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PAPER

Selective catalytic etherification of glycerol formal and solketal with dialkyl carbonates and K_2CO_3 †

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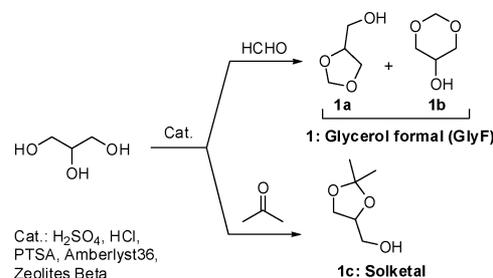
At $T \geq 200$ °C, in the presence of K_2CO_3 as a catalyst, an original etherification procedure of non-toxic acetals such as glycerol formal (GlyF) and solketal has been investigated by using dialkyl carbonates as safe alkylating agents. The effects of parameters including the temperature, the reaction time, and the loading of both the catalyst and the dialkyl carbonate have been detailed for the model case of dimethyl carbonate (DMC). Both GlyF and solketal were efficiently alkylated by DMC to produce the corresponding *O*-methyl ethers with selectivity up to 99% and excellent yields (86–99%, by GC). The high selectivity could be accounted for by a mechanistic study involving a combined sequence of methylation, carboxymethylation, decarboxylation and hydrolysis processes. The *O*-methylation of GlyF and solketal could be successfully scaled up for multigram synthesis even operating with a moderate excess (5 molar equiv.) of DMC and in the absence of additional solvent. Notwithstanding the advantageous reduction of the process mass index, scale up experiments provided evidence that prolonged reaction times may induce the decomposition of DMC mainly by the loss of CO_2 . The K_2CO_3 -catalyzed etherification of solketal with other carbonates such as dibenzyl and diethyl carbonate (DBnC and DEC, respectively), proceeded with the same good selectivity observed for DMC. However, at 220 °C, the solketal conversion did not exceed 81% since both DBnC and DEC were extensively consumed in competitive decarboxylation and hydrolysis reactions.

Introduction

Glycerol is a non-toxic biodegradable compound whose relevance as a chemical is recognized worldwide in a number of applications for the pharma, polymer, and food sectors.¹ Not by chance, in 2004, the National Laboratories of the US Department of Energy, have classified glycerol among the twelve most attractive platform chemicals that can be produced from biomass *via* biological or chemical conversions.² However, due to the exponential increase of biodiesel production and demand, the global market is experiencing a massive surplus of glycerol: in the EU for example, some additional 1.0×10^6 tonnes of such a compound have been available in 2010 (almost tripled since 2005).³

These considerations have fuelled a growing interest of both academic and industrial communities for intensive research programs aimed at the conversion of glycerol and its derivatives into energy and chemicals. In this context, glycerol acetals,

particularly light compounds such as glycerol formal (GlyF) and solketal (**1a–b** and **1c**, respectively) recently caught our attention (Scheme 1). Compounds **1** are non-toxic substances synthesized by acid-catalysed condensations of glycerol with formaldehyde and acetone.⁴ GlyF is commercially available as a mixture of two 5- and 6-membered ring isomers (**1a** and **1b** in a 2 : 3 molar ratio, respectively), while solketal is obtained exclusively as a five-membered ring product.⁵



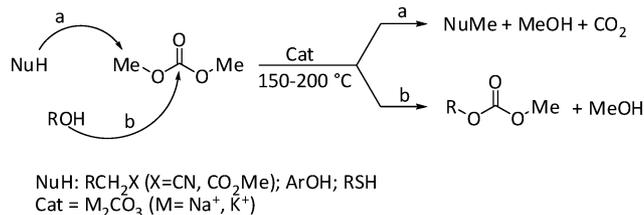
Scheme 1 Light glycerol acetals.

As such, both acetals are mainly used in the field of solvents for injectable pharmaceutical preparations, paints and water-based inks,^{4c,6} and for the preparation of additives for biodiesel formulations.^{3a,5d,7} GlyF and solketal however, are also valuable

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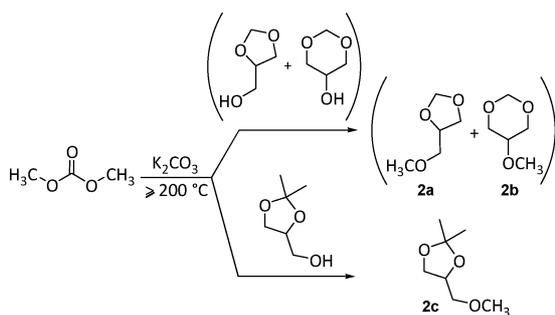
glycerol synthons whose reactivity involves almost exclusively the conversion of their free hydroxyl functionality by conventional esterification and etherification agents (carboxylic acids and alkyl halides, respectively).^{8,9} This aspect prompted us to investigate whether eco-friendly protocols could be devised for such processes, especially for the synthesis of *O*-alkyl derivatives of both **1a–b** and **1c**. To this purpose, dialkyl carbonates (DAICs) appeared attractive compounds since they offer genuine green advantages over classical alkylating reagents:¹⁰ *i*) they are non-toxic compounds; *ii*) their alkylation mediated reactions are always catalytic processes, with no by-products except for alcohols recyclable to the synthesis of DAICs, and CO₂ which does not involve disposal problems; *iii*) very often, (light) organic carbonates can be used not only as reactants, but also as reaction solvents. Moreover, their alkylation reactivity can be tuned for a variety of nucleophiles. This behaviour has been extensively investigated by our research group in the past fifteen years.¹¹ Consider, for example, the model case of base-catalysed methylations mediated by dimethyl carbonate (Scheme 2).



Scheme 2

At 150–200 °C, in the presence of solid alkaline carbonates as catalysts, the reaction of CH₂-active compounds, phenols, and thiols (NuH) with DMC proceeds with an exceptionally high selectivity (>99%) towards the corresponding methyl derivatives (NuMe, path a).

Under these conditions, a different scenario is offered by alcohols: plausibly due to their hard nucleophilic character, a number of primary and secondary alcohols including benzyl substrates, react with DMC to produce predominantly the corresponding transesterification products (path b).^{11h,12} Notwithstanding the alcohol-like reactivity expected for glycerol acetals, this paper demonstrates that reaction conditions can be found for the selective etherification of the hydroxyl group of both GlyF and solketal with DMC. In particular, this unprecedented reaction takes place at 200–220 °C, in the presence of potassium carbonate as a catalyst (Scheme 3).



Scheme 3

An in-depth investigation has been carried out to analyze the course of the overall transformation. Beyond the *O*-methylation process which affords methyl ethers **2** in yields up to 90%, results provide evidence that also the transesterification of acetals **1a–b** and **1c** with DMC takes place, producing the corresponding carboxymethyl derivatives (Scheme 2, path b). These compounds however, disappear as the reaction proceeds: both the reversible nature of the transesterification and the occurrence of competitive processes of decarboxylation and hydrolysis of carboxymethyl products account for this result. Accordingly, a mechanistic hypothesis has been formulated.

The same mechanism plausibly holds true for higher homologues of DMC: both diethyl- and dibenzyl- carbonate react with solketal to yield the related carboxyalkyl and *O*-alkyl derivatives, the latter compounds being the final reaction products. Although an excellent alkylation selectivity (up to 100%) can be achieved, these transformations appear somewhat limited by the consumption of the starting dialkyl carbonates *via* concurrent decarboxylation and hydrolysis processes.

Overall, the catalytic *O*-alkylation of renewable acetals of glycerol with safe dialkyl carbonates, particularly DMC, not only represents a genuinely green procedure, but it unlocks a potential for preparative purposes: this study demonstrates that the reaction can be scaled up for multigram synthesis without any loss of selectivity.

