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Research Article

Glycerol Carbonate as a Versatile Alkylating Agent for the Synthesis of β-Aryloxy Alcohols

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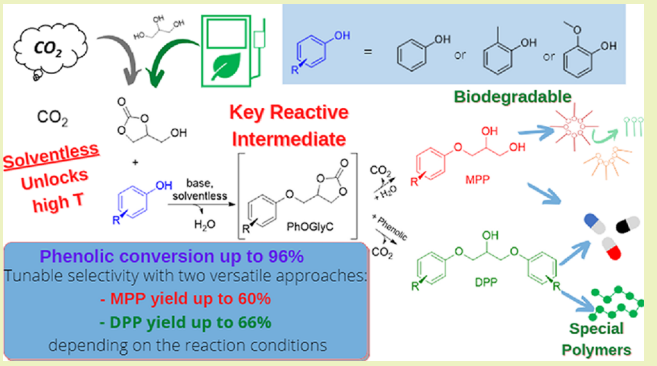
ABSTRACT: The possibility to use glycerol carbonate (GlyC) as an innovative alkylating agent for phenolic compounds in solventless conditions and in the presence of a catalytic amount of both homogeneous and heterogeneous bases is herein described. In particular, the peculiar, polyfunctional structure of GlyC allows one to obtain the formation not only of the mono-phenoxy-1,2-propanediol (MPP) analogue but also of 1,3-diphenoxy-2-propanol (DPP), the latter being elusive using the more traditional, toxic, and carcinogenic reagents such as glycidol and/or 3-chloro-1,2-propandiol. The production of DPP is indeed possible due to the *in situ* formation of a reactive intermediate, 4-(phenoxy)methyl-1,3-dioxolane-2-one (PhOGlyC), which may undergo a consecutive nucleophilic attack of a phenolate, leading to the selective formation of the disubstituted product. This reaction is nonetheless in competition with PhOGlyC decarboxylation that finally limits DPP yield up to 20%, with an MPP yield up to roughly 60% in the optimized conditions (atmospheric pressure, 140 °C, 5 h using Cs_2CO_3 as the basic catalyst) starting directly from a GlyC/phenolic mixture. For this reason, a multistep synthetic strategy has also been developed, first by obtaining the quantitative formation and isolation of the PhOGlyC intermediate and then by promoting the consecutive reaction with phenol, in this way obtaining a DPP yield of 66% after only 1 h of reaction at 170 °C. The obtained phenyl glyceryl ethers are interesting drugs scaffolds (i.e., guaifenesin, mephenesin), intermediates in the preparation of active pharmaceutical ingredients (e.g., chlorphenesin carbamate, methocarbamol), and hydrotropic solvents; preliminary evaluations of MPP and DPP biodegradability and use as alternative surfactants have also been described in this paper.



KEYWORDS: *glycerol carbonate (GlyC), alkylation, phenyl-glyceryl ethers, transcarbonation, basic catalysis*

INTRODUCTION

In the current scenario, environmental and safety issues play a key role in defining industrial strategies, also influencing goals and principles of recent academic research. In this context, organic carbonates (OCs) represent a promising and versatile class of compounds, displaying properties like high solvency, good biodegradability, and low toxicity.[1] Thanks to their features, OCs' applications are flourishing in a variety of fields, as intermediates in pharmaceutical, polymer, lubricant, and aroma industries or as aprotic polar solvents, fuel additives, and electrolytes in the manufacture of batteries.[1−4]

Among OCs, glycerol carbonate (4-hydroxymethyl-1,3-dioxolan-2-one, GlyC) is considered as one of the most promising examples, as confirmed by the increasing number of publications on this topic (see Figure S1). First, it represents an interesting solution to valorize both glycerol and carbon dioxide, two molecules characterized by low value and high abundance.[5−10] The former is co-produced in biodiesel manufacturing and triglyceride hydrolysis with an estimated production of more than 3.5 Mt/year, a value that represents roughly 10% in mass of the final fuel, whereas regarding the latter, there is an increasing demand for innovative routes to recycle the captured CO_2 to the production cycle. Indeed, GlyC could be produced from glycerol following different strategies: (i) the direct condensation pathway with CO_2 in the presence of a dehydrating agent or by coupling a hydration reaction to shift the equilibrium limitations;[6,9,11−17] (ii) via the direct oxidative carbonylation with CO,[18−21] the latter efficiently obtainable from CO_2 reduction, for instance, via electrochemistry processes;[22−24] and (iii) through the transcarbonation reaction with dimethyl carbonate (DMC) or other carbonyl sources.[25,26] Moreover, GlyC shows all the pros of OCs described before, with no hazards currently mentioned in

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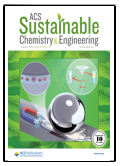
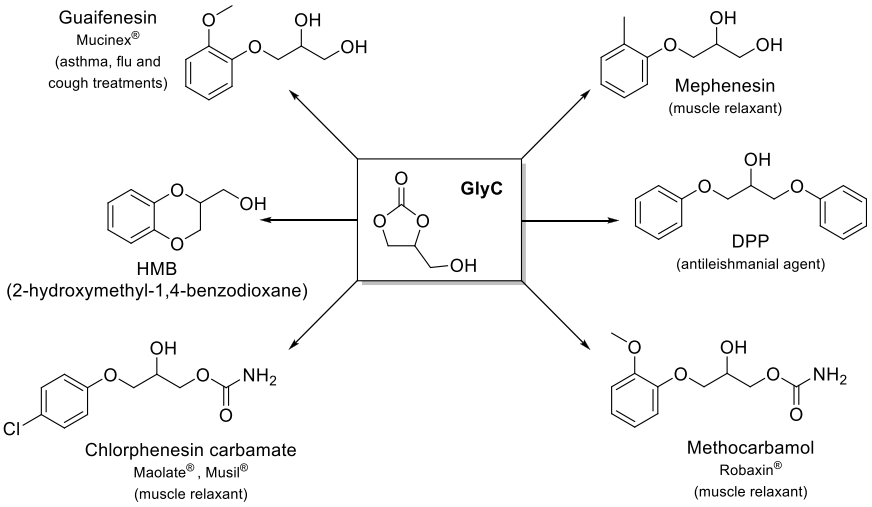


Scheme 1. Glycerol Carbonate (GlyC) Structure and Some Derived Active Pharmaceutical Ingredients (APIs) and 1,3-Diphenoxy-2-propanol (DPP)



the Safety Data Sheet, in addition to a very high boiling point (100−115 °C at 0.1 mmHg).[27] This could represent a crucial advantage allowing one to perform liquid phase reactions involving GlyC (as both reagent and solvent) at relatively high temperatures by working at atmospheric pressure, in this way fostering the kinetics without the need for expensive equipment. For all these reasons, GlyC finds a lot of applications in polymer and pharmaceutical preparation, as a chemical intermediate and solvent, and as an organic electrolyte carrier in batteries and in many other fields.[5,28] GlyC's versatility is mainly related to its peculiar structure, bearing both carbonate and free primary aliphatic −OH functional groups, which lead to reactive electrophilic and nucleophilic sites, respectively. In this context, the most investigated reactivity is the one related to the cyclic carbonyl moiety, in particular to the soft methylenic carbon atoms, which are soft electrophilic sites. By exploiting the reactivity of these sites, GlyC can be used as an alkylating agent of a wide range of nucleophilic substrates like amines, alcohols, and phenolics, avoiding the need for toxic and carcinogenic compounds such as epichlorohydrin, 3-chloro-1,2-propandiol, or glycidol and obtaining products of interest such as alkyl-glyceryl ethers, N-alkylated amines, benzodioxanes, and monoglycerides in a safer way.[29−33]

