbonate, a key intermediate. Then the latter undergoes an intramolecular nucleophilic attack by the free aromatic –OH group, which finally leads either to the desired product (HMB) or to its isomer.



Scheme 6 Catechol and GlyC proposed reaction mechanism leading to HMB and its isomer.

NMR experiments

With the aim of confirming the proposed reaction intermediates, diluted versions of the reactions between GlyC and phenol and GlyC and catechol were performed in DMSO-d_6 followed by NMR. All identified species are summarized in Fig. 10.

The identification of some signals ascribable to phenol, glycerol carbonate, **1**, **3**,[30] **4**,[31] **6**, and **7** has been attributed either by comparison with control experiments (Table S3,† Fig. 11–14, Fig. S5–S21†) on the pure products (except for the mixture of **6** + trace of **7**) or with literature data.

Considering the reaction of GlyC with phenol, performed at 140 °C for 1 h, once excluded signals arising from **1**, **3** and **4**, the remaining peaks and correlations (yellow lines in Fig. 11) are in line with the structure of **2** (see also Fig. S10–S15†).

The correlations between –CH_2 on the carbonate cycle with the C=O of carbonate (approx. 155 ppm) and between the –CH_2 in the lateral chain and an *ipso*-C in the aromatic region (approx. 159 ppm), which are shown in Fig. 12, further confirm the structure of **2**, demonstrating the link between phenol and glycerol carbonate fragments. It is worth noting that product **2** has also been detected by means of GC-MS in a solventless reaction mixture (see the ESI†).

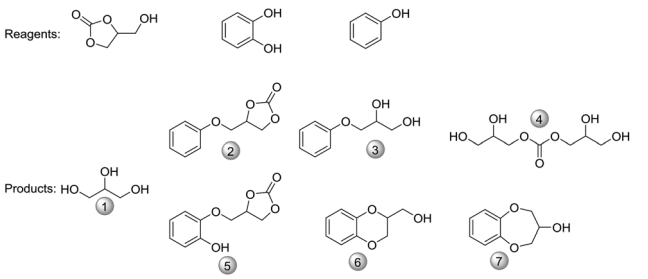


Fig. 10 Reaction mixture obtained from the reaction of GlyC with phenol or catechol.

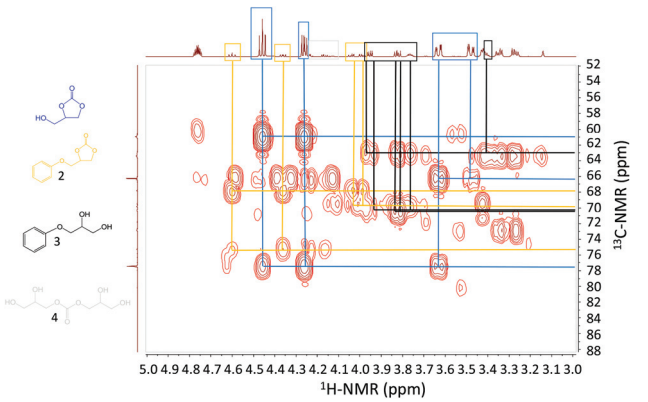


Fig. 11 HMBC-NMR (600 MHz, DMSO-d_6) of the mixture obtained from the reaction between phenol and glycerol carbonate. Details of the aliphatic region. Crosslink of the signal arising from glycerol have been omitted. **4** is attributed by ^{1}H-NMR and ^{13}C-NMR by comparison with the literature,[31] although crosslink signals are not clearly attributable.

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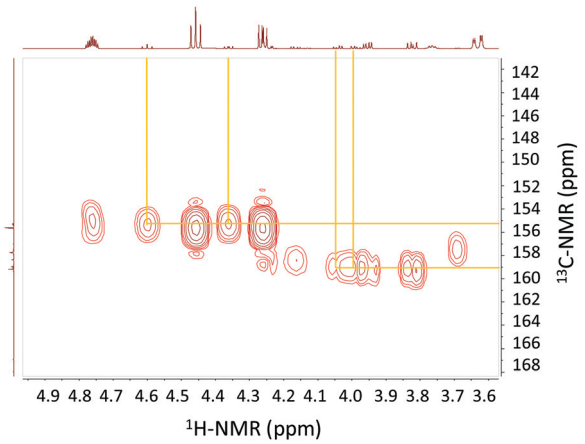

Fig. 12 HMBC-NMR (600 MHz, DMSO-d_6) of the mixture obtained from the reaction between phenol and glycerol carbonate. Details of the ^{1}H-NMR aliphatic region *vs.* ^{13}C-NMR carbonates and the *ipso*-C region (yellow lines correspond to the signals of **2**).