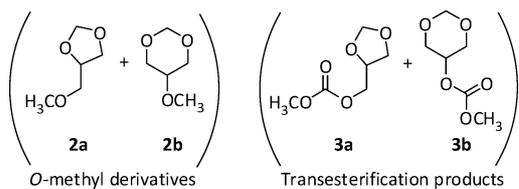
Results

Since previous studies on base catalysed reactions of GlyF and solketal with dialkyl carbonates were not available, a full set of experiments was necessary to examine the feasibility of the process. Our experience on the alkylation reactivity of DMC steered us on the choice of reaction conditions, particularly on the range of major parameters such as catalyst amount, temperature, time, and reactants molar ratios.

The reaction of glycerol formal with DMC in the presence of K₂CO₃

Initial experiments were carried out in a stainless steel autoclave (200 mL) charged with a mixture of commercial glycerol formal (isomers **1a–1b** in a 2:3 ratio; 0.80 g; 7.7 mmol), dimethyl carbonate (DMC, 19 mL, molar ratio $W = \text{DMC}:\text{GlyF} = 30$) and K₂CO₃ (molar ratio $Q = \text{K}_2\text{CO}_3:\text{GlyF} = 1.2$). DMC was used in a large excess, acting simultaneously as a reagent and a solvent. The autoclave was purged with N₂, electrically heated at 200 °C, and kept under magnetic stirring. Reactions were followed for different time intervals of 6, 10, 20 and 24 h, respectively. At the end of each experiment, the reactor was cooled to rt and vented, and the reaction mixture was analyzed by GC-MS. In all cases, major products (≥95%) derived from *O*-methylation and carboxymethylation reactions of GlyF (compounds **2a–2b** and **3a–3b**, respectively; Scheme 4).

Products **2** and **3** were isolated and fully characterized by GC-MS, ¹H and ¹³C NMR (further details are in the experimental section). The structure of isomers **3a–3b** was also confirmed by comparison to authentic samples. Other unidentified by-products (≤5% in total, by GC), were also detected. The results



Scheme 4 Major products of the K_2CO_3 -catalysed reaction of glycerol formal with DMC.

are shown in Fig. 1a–b where the amount (% by GC) of both reagents and products is plotted vs. the reaction time.¹³

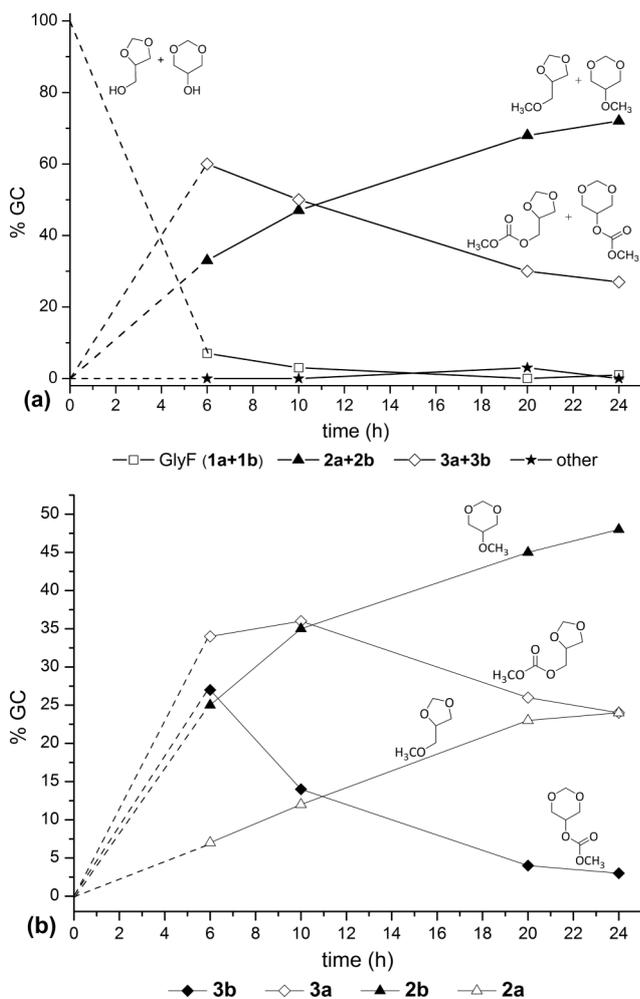


Fig. 1 The reaction of GlyF with DMC carried out at 200 °C: (a) total amounts of each couple of isomers (**1a+1b**, **2a+2b**, **3a+3b**, respectively). “Other” were unidentified by-products; (b) amounts of each single isomer of methyl (**2a–2b**) and carboxymethyl (**3a–3b**) products.

Four main aspects emerged from Fig. 1a: *i*) after 10 h, the reaction conversion was substantially quantitative (97%); *ii*) the amount of *O*-methylation products (**2a+2b**) increased progressively with time, with a methylation selectivity up to 73% after 24 h; *iii*) the amount of carboxymethylation products (**3a+3b**) went up to a maximum in the first 6 h, and then, it dropped to 27% as the reaction proceeded further; *iv*) by-products were negligible. Fig. 1b showed that six-membered ring products (*O*-methyl and carboxymethyl derivatives **2b** and **3b**) formed and reacted, respectively, faster than their five-membered

ring analogues (*O*-methyl and carboxymethyl derivatives **2a** and **3a**). After 24 h, the amount of **2b** was doubled than **2a** (24 and 48%, respectively); while, compound **3b** and **3a** were present in 24 and 3% amounts, respectively.

Once the last experiment (24 h reaction) of Fig. 1 was concluded, K_2CO_3 was filtered and dried under vacuum overnight (8 mbar, 100 °C). The solid was finely powdered and reused to catalyze the reaction of GlyF and DMC under the conditions of Fig. 1 (24 h). The recycle of K_2CO_3 was repeated once more. GC-MS analyses of experiments with both fresh and recycled catalyst showed conversions and product distributions that did not differ by more than 5% from each other. This confirmed that K_2CO_3 was a recyclable catalyst. The result matched the behaviour already reported for DMC mediated carboxylations and methylations of different nucleophiles.¹⁴

Two additional experiments were carried out in the absence of K_2CO_3 . A mixture of GlyF and DMC was set to react for 10 and 24 h under the conditions of Fig. 1. The conversions of GlyF were 60 and 96%, respectively, but only a transesterification reaction took place yielding carboxymethylated compounds (**3a+3b**) as exclusive products. This in line with literature results for the thermal (non-catalytic) transesterifications of esters and organic carbonates which were reported at $T > 170$ °C.¹⁵

Alkali metal exchanged faujasites could also act as efficient catalysts for *O*-alkylation of alcohols with dialkyl carbonates.¹¹ However, attempts to use faujasites in the reaction of GlyF and solketal with DMC, were not successful. For example, at 200 °C, the conversion of GlyF was complete after only 3 h on NaX (weight ratio zeolite : GlyF = 1), but the formation of *O*-methyl derivatives **2a+2b** (72%, by GC) was accompanied by the aperture of the cyclic structures of both GlyF and products **2**, which yielded an extensive amount of by-products (28%). This competitive reaction likely followed the general mechanism of acetal methanolysis,¹⁶ where Brønsted acidity on solid faujasites was the catalyst.¹⁷

Catalyst amount. Under the conditions of Fig. 1 (200 °C, molar ratio DMC : GlyF = 30), the reaction of GlyF and DMC was carried out using different molar ratios K_2CO_3 : GlyF (Q) of 0.5, 2, and 3, respectively. Experiments were run for 10 h. Fig. 2 shows the composition (% by GC) of the reaction mixtures and

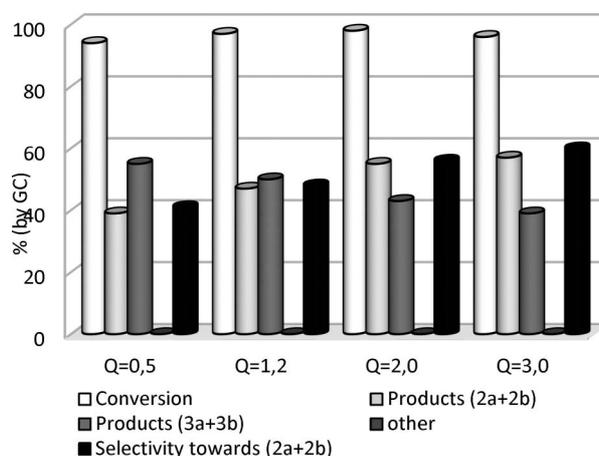


Fig. 2 Effect of the K_2CO_3 amount in the reaction of GlyF with DMC. Q is the molar ratio K_2CO_3 : GlyF.

the *O*-methylation selectivity. The figure also includes the results obtained with $Q = 1.2$ (Fig. 2).