In a recent work, our group investigated the very peculiar reactivity of GlyC as an alkylating agent of catechol in an innovative, one-pot synthesis of 2-hydroxymethyl-1,4-benzodioxane (HMB).[30,34] In particular, the selective formation of this cyclic ether, a key structure for the production of several drugs, was proved to be possible only thanks to the presence of the free −OH group in the GlyC moiety. Indeed, the free −OH allows the formation of another cyclic carbonate, which represents the unique and very reactive intermediate for the ring closure reaction that leads to HMB formation.[30] Galvanized by this achievement, we guessed the potentials of the use of GlyC also for the derivatization of phenol (PhOH) with the aim of obtaining both 3-phenoxy-1,2-propanediol (or mono-phenoxy-1,2-propanediol, MPP) and 1,3-diphenoxy-2-propanol (DPP) and a few selected substituted analogues starting from phenol derivatives. Many of these mono aryl-glyceryl ethers are used as drugs (guaifenesin, mephenesin) or are intermediates in the preparation of active pharmaceutical ingredients (chlorphenesin carbamate, methocarbamol; Scheme 1) and hydrotropic solvents.[35−38] Similarly, the synthesis of 1,3-diphenoxy-2-propanol (DPP), the formation of which is elusive for instance using glycidol, is of interest because of its biological activity as an antileishmanial agent[39] and its use as an intermediate for the synthesis of pharmaceuticals and special polymers.[40]

Noteworthily, the synthesis of MPP analogues is mainly performed by using glycidol or epichlorohydrin, which are toxic and carcinogenic compounds, while DPP is only produced by the phenolysis reaction of phenyl glycidyl ether (i.e., the phenoxy ether of glycidol) in the presence of a catalyst (e.g., homogeneous or supported bases or Lewis acids like bismuth triflate) or by the use of the carcinogenic epychlorohydrin.[41−45] However, despite both the flourishing interest in finding new applications to versatile, bio-based compounds like GlyC and the importance of β-aryloxy alcohols, only few works have been published on the potential applications of GlyC as an alkylating agent for phenolic compounds. In 2013, Truscello *et al.* investigated the synthesis of β-aryloxy alcohols through the reaction between glycerol, diethyl carbonate (DEC), and phenol (or derivatives) in basic catalysis via GlyC *in situ* production. This elegant one-pot strategy, however, suffers from operating temperature limits due to DEC's relatively low boiling point (ca. 126 °C); therefore, it requires long reaction times (8−18 h). Moreover, the coproduction of 2 mol of ethanol per mole of converted DEC decreases the atom economy of the process down to 55%, leading, in addition, to the formation of an even lower boiling point azeotrope (between DEC and ethanol).[46] The only other example regarding the reaction between GlyC and a phenolic compound (i.e., guaiacol) to produce the corresponding β-aryloxy alcohol has been performed by exploiting TBAF (tetrabutylammonium fluoride) as a catalyst in toxic DMF as a solvent.[47]

For all the reasons mentioned above, the solventless reaction between GlyC and phenol (or its derivatives) is herein reported and extensively investigated for the synthesis of both MPP and DPP, adjusting the reaction protocol and conditions to selectively obtain the former or the latter. In particular, considering MPP production, by working with stoichiometric amounts of reagents, a theoretical atom economy of 79% can

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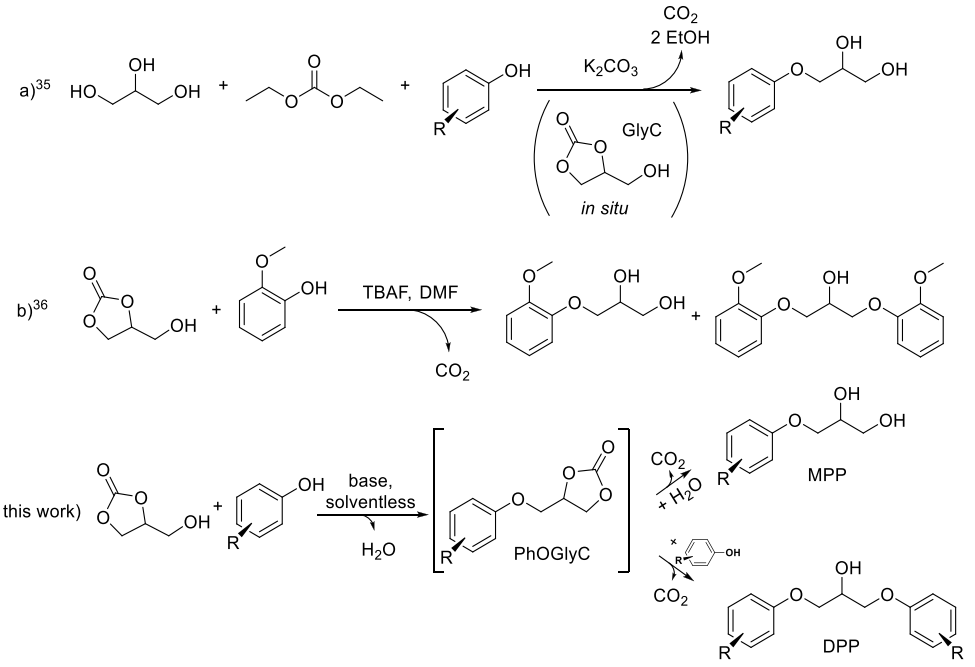
Scheme 2. Possible Synthesis of β-Aryloxy Alcohols Based on GlyC



be achieved with the evolution of only CO_2 as a co-product (Scheme 2). Moreover, only cheap, nontoxic, and environmentally friendly basic catalysts (i.e., inorganic carbonates, alkoxides, alkali earth metal oxides, and zeolites) and solventless conditions have been taken into account, and both the reaction conditions and procedures have been optimized to maximize MPP or DPP yields and selectivity (Scheme 2). Finally, MPP and DPP have been characterized in terms of the critical micellar concentration (CMC) to evaluate their potential application as bio-based surfactants and biodegradability considering the potential environmental impacts after their use.

MATERIALS AND METHODS

Material and Catalyst Preparation. The organic reagents were used without further purification. Dimethyl carbonate (DMC), Nile Red, and 4-hydroxymethyl-1,3-dioxolan-2-one (GlyC) were purchased from Sigma Aldrich, while phenol was purchased from VWR and 3-phenoxy-1,2-propanediol was purchased from TCI.