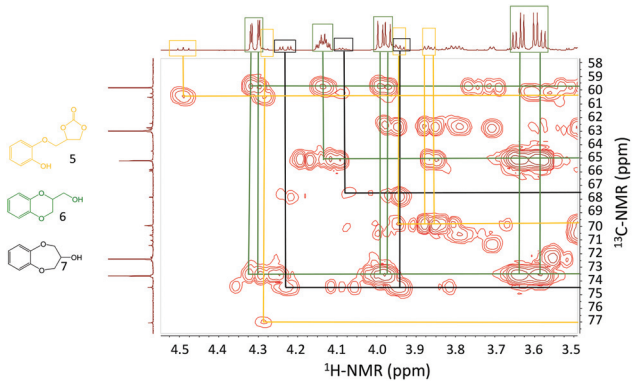

Fig. 13 HMBC-NMR (600 MHz, DMSO-d_6) of the mixture obtained from the reaction between catechol and glycerol carbonate. Details of the aliphatic region.

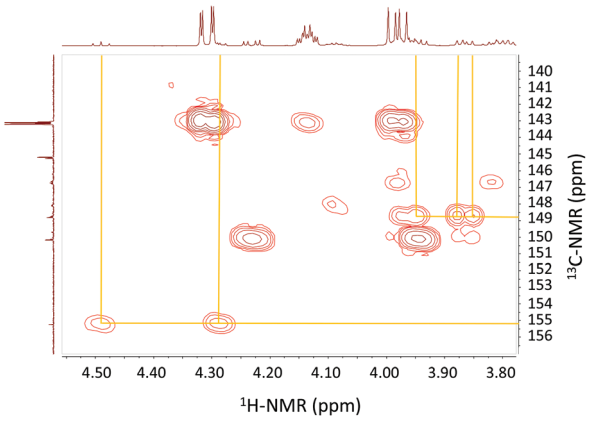

Fig. 14 HMBC-NMR (600 MHz, DMSO-d_6) of the mixture obtained from the reaction between catechol and glycerol carbonate. Details of the ^{1}H-NMR aliphatic region *vs.* ^{13}C-NMR carbonates and *ipso*-C region (yellow lines correspond to the signals of **5**).

The same approach was used for the identification of the mixture obtained by the reaction of GlyC with catechol which has been performed at 170 °C for 1 h.[32]

Signals arising from **5** can be identified even though the reaction between catechol and glycerol carbonate gives much more complicated NMR spectra (Fig. 13 and 14; Fig. S16–S21†), due to overlapping of signals attributable to **5**, **6**, **7**, and other minor products. Nevertheless, HMBC and ^{1}H- and ^{13}C-NMR spectra, which were available for both **2** and products **6** and **7**, made possible the identification of the NMR pattern for compound **5** (yellow lines in Fig. 13 and 14). The remaining signals could be attributed to polymeric compounds, like those described in Scheme S3.†

It is important to stress that, as already observed for intermediate **2**, the correlation between –CH_2 from the five-membered cyclic carbonate of **5** and C=O at approx. 155 ppm (Fig. 14) confirms the presence of the cyclic carbonate. Indeed, the correlation between –CH_2 in the lateral chain and an *ipso* C at approx. 149 ppm (chemical shift typical of a catechol compound with an ether in the lateral chain) made the link between the two fragments of structure **5** unambiguous.

Conclusions

An innovative and straightforward synthesis pathway to 2-hydroxymethyl-1,4-benzodioxane (HMB) and its isomer, without the use of toxic, harmful compounds and solvents, is proposed herein.

The peculiar reactivity of glycerol carbonate (GlyC) as an alkylating agent for aromatic compounds, and in particular with catechol, for the successful synthesis of heterocyclic benzodioxane scaffolds has been widely discussed. Indeed, a mechanistic investigation has underscored the unique behaviour of GlyC compared to other organic carbonates (*e.g.* propylene carbonate) and the importance of GlyC as a multi-functional structure, in particular of the free aliphatic –OH group. The latter plays a fundamental role in obtaining the reactive carbonate intermediate responsible for intramolecular cyclization aimed at the selective formation of HMB, with only water and carbon dioxide as benign co-products. Under the optimized conditions, water is partially removed by distillation or readily reacts with GlyC leading to the formation of glycerol. On the other hand, CO_2 represents the only light compound produced and readily leaves the flask. These behaviours finally prevent the formation of carbonic acid that could poison the basic catalyst.

Noteworthily, for a greater scale some tests can be performed under vacuum in order to collect almost pure CO_2 to be valorised for the synthesis of organic carbonates (*e.g.* glycerol carbonate from glycidol to reintroduce in the production line), urea or other valuable compounds.

Future studies will be aimed at extending the reaction to the formation of enantiomerically pure HMB starting from chiral GlyC.

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Conflicts of interest

There are no conflicts to declare.

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32 It must be taken into account that **2** is more stable than the intermediate **5**, probably because of its rapid rearrangement due to the additional aromatic –OH moiety (favoured at high temperature (*e.g.* GC-MS injector at 280 °C). In order to prevent decarboxylation and overcome the lower stability of **5** the reaction between GlyC and catechol has been performed in a closed J Young valve NMR tube.

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