The conversion of GlyF remained above 94%, even at a Q ratio of 0.5, indicating that the reaction was a truly catalytic process. The base amount however, affected the distribution of *O*-methyl and carboxymethyl derivatives: as the Q ratio increased (from 0.5 to 3.0), the quantity of products (**2a+2b**) and (**3a+3b**) steadily increased and decreased, respectively, from 39 to 57% (light gray bar) and from 55 to 39% (gray bar). Accordingly, the *O*-methyl selectivity went up from 41 to 60% (black bar). Although the relative increments/decrements of compounds **2** and **3** tended to level off at high catalyst loadings ($2.0 \leq Q \leq 3.0$), the trend agreed with that of Fig. 1: as the reaction proceeded, *O*-alkyl derivatives were the ultimate products, while carboxymethyl species progressively decreased.

Temperature and reaction time. The effect of the temperature was examined in three subsequent reactions of GlyF with DMC carried out at 200, 210 and 220 °C. Other conditions were those of Fig. 2 (molar ratio DMC : GlyF = 30; molar ratio K_2CO_3 : GlyF = 1.2); though, a longer reaction time of 20 h was chosen to possibly maximise the formation of products **2**. Results are reported in Fig. 3.

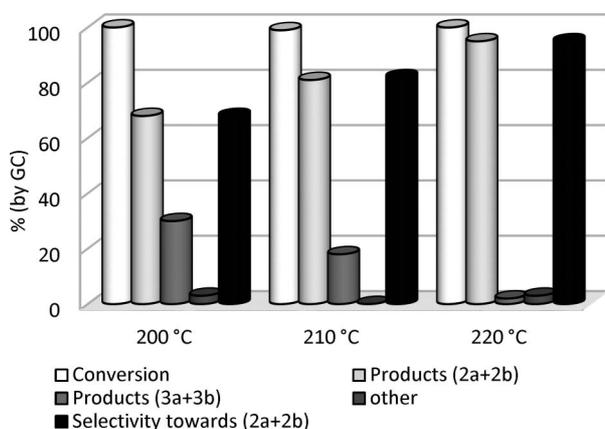


Fig. 3 Reactions of GlyF with DMC at different temperatures.

The increase of the temperature induced a remarkable improvement of the *O*-methylation selectivity (up to 95%, black bar): from 200 to 220 °C, the amount of **2a+2b** (light gray bar) increased progressively from 68 to 96%, while carboxymethyl derivatives (**3a+3b**, gray bar) decreased from 30% to 2%. Further to that, high reaction temperatures did not favour other by-products ($\leq 3\%$ in total). The conversion was substantially quantitative in all cases.

Reactants molar ratio. The reaction of GlyF and DMC was explored using different molar ratios DMC : GlyF (W) of 20, 30, and 40 respectively. According to Fig. 3, the temperature was set to 220 °C. However, experiments were run for 10 h to appreciate possible effects on the product distribution. The molar ratio K_2CO_3 : GlyF was 1.2. Fig. 4 reports the composition (% by GC) of reaction mixtures and the corresponding *O*-methylation selectivity.

Surprisingly, the increase of the W ratio from 20 to 40 brought about a remarkable decrease of the selectivity from 98 to 80% (black bar) due to unconverted carboxymethyl derivatives **3**: the

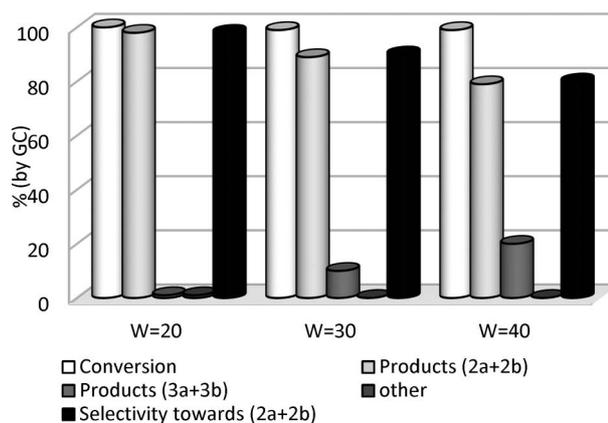


Fig. 4 Effect of DMC loading in the reaction of GlyF and DMC.

alkylation of GlyF was apparently disfavoured by a larger excess of DMC.

Mass balance and scale up of the *O*-methylation of GlyF.

A mixture of commercial glycerol formal (0.80 g; 7.7 mmol), dimethyl carbonate (DMC, 19 mL, molar ratio $W = \text{DMC} : \text{GlyF} = 30$), K_2CO_3 (molar ratio $Q = K_2CO_3 : \text{GlyF} = 1.2$) was set to react in the presence of *n*-dodecane (C_{12} ; 0.175 mL, 0.131 g, molar ratio $Z, \text{GlyF} : C_{12} = 10$) as an internal standard. Conditions were those of Fig. 3 (220 °C, 20 h). The analysis of the final reaction mixture gave conversion and selectivity towards *O*-methyl derivatives (**2a+2b**) of 98% and 95%, respectively. The calculated yield of (**2a+2b**) was 95%. No significant mass loss took place during the reaction.

The reaction of GlyF with DMC was then scaled up. At 220 °C, two experiments (A and B) were performed multiplying by a factor of 5 the amounts of reagents and catalyst. In the first reaction (A), conditions were those of Fig. 3 ($W = 30$ and $Q = 1.2$), while in the second test (B), the DMC volume was significantly decreased to reach a W ratio (molar ratio DMC : GlyF) of 5. Accordingly, a mixture of glycerol formal (4.0 g, 38 mmol) and K_2CO_3 (6.3 g, 46 mmol) was set to react with 96 and 17 mL of DMC, respectively (A and B).

Under the conditions of experiment (B), a further reaction was carried out in the presence of *n*-dodecane (0.91 mL, molar ratio GlyF : $C_{12} = 10$) as the internal standard. This experiment was repeated three times: calculated conversions and product distributions did not differ more than 5% from one test to another. Also, the yield of *O*-methyl products **2a+2b** was determined. Results are summarized in Table 1.

The reaction proved to be feasible on a multigram scale. In analogy to results of Fig. 1b, C_6 isomers of compounds **2** and **3** were more reactive than the corresponding C_5 isomers: for example, after 26 h at 220 °C, the amounts of **2a** and **2b** were 20 and 41% respectively, while those of **3a** and **3b** were 27 and 5% (conditions of entry 1, Table 1). However, once the reaction was complete, *O*-methyl derivatives (**2a+2b**) were always obtained with a high selectivity (up to 97%) and an excellent yield (99%, by GC).