All the inorganic carbonates ($Na_2CO_3{\cdot}H_2O$, K_2CO_3, Rb_2CO_3, and Cs_2CO_3) and sodium methoxide were used as purchased (Sigma Aldrich, overall purity ranging from 95 to 99.9%) without any further purification. The zeolite, sodium mordenite (Na-Mord), 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.[30] The zeolite was dried at 120 °C overnight before each test and used as purchased. On the other hand, high specific surface area magnesium oxide was synthesized by precipitation following a procedure reported in the literature.[26]

Heterogeneous Catalyst Characterization. Magnesium oxide (MgO) and sodium mordenite were characterized by X-ray diffraction; temperature programmed desorption (TPD) of CO_2 and NH_3 for the analysis of basic and acidic sites, respectively; and nitrogen physisorption for the quantification of BET specific surface area (see the Electronic Supporting Information, ESI, for the detailed experiment procedures).

In this way, the SSA of MgO was found to be equal to 160 ± 5 m^2/g, while CO_2-TPD analysis allowed us to quantify the overall basic sites (0.64 mmol CO_2/g, see Figures S4 and S5 and Table S1 ESI); no acidity has been found through NH_3-TPD (Figures S6 and S7), as expected from an alkali earth basic oxide.

Accordingly, sodium mordenite (Na-Mord) Zeocat FM-8, featuring 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, was characterized by CO_2 and NH_3-TPD to quantify its basic and acidic sites (respectively, 1.0 mmol CO_2/g and 1.5 mmol NH_3/g, Figures S8−S11, respectively).

Phenolic Alkylation with GlyC: Reaction Procedure and Analysis. The alkylation of phenol (or its derivatives) with GlyC was carried out in a one-neck, round-bottom glass flask, charging 0.25 g of aromatic and a suitable amount of GlyC and catalyst. The temperature was controlled by an oil bath on a hot plate, which also provided magnetic stirring, generally set at 350 rpm. After the reaction, the mixture was cooled in a water/ice bath, and then it was collected and diluted using acetone in a 25 mL volumetric flask and filtered. A 5.0 mL aliquot was taken and, after addition of 20 μL of octane, used as the internal standard, diluted in a 10 mL volumetric flask, and analyzed in a Thermo Focus gas chromatograph equipped with an 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}) and an FID detector. The temperature ramp was composed of an initial 2 min isothermal step at 50 °C, then a 10 °C/min ramp up to 130 °C, 2 min isothermal step, 20 °C/min ramp up to 280 °C, and a final isothermal step of 5 min.

The structure of the products was assigned by GC−MS, Agilent Technologies 6890 GC equipped with an Agilent HP-5 capillary column (30 m × 250 μm × 1.05 μm) and an Agilent Technologies 5973 mass analyzer, with a temperature profile analogous to the one used in the Thermo-Focus GC-FID, by using their internal databases, by comparison with the literature, and, whenever possible, by comparison to authentic commercial samples.

The tests were performed in triplicate to ensure reproducibility: results showed conversions and yields that differed by less than 5%.

All the reagents and products have been calibrated in an appropriate concentration range, and the conversion (X_i), yield (Y_i), and selectivity (S_i) were calculated according to the following equations:

$$X_i = \frac{n_i^s - n_i^f}{n_i^s} \cdot 100 \quad (1)$$

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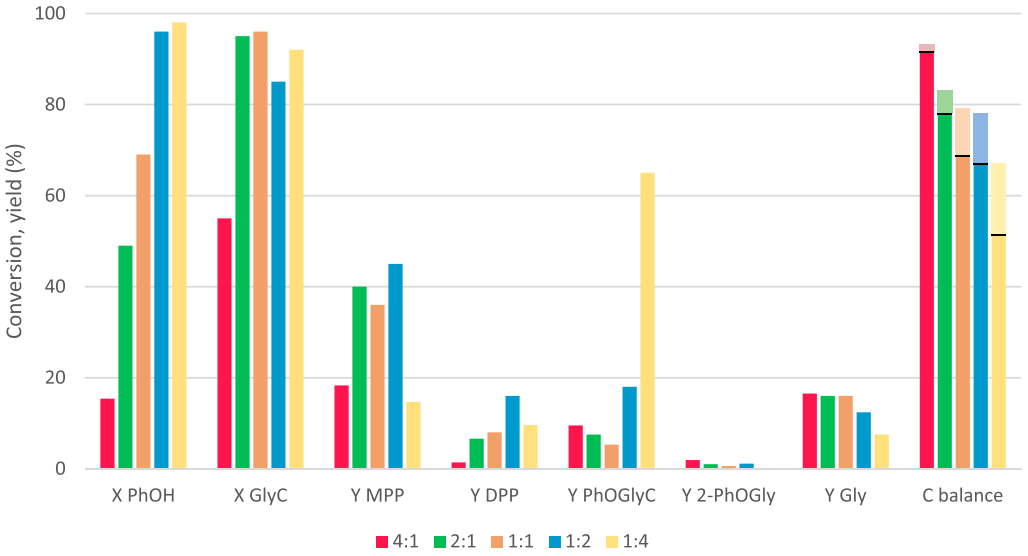

Figure 1. Effect of the PhOH/GlyC molar ratio. The estimated contribution of CO_2 to the carbon balance is reported in lighter colors on the C -balance bars. Reaction conditions: T = 140 °C; t = 5 h; atmospheric pressure; catalyst: $NaOCH_3$ = 6.7 mol % (with respect to the limiting reagent). X = conversion; Y = yield.

$$Y_i = \frac{n_i^f}{n_{LR}^s} \cdot 100 \quad (2)$$

$$S_i = \frac{n_i^f}{n_{LR}^s - n_{LR}^f} \cdot 100 = \frac{Y_i}{X_{LR}} \cdot 100 \quad (3)$$

where superscripts s and f represent "starting" and "final", respectively, and the subscript LR stands for "limiting reagent".

The mass balance was calculated in two different ways: (a) as a "standard" carbon balance by dividing the sum of the carbon atoms detected in the reaction mixture by the sum of the carbon atoms of the reagents fed and (b) as the ratio between the sum of the yields of the aromatic products and the conversion of the limiting reagent, generally phenol or its derivatives ($\sum Y/X$). This choice is due to the coproduction of CO_2 during the reaction, which intrinsically limits the standard C-balance achievable by recovering only the liquid phase.

Multistep Process for the Selective Production of DPP. To synthesize selectively DPP, a multistep approach was set up, starting from commercial MPP, via the production of 4-(phenoxy)methyl-1,3-dioxolane-2-one ("intermediate", PhOGlyC) and subsequent reaction with another equivalent of phenol.

The synthesis of the intermediate has been performed through the carbonate interchange reaction between MPP and DMC. To foster the reaction and shift the equilibrium toward the products, a recently reported reactive distillation apparatus, known as the reactive vapor absorption (RVA), has been used.[48] In particular, catalytic tests were carried out by loading the desired amount of MPP, dimethyl carbonate (DMC), and $NaOCH_3$ (molar ratio 1:40:0.033) in a Pyrex-glass double-neck round-bottom flask equipped with a magnetic stirrer fitted with suitable reflux condensers. Between the vertical condenser and the flask, a vertical adapter, fitted with a porous glass frit loaded with 10 g of molecular sieves (4 Å), was inserted to selectively sequester the co-formed methanol. The reactions have been performed under magnetic stirring (350 rpm) at vigorous reflux conditions (oil bath temperature has been kept at 120 °C) for 4 h. After the reaction, the solution was rapidly quenched in an ice bath, and the product was recovered using the procedure as follow: the reaction mixture was dried under a vacuum (rotavapor) to recover the DMC excess (≈88% of the initial DMC was recovered and recycled for another synthesis with no evident drawbacks), and the intermediate (PhOGlyC) was obtained as a white solid in quantitative isolated yield, with 95% purity estimated by GC.