The alkylation rate was considerably altered by the DMC volume: reaction times were of 52 and 20 h at $W = 30$ and 5, respectively (entries 1 and 2–3). Apparently, a lower amount of DMC ($W = 5$) had not only the positive effect of reducing the

Table 1 Scale up of the reaction of GlyF and DMC

Entry	W^a (mol : mol)	t (h)	IS ^b (n -C ₁₂)	Conv. (%) ^c	Selectivity (%) ^c	Yield (2,%) ^c	
						(by GC)	Isolated ^d
1	30	52	None	99	94		65
2	5	20	None	98	96		64
3	5	20	Yes	99	97	99	67

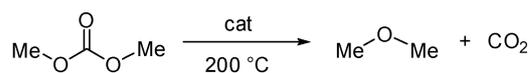
^a Molar ratio DMC : GlyF. ^b IS: internal standard (n -dodecane). ^c Conversion of GlyF and selectivity/yield of O -methyl products **2a+2b**. Entry 3: values of both conversion, selectivity and yield were averaged over three different runs and they were calculated based on GC calibration curves.

^d Isolated yield of distilled products **2a+2b**.

mass index of the process, but it allowed an even faster reaction thereby confirming the trend of Fig. 4.

Final mixtures from experiments of entries 1–3 of Table 1, were filtered and O -methylation products **2** were distilled under vacuum (further details are in the experimental section). Pure ($\geq 96\%$) liquid mixtures of isomers **2a** and **2b** were obtained, though isolated yields did not exceed 67%. Technical limitations of the available distillation apparatus always brought to middle fractions containing the work-up solvent, DMC, and not negligible amounts of products **2**.

Decarboxylation of DMC and carboxymethyl derivatives 3a–3b. Dimethyl carbonate is thermally stable at temperatures up to 390 °C.¹⁸ However, very recent studies by us and by other have demonstrated that at $T \geq 200$ °C, dialkyl carbonates partially decomposed through a decarboxylation reaction catalysed by solid bases.¹⁹ Scheme 5 illustrates the case of DMC where dimethyl ether and CO₂ were the observed products.



Cat.: faujasites, hydrotalcite, alkaline carbonates

Scheme 5

Since conditions for such a process encompassed those of Fig. 1–4, a decarboxylation was expected in the reaction of GlyF with DMC, involving not only DMC, but also non symmetrical carbonates such as carboxymethyl isomers **3a** and **3b** (Scheme 4). Bearing this in mind, a more in-depth analysis of this aspect was undertaken.

Initially, the decarboxylation of DMC was investigated. Experiments were carried out under the conditions of Fig. 3. In an autoclave, a mixture of DMC (19 mL, 0.23 mol) and K₂CO₃ (1.28 g, 9.4 mmol, the molar ratio, W_1 , DMC : K₂CO₃ was 24), was set to react at temperatures of 200, 210 and 220 °C, and for 20 h. Once the reactor was cooled to rt, a residual pressure up to 5 bar indicated the formation of gaseous products. GC-MS analyses of such gas-phase confirmed the presence of CO₂ and dimethyl ether (DME) (Scheme 5). These compounds were recovered by a cold-trap apparatus,^{19a} and weighed: their total amounts were 0.36, 1.26, 2.43 g, at 200, 210, 220 °C, respectively. According to the stoichiometry of Scheme 5, the corresponding conversions of DMC were 2, 6, and 12%. Although of minor entity, the decarboxylation of DMC took place under the conditions used for the methylation of GlyF. The analysis of the residual DMC in the autoclave showed traces of methanol (not

exceeding 2%, by GC), indicating that the starting carbonate was also subjected to hydrolysis.²⁰

Then, the reactivity of isomers **3a–3b** was examined. Compounds **3** were prepared from GlyF and DMC according to a conventional method for base-catalysed transesterification reactions.²¹ The products were isolated as a mixture of **3a** and **3b** (in the same 2 : 3 ratio of the starting isomers of GlyF) in a 79% yield. They were fully characterized by ¹H and ¹³C NMR, and GC-MS.

The reaction of **3a–3b** was performed under the conditions of previous experiments (Fig. 1–4), by replacing DMC with dimethoxyethane (glyme) as the reaction solvent.²² In particular, a mixture of **3a–3b** (1.25 g, 7.7 mmol), K₂CO₃ (1.28 g, molar ratio $Q_1 = \text{K}_2\text{CO}_3 : \mathbf{3a-3b} = 1.2$) and glyme (19 mL) was set to react at 220 °C, in an autoclave, for 10 h. Once cooled to rt, a residual pressure up to 3 bar inside the reactor, indicated that gaseous products were originated. These were recovered and analysed by GC-MS: the exclusive formation of CO₂ was observed (details are in the experimental section). This proved unambiguously that, alike to DMC, compounds **3** underwent a decarboxylation reaction. In addition, the (weighed) amount of CO₂ (0.20 g) allowed to estimate a 63% conversion of carboxymethyl reagents (**3a–3b**). The result was in good agreement with the GC analysis of the residual liquid mixture in the autoclave, by which the conversion of **3** resulted 73%. However, the analysis of the liquid phase also indicated that the expected methyl derivatives (**2a–2b**) were present in a minor amounts [8%, Scheme 6, path (a)], while major products were GlyF isomers (65%). The presence of water in the reaction mixture likely accounted for this behaviour [Scheme 6, path (b)].

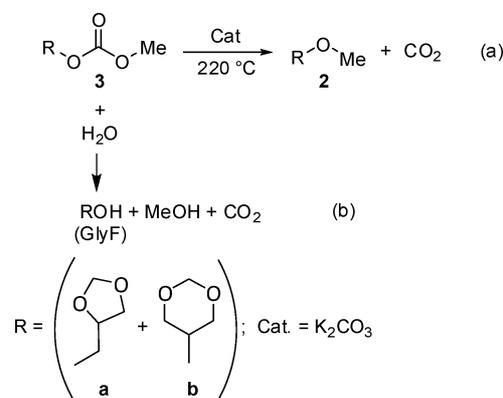
**Scheme 6** Decarboxylation of the carboxymethyl derivatives (**3a–3b**) over K₂CO₃.

Table 2 The mass balance and the scale up of the reaction of solketal and DMC

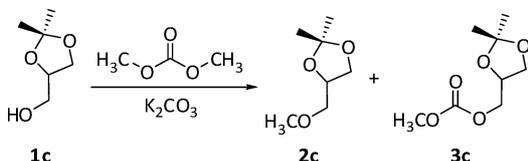
Entry	Solketal 1c (g)	DMC: 1c (W, mol: mol) ^a	T/°C	t (h)	IS ^b (<i>n</i> -C ₁₂)	Conv. (%) ^c	Sel. (%) ^c	Yield (2c ,%)
1	1.02	30	220	80	Yes	95	92	86 ^c
2	3.50	5		50	None	92	99	66 ^d

The K₂CO₃: **1c** molar ratio was 1.2.^a Molar ratio DMC: GlyF. ^b IS: internal standard (*n*-dodecane, C₁₂). The **1c**: C12 molar ratio was 10. ^c Conversion of solketal and selectivity/yield of *O*-methyl product **2c**. Entry 1: values of both conversion, selectivity and yield were calculated based on GC calibration curves. ^d Isolated yield of **2c**.

To reduce/eliminate the competitive hydrolysis of compounds **3**, an additional experiment was carried out using anhydrous glyme and K₂CO₃. The latter was dried under vacuum (70 °C, 18 mm, overnight). The reaction was performed under the conditions of Scheme 6. However, modest variations were observed: the conversion was 70%, and the amounts of *O*-methyl products (**2a–2b**) and GlyF isomers were 19 and 51%, respectively. Overall, the decarboxylation of compounds **3a–3b** occurred, but this reaction took place along with a competitive hydrolysis of reactants themselves.

The reaction of solketal with DMC in the presence of K₂CO₃

The reaction of solketal with DMC was studied based on the results previously obtained for GlyF. Initial reactions were performed in a stainless steel autoclave (200 mL) charged with commercial solketal (**1c**: 1.02 g; 7.7 mmol), dimethyl carbonate (DMC, 19 mL, molar ratio, *W*, DMC: **1c** = 30) and K₂CO₃ (molar ratio, *Q*, K₂CO₃: **1c** = 1.2). Five experiments were carried out at 220 °C for 20, 30, 50, 60, and 80 h, respectively. Major products (≥95% by GC-MS) were from *O*-methylation and carboxymethylation reactions of solketal (Scheme 7: compounds **2c** and **3c**, respectively).



Scheme 7 Major products of the reaction of solketal with DMC catalysed by K₂CO₃.

These compounds were isolated and fully characterized by GC-MS, ¹H and ¹³C NMR (further details are in the experimental section). Other unidentified by-products whose total amount was ≤5% (by GC), were also detected. The results are reported in Fig. 5.

As for the case of GlyF, the evaluation of the mass balance and the scale up of the methylation of solketal with DMC were investigated. Results are reported in Table 2.

The mass balance was examined in the presence of *n*-dodecane as internal standard (entry 1). Reaction conditions were those of Fig. 5 (80 h). Calculated conversion, *O*-methyl selectivity, and yield on **2c** were 95, 92 and 86%, respectively. With respect to solketal, these values confirmed that no significant mass loss took place during the reaction.

The reaction was then scaled up. With respect to conditions of Fig. 5, the amounts of solketal and the catalysts were multiplied by a factor of 3.5. Instead, the volume of DMC was adjusted

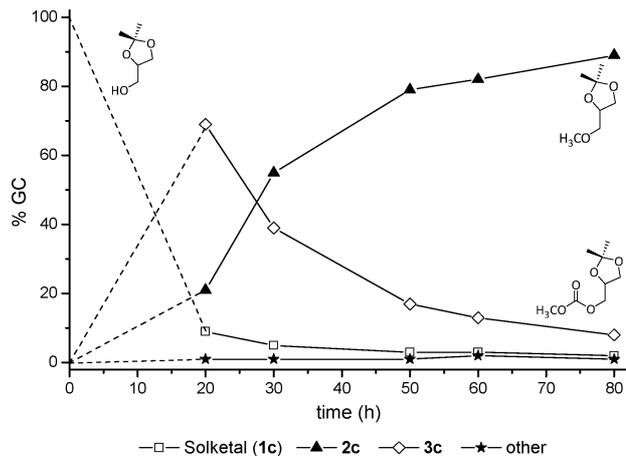


Fig. 5 The reaction of solketal with DMC carried out at 220 °C.

(lowered) to reach a molar ratio DMC: solketal = 5. After 50 h, conversion and *O*-methyl selectivity were excellent (92 and 99%, respectively; entry 2), thereby proving the feasibility of the reaction on a multigram scale. The final mixture appeared as a thick slurry whose analysis showed that only minor amounts of DMC (20% with respect to product **2c**) were still present. Not only the occurrence of the decarboxylation/hydrolysis of dimethyl carbonate was confirmed, but the process became rather extensive at long reaction times.

The mixture was diluted with diethyl ether and filtered, and the *O*-methylation product **2c** was distilled under vacuum (56 °C, 3 mmHg) as a pure (98%, by GC) colourless liquid. The isolated yield of **2c** was of 2.50 g (66%). As for GlyF, the available distillation apparatus brought also to middle fractions containing the work-up solvent, DMC and MeOH, and not negligible amounts of **2c**.

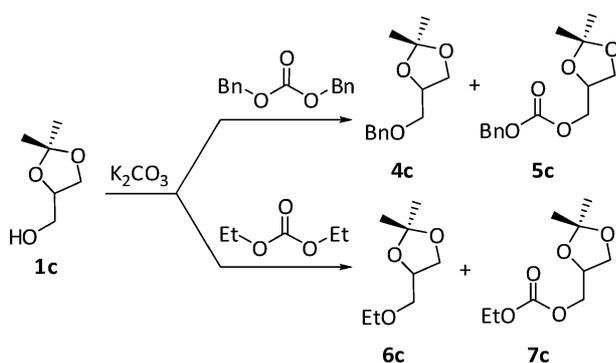
The K₂CO₃-catalyzed reaction of solketal with dibenzyl- and diethyl-carbonate

In order to expand the scope of the alkylation of glycerol acetals with dialkyl carbonates, the reaction of solketal with both dibenzyl- and diethyl-carbonate (DBnC and DEC, respectively) was investigated.²³ Experiments were carried out under conditions similar to those used for DMC. In a stainless steel autoclave, a mixture of solketal (**1c**, 1.8 mL, 14.6 mmol), K₂CO₃ (2.4 g, molar ratio, *Q*, K₂CO₃: **1c** = 1.2) and different amounts of DBnC or DEC (molar ratios, *W*, dialkyl carbonate: **1c** = 5 and 8 were used) was set to react in the range of 190–220 °C, for 18–66 h. Final reaction mixtures were analysed by GC-MS. Both products of *O*-alkylation and carboxyalkylation of solketal were observed (Scheme 8: derivatives **4c–5c**, and **6c–7c**, respectively).

Table 3 The reaction of solketal with dibenzyl- and diethyl-carbonate

Entry	DAIC	DAIC: 1c , <i>W</i> (mol: mol)	<i>T</i> /°C	<i>t</i> (h)	Conv. (%) ^a	<i>O</i> -alkyl selectivity (%)	Products (% by GC) ^b					Yield (%) ^c
							4c	5c	6c	7c	Others	
1	DBnC	5	190	18	85	22	19	62			4	
2		8			83	8	7	71			5	
3		5	220	18	78	97	76	1			1	
4		8			80	85	68	12				
5		8			81	100	81					
6	DEC	5	220	18	80	1		1	76	3		
7				66	54	100		54				

^a Conversion of solketal. ^b **4c** and **6c**: *O*-benzyl and *O*-ethyl derivatives of solketal, respectively. **5c** and **7c**: *O*-carboxybenzyl and *O*-carboxyethyl derivatives of solketal, respectively. ^c Isolated yield of product **4c**.

**Scheme 8** Major products of the K_2CO_3 -catalysed reaction of solketal with DBnC and DEC.

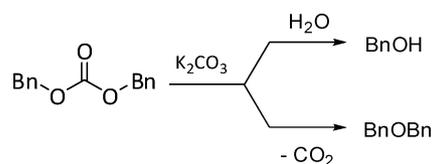
Compounds **4c** and **5c** were isolated and characterized by GC-MS, 1H and ^{13}C NMR, while the structures of products **6c** and **7c** were assigned from their mass spectra. Results are reported in Table 3.

Dibenzylcarbonate. As for DMC (Fig. 4), the alkylation of solketal was disfavoured by an excess of DBnC: at both 190 and 220 °C, after 18 h, an appreciable reduction of *O*-benzyl selectivity was observed when the *W* ratio was increased from 5 to 8 (entries 1–2).

The increase of the temperature from 190 to 220 °C boosted the formation of product **4c**: the *O*-benzyl selectivity rose from 8–22% to 97% (entries 1–2 and 3–4). Contrary to our expectations, the conversion of solketal remained rather constant in all experiments (around 80%, entries 1–4).

This incongruity was plausibly due to: *i*) a partial hydrolysis of the carboxybenzyl product **5c** which brought back to the starting reactant **1c** (as in Scheme 6); *ii*) extensive decarboxylation/hydrolysis reactions of DBnC. Processes (*ii*) were confirmed by the analysis of the final reaction mixture: at 220 °C, after 18 h (*W* = 8), DBnC was absent and sizeable amounts of dibenzyl ether and benzyl alcohol (41 and 46%, respectively, with respect to *O*-methyl product **4c**, 13%) were detected (entry 4).²⁴ (Scheme 9).