To produce DPP, the intermediate obtained previously was reacted with phenol in 1:1 molar ratio in the presence of a base for 1 h at 170 °C.

MPP and DPP Characterization: Biodegradability and CMC Determination. The critical micellar concentration (CMC), meaning the concentration of a certain surfactant above which molecules tend to self-aggregate, forming micelles in an aqueous solution, of MPP and DPP have been measured. For each product, CMC has been determined using Nile Red as the fluorescence probe.[49] In detail, fluorescence spectra of 2.0 μM Nile Red solutions in water containing increasing concentrations of MPP ranging from 0.1 to 20 mM have been recorded with a Varian Cary Eclipse fluorescence spectrophotometer. For DPP, concentrations investigated ranged from 0.1 to 2.0 mM due to the solubility limit of DPP in water. The recorded intensities in correspondence of the emission peak of Nile Red (λ = 650 nm) have been plotted versus the concentration of the investigated product (see Figure S16).

Moreover, the aerobic biodegradability of MPP and DPP has been determined according to the manometric respirometry test (OECD 301F).[50] The results have been reported as the ratio between the biochemical oxygen demand after 28 days (BOD_{28}), measured using an Oxitop respirometer bottle (Xylem, USA), and the calculated theoretical oxygen demand (ThOD) (2.00 g O_2/g MPP and 2.29 g O_2/g DPP, respectively) for each product.

RESULTS AND DISCUSSION

Homogeneous Catalysis: Operating Condition Optimization and Reaction Scheme Investigation. The alkylation of phenol (PhOH) with GlyC has been studied in solventless conditions, exploiting GlyC as both reactant and solvent. The choice of reacting directly GlyC instead of producing it *in situ* by transcarbonation reaction between glycerol (Gly) and a different organic carbonate allows one to (i) work at higher temperatures and atmospheric pressures, thanks to the very high boiling point of GlyC, thus enhancing the kinetic of the reaction, and (ii) to enhance the selectivity of target products, thus avoiding the parasite alkylation reactions that may occur by working with a mixture of OCs.

Starting from the results recently reported by our group for the reaction between GlyC and catechol,[30] the alkylation of phenol with GlyC was carried out using sodium methoxide ($NaOCH_3$) as the catalyst. Preliminary tests, reported in

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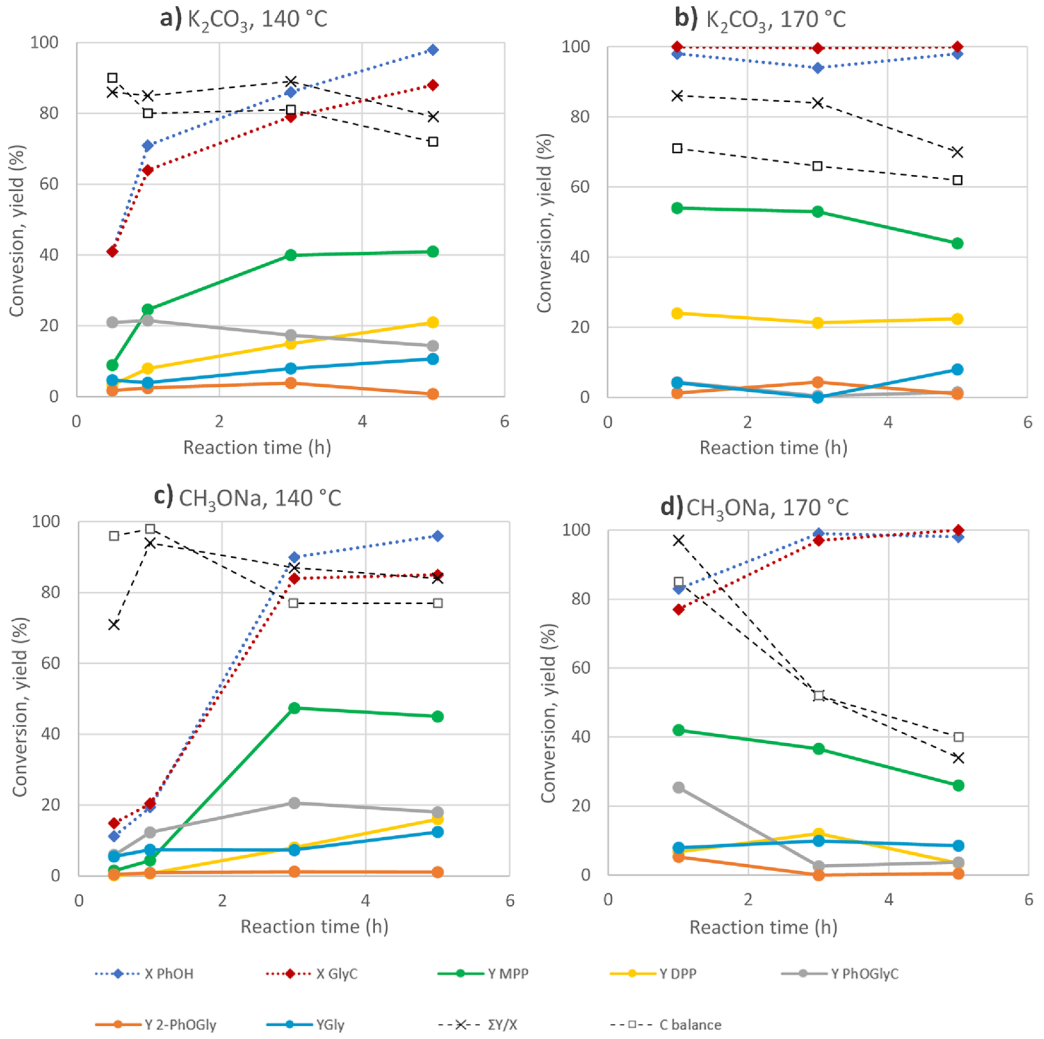

Figure 2. Comparison of the catalytic activity between potassium carbonate and sodium methoxide at different temperatures and reaction times. Reactants' conversions are reported in dotted lines, and carbon balances are in dashed lines (C-balance here includes the evolution of CO_2). Reaction conditions: PhOH/GlyC/cat molar ratio = 1:2:0.067, catalyst (a, b) K_2CO_3, (c, d) CH_3ONa; atmospheric pressure: T = (a, c) 140 °C and (b, d) 170 °C.

Figure S12, allowed us to choose a base loading of 6.7 mol % with respect to PhOH as the best compromise to obtain a relatively fast kinetic with a limited amount of base. First, the effect of PhOH/GlyC molar ratio was investigated (Figure 1). As can be observed, phenol conversion increases by increasing the amount of GlyC, whereas MPP, generally observed as the main product, and DPP yields display a maximum value when the PhOH/GlyC molar ratio is 1:2 (with a phenol conversion of 96%). By increasing the amount of GlyC to 4 mol per mole of PhOH, the intermediate PhOGlyC forms as the main product; these results gave some insights on the reaction scheme that will be presented later. In these cases, the overall carbon balances are reported, in which the contribution of the loss due to CO_2 evolution is highlighted in lighter colors, on a horizontal line, over the carbon balance columns. The results clearly show a worsening of the carbon balance by increasing the amount of GlyC fed into the system, an effect that can be explained considering that, at high phenol conversion, a strong base as sodium methoxide is also able to activate the aliphatic hydroxyl group on GlyC, MPP, and glycerol, in this way promoting the formation of heavier oligomeric compounds not detectable by GC analyses.