Under the same conditions (220 °C, *W* = 8), an additional reaction carried out for a prolonged time (32 h) proceeded with total selectivity towards compound **4c**, but the conversion of

**Scheme 9** Hydrolysis and decarboxylation of DBnC.

solketal did not exceed 81% (entry 5). Again, not traces of DBnC were detected in the final mixture.

Diethylcarbonate. DEC was remarkably less active than DBnC. At 220 °C, after 18 h, the reaction of solketal with DEC produced almost exclusively the carboxyethyl derivative **7c** (entry 6). The selective formation of *O*-ethyl product **6c** was achieved only after 66 h (entry 7); though, a simultaneous decrease of the reaction conversion (54%) was observed. As for DBnC, the hydrolysis of **7c** along with the decarboxylation/hydrolysis of DEC offered an explanation for the result. DEC in fact, was no longer present in the final mixture of entry 7.

Discussion

The mechanism of DMC-mediated methylations of GlyF and solketal

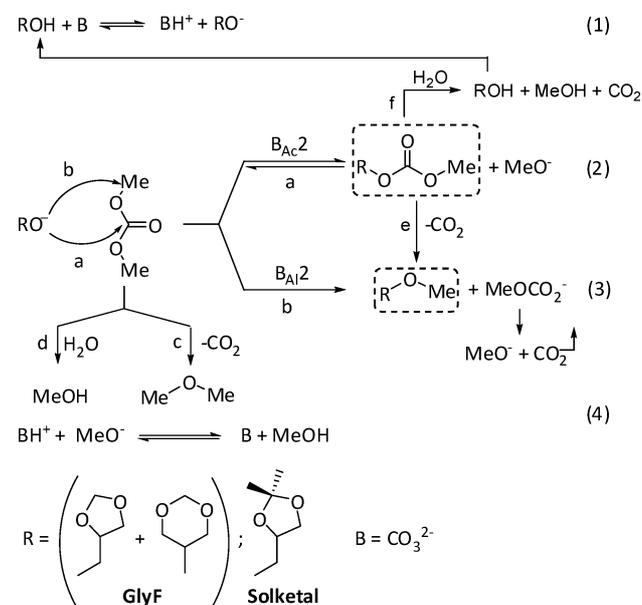
In the presence of K_2CO_3 as a catalyst, the reactions of dimethyl carbonate with glycerol formal (GlyF) and with solketal show remarkable analogies. First of all, experimental conditions can be found for the formation of *O*-methyl ethers of both substrates with a very high selectivity (>90%) at complete conversion (Fig. 3 and 5, Tables 1 and 2). This unexpected and never previously reported result fulfils the synthetic goal of the present work. It should be noted that under basic catalysis, alcohols are claimed to react with dialkyl carbonates to form transesterification and not alkylation products (Scheme 2). Other important similarities between the methylation of GlyF and of solketal emerge when the effects of the temperature (*T*) and of the reaction time (*t*) on the product distribution are considered (Fig. 1, 3, and 5).

Both alkylations of GlyF and solketal yield *O*-methyl and carboxymethyl derivatives (**2** and **3**, respectively); however, as *T* and/or *t* are increased, the amount of carboxymethyl

compounds rises to a maximum and then, it drops to zero. At the same time, *O*-methyl compounds always increase (though at different rates with respect to **3**) to become final reaction products.

Two plausible explanations can be offered for the formation/disappearance of compounds **3**: *i*) these products are originated by a reversible reaction (transesterification), *i.e.* an addition/elimination at the DMC carbonyl;²⁵ *ii*) compounds **3a–3b** (from GlyF) are consumed by competitive decarboxylation/hydrolysis processes which are triggered by temperature (Fig. 3 and Scheme 6).²⁶

Based on these observations and on the sequence for base-catalyzed DMC-mediated reactions,^{10,11} Scheme 10 illustrates a mechanistic hypothesis for the *O*-methylation of GlyF and solketal with DMC.



Scheme 10 The mechanism for the methylation of GlyF and solketal with DMC.

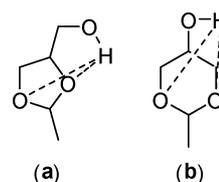
In the first step, the base (**B**) converts the acetal/ketal (**ROH**: GlyF or solketal) in the corresponding alcoholate anion [**RO**[−], eqn (1)] that reacts with both electrophilic centers of DMC [paths **a** and **b**, **B_{Ac}2** and **B_{Al}2** mechanisms of eqn (2) and (3)]. Since the carbonyl carbon is a stronger electrophilic site than the methyl one, a lower activation energy is expected for the transesterification [path (**a**)] with respect to the methylation reaction [path (**b**)]. This may account for the faster formation of carboxymethyl- (**3**: **ROCO₂Me**) with respect to methyl- (**2**: **ROME**) derivatives (Fig. 1 and 5). However, the onset of the methylation process makes the reversible transesterification backtrack: after an initial accumulation of compounds **3**, they decrease to zero, while **ROME** become final products.

A further contribution to the disappearance of carboxymethyl products is given by competitive decarboxylation and hydrolysis reactions,²⁰ shown in paths (**e**) and (**f**), respectively. For a complete view, also the decarboxylation/hydrolysis of DMC is indicated [paths (**c**)–(**d**)]: the extent of such transformations become relevant only for long reaction times.

The catalytic cycle terminates when the protonated base (**BH**⁺) reacts with an alcoholate anion (*e.g.* **MeO**[−]) to restore the free base (**B**) and produce **MeOH** [eqn (4)].

Overall, several concurrent processes take place, but if temperature is high enough and sufficient time is allowed, the system equilibrates to thermodynamically favoured products: the result is the selective formation of *O*-methyl derivatives of both GlyF and solketal.

In the case of GlyF, the higher rate of formation/disappearance of 6-membered ring isomers (**2b** and **3b**) with respect to their 5-membered ring analogues (**2a** and **3a**) is an additional aspect (Fig. 1b and Table 1). Despite the huge literature on glycerol formal, very few papers describe fundamental studies on the behaviour of isomers of glycerol acetals and ketals. Among them, a work by Aksnes *et al.* has investigated 5- and 6-membered ring acetals obtained by the reaction of glycerol with acetaldehyde (Scheme 11: compounds **a** and **b**, respectively).²⁷



Scheme 11 (a) 4-Hydroxymethyl-2-methyl-1,3-dioxolane; (b) 5-hydroxy-2-methyl-1,3-dioxane. Dashed lines: intramolecular H-bonds.

Authors provide evidence for intramolecular H-bonds (dashed lines of Scheme 11) between the hydroxyl proton and endocyclic oxygen atoms of both acetals (**a**) and (**b**). Moreover, stereochemical reasons particularly, the mutual interactions between axial hydrogen atoms, offer an explanation for the different stability of (**a**) with respect to (**b**). This seems a promising basis also for the investigated reaction even though our experimental conditions, above all the high temperature (≥ 200 °C), plausibly tend to smooth energetic differences due to hydrogen bonds or to conformational barriers. Further studies will be devoted to a more in-depth analysis of such aspects.

The role of the catalyst (**K₂CO₃**)

Fig. 2 shows that the reaction of GlyF with DMC takes place even when a substoichiometric amount of **K₂CO₃** is used ($Q = 0.5$). Increase of the catalyst loading speeds up the reaction until a sort of plateau is reached: at $Q \geq 2$, further improvements of rate and/or selectivity are less, if at all, appreciable. Although a kinetic analysis is beyond the scope of this work, it should be considered that **K₂CO₃** is only moderately soluble in DMC (0.58 g L^{-1} at 180 °C,^{11a}). Therefore, the investigated reaction is plausibly partitioned between a liquid homogeneous phase saturated with the base and the solid catalytic surface where organic reactants/products may adsorb/desorb. As the Q ratio increases, the homogeneous contribution should remain constant, while the heterogeneous reaction over **K₂CO₃** should be favored until the solid surface accommodates the maximum allowed quantity of organic substrates. After that, the reaction rate cannot increase any further and the selectivity levels off as well.

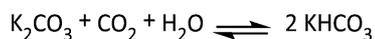
A similar behavior has been observed also for other base-catalysed reactions of DMC, for example in the methylation of CH₂-active compounds.²⁸

The DMC amount

Fig. 4 and Tables 1–2 indicate that the decrease of DMC:substrate molar ratio (*W*) favors the alkylation of both GlyF and solketal. This is particularly evident in scale-up experiments which show that the reaction time halves when the *W* ratio is reduced from 30 to 5. The reasons of this behaviour are not clear, but some speculations can be made. A dilution effect is hardly responsible for the result since DMC is also a reactant. However: *i*) at *W* = 5, the high concentration of GlyF or solketal may favour the base dissolution. It should be noted that the solubility of K₂CO₃ boosts by a factor of 22 (from 0.58 to 12.7 g L⁻¹) when DMC is compared to methanol,²⁹ and both acetals (GlyF or solketal) possess polar alcohol-like structures. An increase of the reaction rate is plausible if the catalyst solubility is improved. Moreover, as the reaction proceeds, GlyF (or solketal) is gradually converted to the corresponding methyl and carboxymethyl derivatives, but an equivalent amount of methanol is originated to restore a medium polarity similar to that of the starting solution. The effect of decarboxylation/hydrolysis of DMC may also play a role, especially for prolonged experiments (above 50 h), where such transformations occur to a sizeable extent. *ii*) As mentioned above, the investigated reaction is likely to occur both in solution and over solid K₂CO₃. For a number of reasons including solvation effects, competitive adsorption, alteration of diffusion constants, *etc.*, the modes of (physical/chemical) interactions of reagents (GlyF/solketal and DMC) on the catalytic surface as well as the regime of the reaction can be modified by varying the volume of the solvent (DMC).³⁰

The K₂CO₃-catalyzed decarboxylation of DMC and carboxymethyl derivatives 3

We have recently reported that a class of zeolites (alkali metal exchanged faujasites) are efficient catalysts for the decarboxylation of dialkyl carbonates.^{19a} The more basic the zeolite (NaX, CsY), the higher its activity. This feature has been explained by the excellent potential for CO₂ capture/storage of these catalysts that are able to adsorb reversibly up to 5.5 mmol of CO₂ per g of solid.³¹ Accordingly, the breakdown of dialkyl carbonates is favoured and, at the same time, the reversibility of the CO₂ uptake prevents the saturation of the catalytic surface by the gas. This leaves a sufficient solid basicity to allow the decarboxylation to proceed. An similar interpretation may be offered for the activity of K₂CO₃ in the decarboxylation reactions of both DMC and compounds **3a–3b** and **3c** (Schemes 5–6 and Fig. 5). In fact, K₂CO₃ as such or supported on various porous materials (C or silica gel), is a very good CO₂ sorbent system on condition that water acts as a co-reagent (Scheme 12).³²



Scheme 12 The chemical adsorption of CO₂ over K₂CO₃.

This process may take place under the conditions described in this work where water is plausibly present due to hygroscopic

properties of K₂CO₃ or the reactants.³³ Whatever its origin, the presence of water in our system is witnessed by the extensive hydrolysis observed for carbonates **3a–3b** (Scheme 6) and DBnC as well. It should be finally noted that the solid basicity *per se* is not a sufficient requisite for a rapid decarboxylation reaction: solid K₂CO₃ is by far a poorer catalyst with respect to amphoteric faujasites. A possible reason lies in an inefficient adsorption of dialkyl carbonates on K₂CO₃ with respect to zeolites.³⁴

Other dialkyl carbonates

Previous studies by our group have demonstrated that in the alkylation of several nucleophiles (including CH₂-active compounds and amines), dibenzyl carbonate (DBnC) displays a reactivity comparable if not higher than DMC;³⁵ while, diethyl carbonate (DEC) is a less active alkylation agent than DMC.³⁶ The same behavior holds true for the alkylation of solketal investigated here (compare Tables 2 and 3). Moreover, although the study of such a reaction is at a preliminary stage, the formation of *O*-alkyl and carboxyalkyl compounds (**4c–6c**, and **5c–7c**, respectively) from DBnC and DEC, is plausibly explained by a mechanism analogue to that outlined in Scheme 10 for DMC. Table 3 also shows that excellent *O*-alkyl selectivities (up to 100%) are achieved; in all cases, notwithstanding the excess of dialkyl carbonates, conversions are never quantitative and they level off, if not decrease, at high temperature and for prolonged reactions. As for DMC, the occurrence of decarboxylation/hydrolysis processes decompose the starting carbonates: results indicate that DBnC is a more efficient alkylating agent, but it also disappears at a higher rate with respect to DEC. Resonance effects similar to those invoked for S_N2 displacements likely enhance the reactivity of the benzyl system.³⁷

Conclusions

The set up of innovative transformations of glycerol and its derivatives represents an appealing challenge of modern chemistry. Not only for the fact that glycerol is among the most valuable biomass derived platform chemicals, but also for the market surplus of glycerol due to biodiesel productions. This work demonstrates that in the presence of K₂CO₃ as a base catalyst, dimethyl carbonate reacts with acetals of glycerol such as glycerol formal and solketal, to give the selective formation of the corresponding methyl ethers: at complete conversion, these products are obtained with selectivity up to 99%. These never previously reported reactions can be also scaled up for multigram synthesis without loss of selectivity; interestingly, under such conditions, the use of a reduced volume of DMC allows a consistent decrease of the reaction time and of the mass index of the process. Although the reaction is rather energy intensive, the procedure has a genuine potential for its low environmental impact. It is a catalytic process that couples the use of non-toxic dimethyl carbonate with renewable-derived acetals/ketals. Also, no additional solvents are required and major by-products are methanol and CO₂. An accurate analysis of the mass balance indicates that excellent GC yields (>90%) of *O*-methylation products (**2**) can be achieved, meaning that no mass loss occurs with respect to starting acetals. However,

due to technical limitations of the purification (distillation) step, compounds **2** are isolated in moderate yields not exceeding 67%.

Beyond the methylation process, the overall transformation includes the transesterification of both GlyF and solketal with DMC to produce the corresponding carboxymethyl derivatives. These compounds follow an intermediate-like behaviour which makes them disappear as the reaction proceeds: the reversible nature of the transesterification and the decarboxylation/hydrolysis of carboxymethyl products account for this result. The latter processes become significant also for DMC when prolonged reactions are performed. To the best of our knowledge, this behavior has never been previously described for reactions of alcohols and dialkyl carbonates under basic catalysis conditions, and it may open interesting synthetic perspectives. Also, a mechanistic hypothesis has been formulated on this basis.

The preliminary investigation of the reaction of solketal with both dibenzyl- and diethyl-carbonate suggests that the alkylation of glycerol acetals with dialkylcarbonates may be of a general scope. However, the extensive decarboxylation/hydrolysis of the starting carbonates does not allow the complete conversion of solketal. To limit side-reactions, studies are in progress with other base catalysts able to operate at lower temperatures than K_2CO_3 .