For the following tests, the PhOH/GlyC molar ratio of 1:2 was selected as the best condition to obtain MPP and DPP in good yields. Moreover, a study of the effect of the reaction temperature was carried out between 110 and 170 °C and confirmed 140 °C as the best compromise between kinetic and side reactions (see Figure S13). Then, besides sodium methoxide, another common and cheap basic inorganic salt, potassium carbonate (K_2CO_3), has been tested as a suitable alternative catalyst, being already applied in analogue processes reported in the literature and featuring a lower basicity, which would limit parasite oligomerization reactions.[46] The comparisons of catalytic results obtained with both basic materials at different times and temperatures (140 and 170 °C), with a slight excess of GlyC, are shown in Figure 2.

At first glance, it is possible to observe that both the catalysts tested are active for the alkylation of phenol with GlyC, giving MPP as the main product (yield up to 54%). Moreover, at the lowest temperature, 140 °C, and short times, potassium carbonate is more active than sodium methoxide. Raising the temperature to 170 °C, the reaction rates increase, as expected, reaching high conversion at short times with both catalysts. Considering the C-balance trends over time, a recurring

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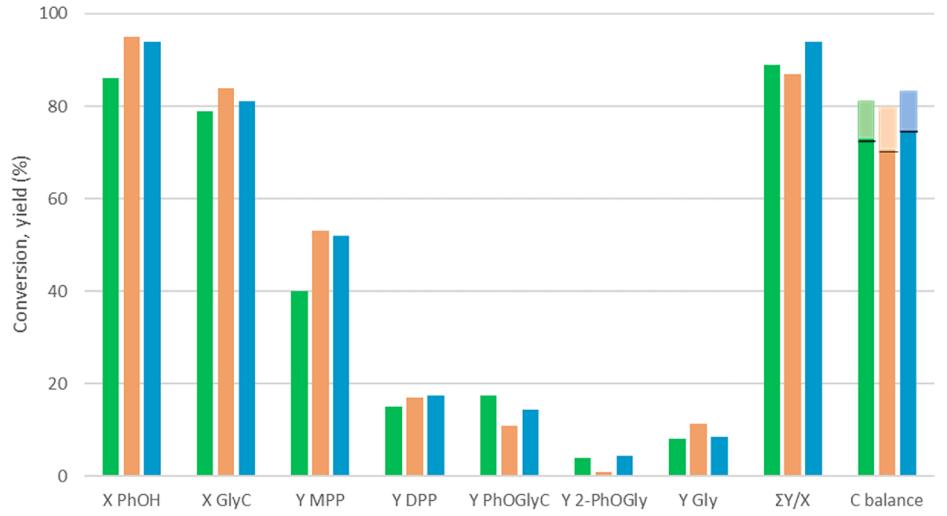

Figure 3. Screening of the catalytic activity of inorganic carbonates. The estimated contribution of CO_2 to the carbon balance is reported in lighter colors on the C-balance bars. K_2CO_3 (green bars), Rb_2CO_3 (orange bars), and Cs_2CO_3 (blue bars). Reaction conditions: PhOH/GlyC/cat molar ratio = 1:2:0.067; atmospheric pressure; T = 140 °C; t = 3 h.

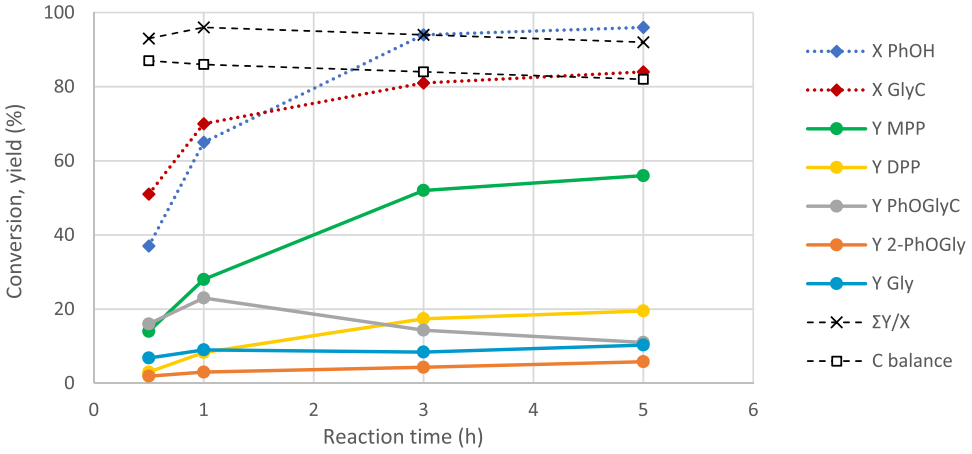

Figure 4. Trends of yields and conversions according to the reaction time. Carbon balances in dashed lines (C-balance here includes the estimated evolution of CO_2). Reaction conditions: PhOH/GlyC/Cs_2CO_3 molar ratio = 1:2:0.067; atmospheric pressure; T = 140 °C.

behavior has been observed. In particular, this parameter seems to be strongly affected by the PhOH conversion value, decreasing rapidly when PhOH is scarcely present in the reaction environment (i.e., X > 80%). This is particularly true when a stronger base (i.e., sodium methoxide) is used, which is able to activate consecutive reactions on aliphatic hydroxyl groups present in MPP, DPP, GlyC, and glycerol, producing heavy byproducts, which are not detectable with the analytical techniques used, finally lowering the C-balances. In this context, the presence of the unreacted, stronger, acidic, and aromatic −OH groups in PhOH moieties effectively prevents the undesired activation of those parasitic reactions. Thus, potassium carbonate was demonstrated to be a valid catalyst, giving good yields and carbon balances for long reaction times at high temperatures; therefore, a screening of different inorganic carbonates, ranging from potassium to cesium, was carried out to look for possible cation effects (Figure 3). The obtained results showed that there are no significative differences in terms of conversions, yields, and mass balances between rubidium and cesium carbonate, while K_2CO_3 displayed a slightly lower activity and higher selectivity to the intermediate PhOGlyC.

Therefore, given the lower price with respect to Rb_2CO_3, cesium carbonate was then selected for further studies on the reaction kinetics to better understand the mechanism of the reaction and to confirm the trends of yields and conversions based on the reaction time (Figure 4).

Considering the conversions of the reagents, they display the expected growing trend, reaching an almost complete conversion of the limiting reagent after 3 h. Both MPP and DPP show increasing yields in time, reaching almost 60% for the former, obtained as the main product, and 20% for the latter at 96% phenol conversion. Regarding PhOGlyC, it displays an initial growth in yield and then it decreases at longer reaction times, showing the characteristic trend of reaction intermediates.

The trends observed suggest a reaction scheme in which phenol is initially activated by the basic catalyst via deprotonation, promoting a nucleophilic attack on the activated soft electrophilic sites of the GlyC ring, preferentially on the less hindered site, in this way opening the cyclic moiety of the carbonate, whereas the direct condensation of the free OH groups of phenol and GlyC does not take place, as already reported.[30] Similarly, the direct etherification between the

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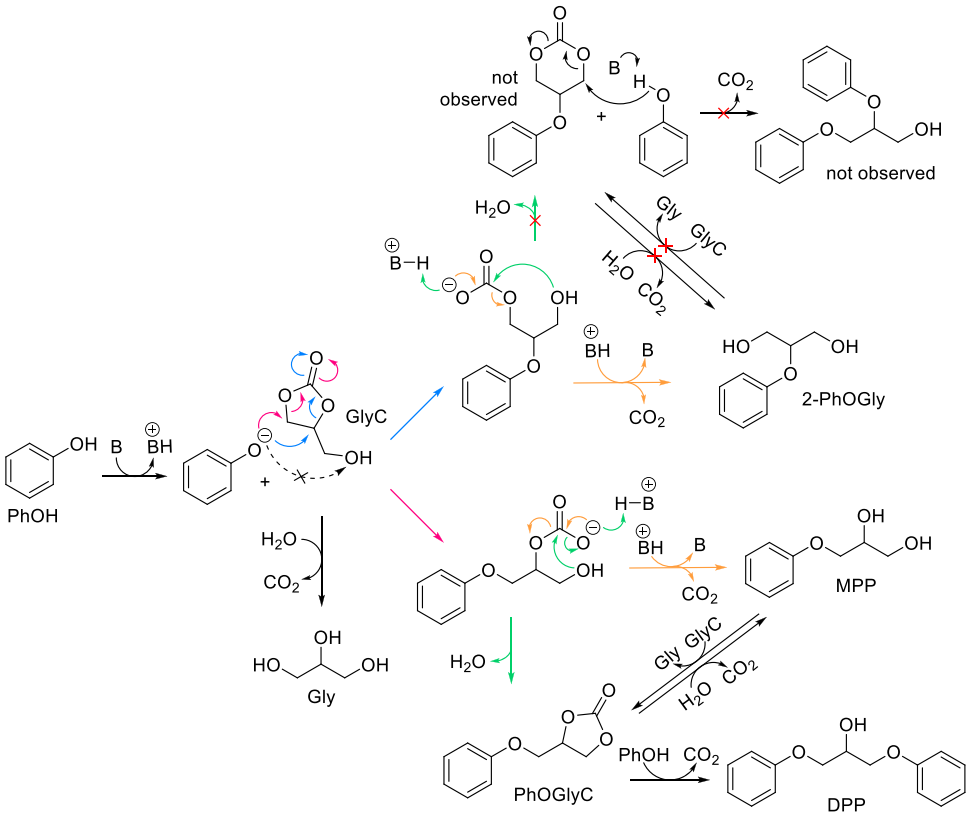
Scheme 3. Proposed Reaction Network for the Production of MPP, PhOGlyC, and DPP in the Presence of a Basic Catalyst



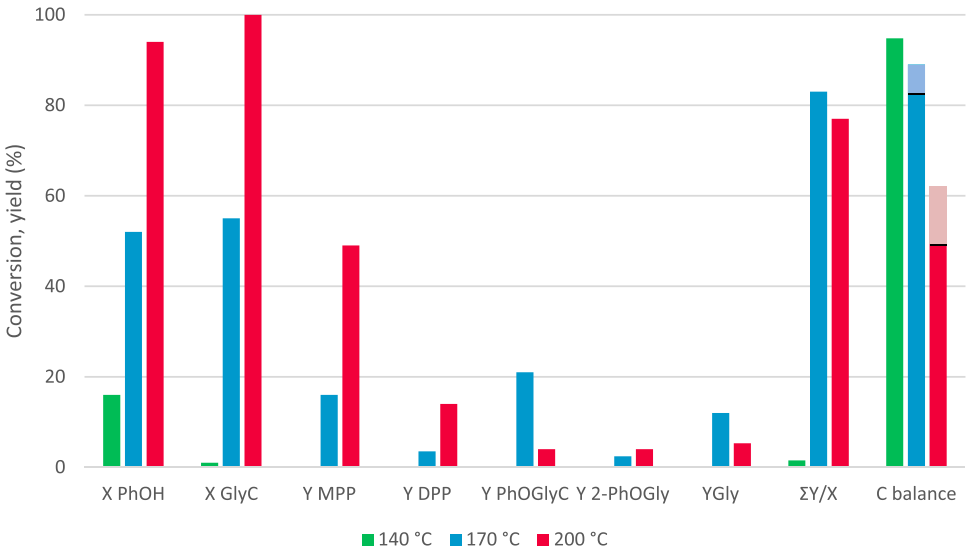


Figure 5. Effect of reaction temperature on the catalytic activity of MgO for the reaction between PhOH and GlyC. Reaction conditions: PhOH/GlyC molar ratio = 1:2; MgO 5 wt %; atmospheric pressure; t = 5 h.

PhOH aromatic hydroxyl group and the aliphatic −OH group of MPP has been excluded by a dedicated control test (see ESI for further details). The intermediate formed can then decarboxylate, yielding MPP, or dehydrate to restore the cyclic carbonate in PhOGlyC. Moreover, these products can interconvert each other through transcarbonation or hydrolysis/decarboxylation reactions, as highlighted by the high yield of PhOGlyC in case of a greater excess of GlyC (see Figure 1, GlyC/PhOH molar ratio of 4); therefore, MPP can be considered as both the final product and intermediate. PhOGlyC can also undergo further nucleophilic attack by PhOH, this one being the only possible way to produce DPP. Since the formation of PhOGlyC via dehydration/ring closure of the intermediate coproduces water, hydrolysis of GlyC can take place, yielding glycerol and CO_2. Considering an effective GlyC hydrolysis, it becomes impossible to determine whether the glycerol observed is produced by carbonate interchange reaction between MPP and GlyC or GlyC hydrolysis since it is coproduced in equal amounts. The proposed reaction pathway is reported in Scheme 3.

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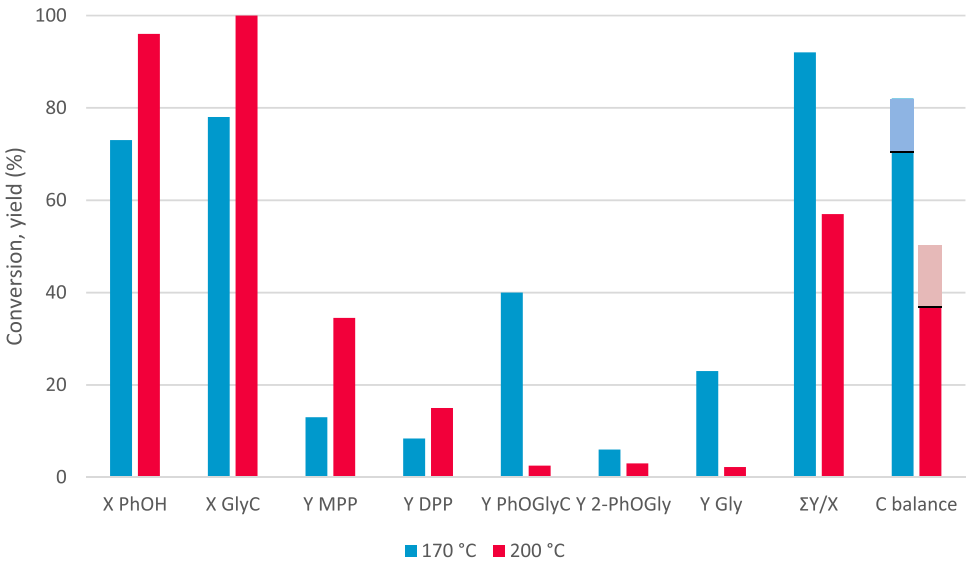

Figure 6. Effect of reaction temperature on the catalytic activity of Na-mordenite for the reaction between PhOH and GlyC. Reaction conditions: PhOH/GlyC molar ratio = 1:2; Na-mordenite 5 wt %; atmospheric pressure; t = 5 h.

As shown in all the results reported, the MPP isomer, 2-phenoxy-1,3-propanediol (2-PhOGly), is always present among the products, even if in low amounts. Therefore, the attack of activated phenol on the more hindered carbon of GlyC is possible, even if unfavored, but the formation of the PhOGlyC analogue, with a six-membered cyclic carbonate moiety, was not observed, probably because of the lower stability of this kind of cyclic carbonates with respect to the ones with five-membered cycles that hampers its formation.[51] As a consequence, the DPP isomer, 2,3-diphenoxy-1-propanol, also was never observed.

Heterogeneously Catalyzed Production of MPP and DPP. A key aspect in the industrial processes is the downstream separation of the products from additional substances such as solvents and catalysts. Regarding this issue, the substitution of homogeneous catalysts with heterogeneous ones facilitates the separation, recovery, and recycling of the catalyst.[52] For this reason, one of the most common basic heterogeneous catalysts, i.e., magnesium oxide, was tested for the reaction. Since heterogeneous catalysts generally need higher temperatures to be active, an initial screening of the catalytic activity of MgO at different temperatures has been carried out and is reported in Figure 5.

It is possible to observe that, at 140 °C, the conversion of the reagents is relatively low, and the yields of the target products are nearly negligible, meaning that most of the converted reagents are indeed adsorbed on the catalyst surface. At 200 °C, it is instead remarkable that the results obtained, in terms of conversions and yields, are comparable to the ones obtained in homogeneous catalysis, even if with lower carbon balances.

Subsequently, a commercial zeolite, Na-mordenite, was tested in the same reaction in a temperature range of 170−200 °C. The results, reported in Figure 6, show that this catalyst is active in this temperature range. But interestingly, at 170 °C, it displays a higher selectivity toward PhOGlyC, while at 200 °C, the selectivity mirrors the one observed with MgO. This effect can be related to the different active sites and pores of Na-mordenite, which feature higher selectivity toward transcarbonation at 170 °C, while at 200 °C, a higher activity is observed, both in the PhOGlyC transformation to MPP (via hydrolysis) and DPP and in the production of heavy compounds and degradation reactions, as demonstrated by the lower mass balance. The herein reported results with heterogeneous catalysis need to be considered as preliminary data. In particular, working with a neat mixture of GlyC and PhOH, without any additional external solvent, has probably led to internal diffusional limitations when a microporous material like Na-mordenite is used as basic catalyst. Dedicated tests by promoting the fine tuning of the internal porosity of the zeolite (using synthesized materials or different zeolites) will be taken into account in the future and are out of the scope of the current manuscript. Nonetheless, the reaction over Na-mordenite is probably performed over the external surface of the zeolite or, in a lesser amount, inside the greater pores of the material (pore size 6.5 × 7.0 Å). Considering this, the higher selectivity toward the intermediate PhOGlyC at 170 °C may be also due to steric hindrance phenomena that inhibit the consecutive nucleophilic attack of an activate phenol, finally leading to this peculiar behavior in the product distribution.

DPP Synthesis Optimization via an Alternative, Two-Step Approach. Among the catalysts and the reaction conditions tested, none of them permitted obtaining fully satisfying yields in DPP; therefore, an alternative reaction protocol has been set up. It consisted of a two-step approach in which the formation of PhOGlyC was first promoted in a highly efficient and selective way through a carbonate interchange reaction (transcarbonation) between dimethyl carbonate (DMC) and MPP, obtained as the main product in the majority of the one-step tests (with a maximum yield of 56% at 140 °C for 5 h in the presence of Cs_2CO_3 catalyst). To do so, a recently reported reactive distillation apparatus, known as the reactive vapor absorption (RVA), which allows one to foster the reaction and shift the equilibrium toward the target product, has been used.[48] In this way, a complete conversion of MPP was achieved in only 4 h at 90 °C in the presence of an excess of dimethyl carbonate (DMC/MPP = 20:1) and a genuine catalytic amount of cesium carbonate as the catalyst (3.3 mol %). PhOGlyC, obtained with 100% selectivity, was

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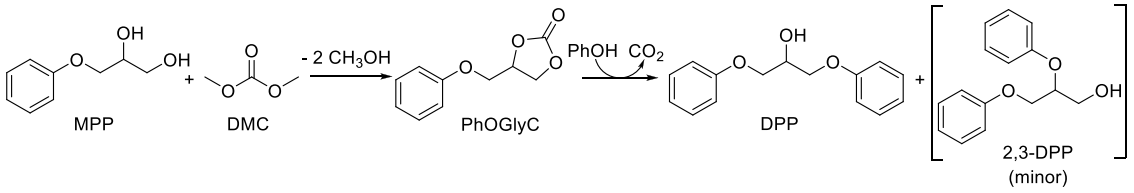
Scheme 4. Multistep Approach to Obtain DPP in High Yields



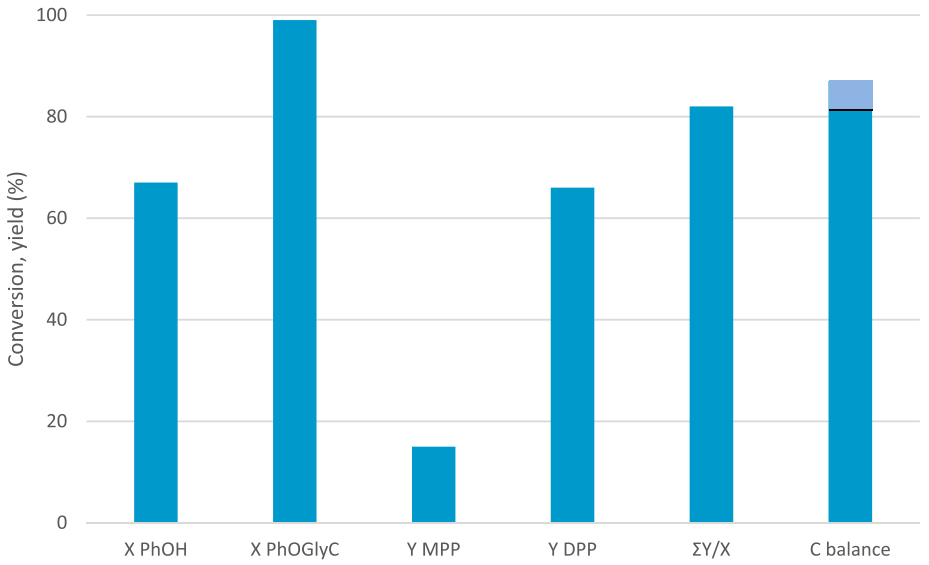


Figure 7. Outcome of the reaction between PhOH and PhOGlyC. Reaction conditions: PhOH/PhOGlyC/Cs_2CO_3 molar ratio = 1:1:0.067; atmospheric pressure; T = 170 °C; t = 1 h.

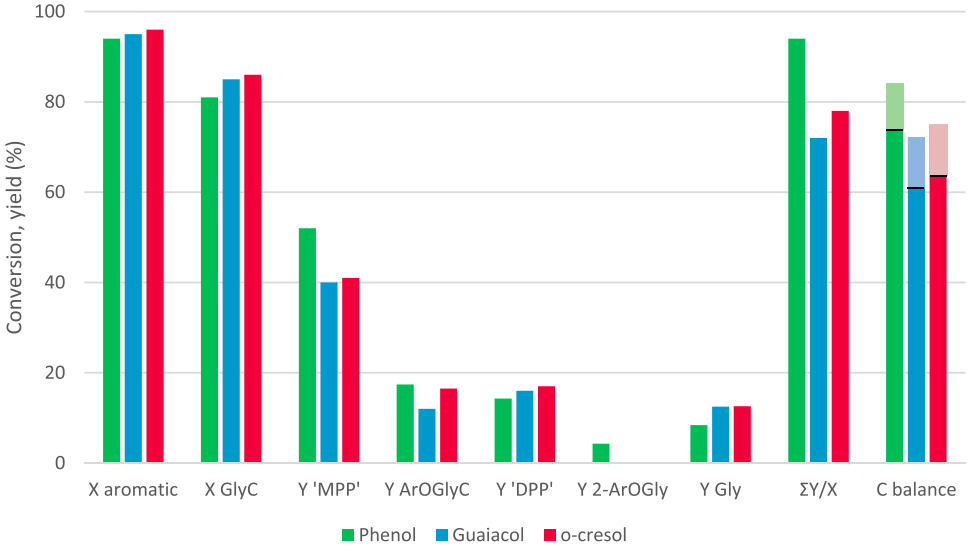


Figure 8. Comparison among the reactivity of phenol and its derivatives. Conditions: aromatic/GlyC/Cs_2CO_3 molar ratio = 1:1:0.067; atmospheric pressure; T = 140 °C; t = 3 h.

easily recovered in 98% isolated yield via DMC distillation and finally reacted with a stoichiometric amount of PhOH to obtain DPP (Scheme 4). Noteworthily, 88% of DMC has been successfully recovered after the distillation and recycled for the production of new PhOGlyC.

The results obtained in terms of yields and conversions are reported in Figure 7.

Interestingly, after only 1 h of reaction at 170 °C, a roughly 66% yield in DPPs has been achieved. For the first time, in these conditions, the formation of the 2,3 isomer (2,3-diphenyl-1-propanol, 2,3-DPP) has been observed with a 1.7% yield, corresponding to a DPP/2,3-DPP molar ratio of 36 (yields included in DP count in Figure 7). Nonetheless, the presence in the final mixture of MPP is a clear indication of a parasite decomposition reaction that increases PhOGlyC conversion, lowering the selectivity of the process. Nonetheless, the use of an inert atmosphere on nitrogen and of

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anhydrous reagents could enhance the selective conversion of PhOGlyC to DPP.

Phenolic Compounds' Alkylation with Glycerol Carbonate. Lastly, the investigation has been extended to other aromatic substrates to apply the optimized conditions to the synthesis of actual APIs such as guaifenesin and mephenesin, obtainable from the alkylation with GlyC of, respectively, guaiacol (2-methoxyphenol) and *o*-cresol (2-methylphenol). The results obtained, reported in Figure 8, demonstrate a similar reactivity among phenol and its derivatives, demonstrating the versatility of the proposed protocol to obtain other products of industrial interest.

Biodegradability and CMC Determination. Considering the main products of this work, MPP and DPP, the determination of both biodegradability and CMC for these compounds represents a crucial point for their forthcoming use, especially for environmental applications. To evaluate the potential application of as-obtained MPP and DPP and in particular as bio-based surfactants, CMCs for both products have been determined using Nile Red as the fluorescence probe. After plotting the emission intensity of Nile Red in the presence of different concentrations of MPP, a CMC of 12.95 mM was found (Figure S16). Unfortunately, in the case of DPP, no CMC was determined due to the low solubility of the product in distilled water.

Moreover, the measured biological oxygen demand after 28 days (BOD_{28}) of MPP and DPP was 105 and 17 mg O_2/L, respectively. From those data, the aerobic biodegradability of both products has been calculated according to the following definition:

$$\text{Biodegradability} = \frac{BOD_{28}}{\text{theoretical oxygen demand (ThOD)}} \quad (4)$$

The as-obtained results allowed us to classify MPP as inherently biodegradable (biodegradability = 52.5%) and DPP as nonbiodegradable (biodegradability = 7.4%).

These results indicate that the further evaluation of MPP as bio-based and biodegradable surfactants is indeed possible, paving the way for future applications (i.e., surfactant assisted extraction). On the other hand, DPP deserves further characterization to find proper applications, a matter that will be investigated in future works.

CONCLUSIONS

In summary, the reactivity of glycerol carbonate as a suitable, innovative, and alternative alkylating agent for phenolics is herein reported. The peculiar structure and properties of GlyC allow one to work in the liquid phase, at atmospheric pressure, and in a wide range of temperatures (up to 200 °C) without the need for any external solvents. The reaction proceeds smoothly in the presence of a genuine catalytic amount of the base, allowing one to obtain phenol conversion of up to 95% in a few hours at 140 °C with MPP and DPP yields as high as 60 and 20%, respectively. Among the bases investigated, inorganic carbonates are the most promising, leading to better carbon balances by suppressing parasite oligomerization reactions on the aliphatic −OH groups, the latter being catalyzed by sodium methoxide in particular at high phenol conversion. Noteworthily, the reaction has also been performed by the use of heterogeneous bases (e.g., MgO and Na-Mord) by working at a slightly higher temperature (200 °C). Moreover, the key role of the *in situ* formed intermediate (PhOGlyC) in the formation of DPP has been highlighted, allowing us to develop an alternative, multistep, synthetic strategy first by promoting the quantitative formation and isolation of the PhOGlyC intermediate and then fostering the consecutive reaction with phenol, in this way obtaining a DPP yield of 66% after only 1 h of reaction at 170 °C. The proposed versatile synthetic strategy allows one to obtain different phenyl glyceryl ethers useful for the preparation of pharma (i.e., guaifenesin, mephenesin), and preliminary evaluations of MPP and DPP biodegradability have highlighted the possibility to use MPP as an alternative biodegradable surfactant.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.2c02795.

Experimental details for the characterization of catalysts and products; XRD and NH_3- and CO_2-TPD graphs; analyses of the specific surface area of the material; effect of the reaction temperature on the catalytic activity of $NaOCH_3$; DSC thermograms of products and evaluation of the CMC of MPP; and workup of the crude mixture and product separation (PDF)

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Notes

The authors declare no competing financial interest.

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