Experimental

General

Glycerol formal (GlyF, **1a+1b**), solketal (**1c**), benzyl alcohol, dimethyl carbonate (DMC), diethyl carbonate (DEC), dimethoxyethane (glyme), *n*-dodecane (C_{12}), K_2CO_3 , ethyl acetate (EA), petroleum ether (PE) and diethyl ether (Et_2O), were ACS grade from Aldrich. If not otherwise specified, they were employed without further purification. Dibenzyl carbonate (DBnC) was prepared *via* the transesterification reaction of benzyl alcohol with DMC, by adjusting a method reported in the literature¹⁸ (further details are in the ESI†). NaX faujasite was from Aldrich: before its use, it was dehydrated under vacuum (70 °C, 18 mm, overnight). GC-MS (EI, 70 eV) analyses were run using a FFAP capillary column (30 m), and CG/FID analyses were run using a DBWAX capillary column (30 m). ¹H NMR were recorded at 400 MHz, ¹³C NMR spectra at 100 MHz, and chemical shifts were reported in δ values downfield from TMS; $CDCl_3$ was used as solvent.

Reaction procedures

Reactions of 1a–1b, 1c with DMC in the presence of K_2CO_3 . In a typical procedure, a stainless steel autoclave (200 mL of internal volume) equipped with a pressure gauge, a thermocouple, and two needle valves, was charged with a mixture of 7.7 mmol of GlyF (**1a+1b**, 0.80 g; solketal, **1c**, 1.02 g), dimethyl carbonate (DMC, 19 mL, molar ratio, W , DMC:1 = 30) and K_2CO_3 (1.28 g, molar ratio, Q , K_2CO_3 :1 = 1.2). Where indicated, reactions with internal standard were carried out by adding *n*-dodecane (0.175 mL, 0.131 g, molar ratio, Z , 1: C_{12} = 10) to the mixture. The autoclave was purged with N_2 , electrically heated at the desired temperature (200–220 °C) and kept under magnetic stirring throughout the reaction. At the end of the experiment,

the autoclave was cooled to rt and then to –60 °C. The reactor was slowly vented until it returned to rt. The reaction mixture was finally analyzed by GC.

This procedure was adapted to examine the effect of reaction parameters on the alkylation of both GlyF and solketal with DMC: accordingly, the temperature, the time, the catalyst loading and DMC amount were modified as reported in Fig. 1–5 and Table 2.

Scale up of reactions. The procedure above described was used to scale up of the reaction of GlyF with DMC. The amounts of reagents and GlyF were multiplied by a factor of 5: a mixture of GlyF (**1a+1b** isomers, 4.0 g, 38 mmol), DMC [96 mL, 103 g, the molar ratio W = DMC:GlyF = 30] and K_2CO_3 [6.3 g, 46 mmol, the molar ratio Q = K_2CO_3 :GlyF = 1.2] was set to react at 220 °C (Table 1). Since a sizeable quantity of CO_2 was generated during the reaction, once a pressure of 60 bar was reached (after ~25 h), the autoclave was rapidly cooled to rt, and then to –60 °C in a liquid nitrogen bath, and slowly vented. After that, the autoclave was re-purged with N_2 and re-heated at 220 °C. The release of CO_2 overpressure was repeated at 37 and 43 h, respectively. The reaction was finally stopped after 52 h (Table 1, entry 1).

The same procedure was used to scale up the reaction in the presence of: i) a reduced volume DMC (17 mL, molar ratio, W , DMC:GlyF = 5; Table 1, entry 2), and ii) *n*-dodecane as an internal standard (0.861 mL, 0.646 g, molar ratio 1: C_{12} = 10; Table 1, entry 3).

The same procedure was used to scale up the reaction of solketal with DMC. In this case, the amounts of solketal and K_2CO_3 were multiplied by a factor of 3.5, while DMC was used in a 5-molar excess over the substrate: a mixture of solketal (**1c**, 3.5 g, 26 mmol), DMC (11 mL) and K_2CO_3 [4.3 g, 31 mmol, the molar ratio, Q , K_2CO_3 :**1c** = 1.2] (Table 2, entry 2) was set to react at 220 °C for 50 h.

Reactions of solketal (1c) with DBnC and DEC. Experiments were carried out according to the general procedure described above. The autoclave was charged with a mixture of solketal (1.8 mL, 14.6 mmol), K_2CO_3 (2.4 g, molar ratio, Q , K_2CO_3 :**1c** = 1.2) and different amounts of DBnC [16.5 and 26.4 g, molar ratio, W , DBnC:**1c** = 5 and 8, respectively] or DEC [8.0 g, molar ratio, W , DEC:**1c** = 5]. Reactions were carried out in the range of 190–220 °C, for 18–66 h (see Table 3).

Decarboxylation of DMC and carboxymethyl derivatives 3a–3b. The study of K_2CO_3 -catalysed decarboxylation of DMC and of carboxymethyl derivatives of GlyF **3a–b**, was carried out in an autoclave, using a procedure already reported by us.^{19a} In the case of DMC, a mixture of DMC (19 mL, 0.23 mol) and K_2CO_3 (1.28 g, 9.4 mmol, the molar ratio, W_1 , DMC: K_2CO_3 was 24), was set to react for 20 h at temperatures of 200, 210 and 220 °C. In the case of carboxymethyl derivatives **3a–3b**, a mixture of isomers **3a+3b** (1.25 g, 0.0077 mmol), K_2CO_3 (1.28 g, molar ratio, Q_1 , K_2CO_3 :**3a–b** = 1.2), and dimethoxyethane (glyme, 19 mL) as solvent, was set to react at 220 °C for 10 h. Under these conditions, an additional experiment was carried out using anhydrous solvent and catalyst: glyme was dried through conventional methods,³⁸ while K_2CO_3 was dried under vacuum (70 °C, 18 mm, overnight).

At the end of experiments, gaseous products generated from decarboxylation reactions, were recovered by a cold-trap apparatus,^{19a} weighed and analysed by GC-MS. In the case of DMC, mixtures of CO₂ and dimethyl ether (DME) were obtained:³⁹ the corresponding amounts were 0.36, 1.26 and 2.43 at 200, 210 and 220 °C, respectively. In the case of carboxymethyl derivatives **3a–3b**, only CO₂ was recovered: the amount was 0.20 and 0.23 g for experiments in non-anhydrous and anhydrous glyme/catalysts, respectively.

Isolation and characterization of *O*-alkyl products

4-(Methoxymethyl)-1,3-dioxolane (2a) and 5-methoxy-1,3-dioxane (2b).^{9a,40} These products were isolated at the end of experiments reported in Table 1. The final reaction mixtures were filtered (Gooch #4) to remove K₂CO₃, and the solid was washed with diethyl ether (3 × 50 mL). The resulting solution was concentrated by rotary evaporation (40 °C, 600 mbar), and then vacuum distilled. Two cold traps and a dephlegmator were used during the distillation. *O*-Methylated products **2a–2b** were isolated (58 °C, 3 mmHg) as mixtures of isomers in approximately the same 2:3 ratio of the starting isomers of GlyF. Yields of **2a+2b** were 2.91, 2.87 and 3.00 g (65, 64 and 67%; Table 1 entries 1, 2, and 3, respectively). Compounds **2a–2b** were fully characterized by GC-MS, ¹H and ¹³C NMR.

GC-MS (relative intensity, 70 eV) *m/z*: **2a** 118 (M⁺, <1%), 117 ([M – H]⁺, 1), 88 ([M–H₂CO]⁺, 15), 73 ([M–H₂COCH₃]⁺, 22), 72 (14), 59 (11), 45 ([CH₂=OCH₃]⁺, 100), 44 (17), 43 (11), 31 (15), 29 (29), 28 (12), 27 (10); **2b** 118 ([M]⁺, 2%), 88 ([M–H₂CO]⁺, 11), 58 ([M–(H₂CO)₂]⁺, 100), 43 ([M–(H₂CO)₂–CH₃]⁺, 34), 31 (14), 29 (30), 28 (20). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): **2a** 5.01 (s, 1H), 4.86 (s, 1H), 4.22–4.15 (m, 1H), 3.94 (dd, 1H, *J*₁ = 8.1 Hz, *J*₂ = 6.9 Hz), 3.66 (dd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 6.0 Hz), 3.47–3.41 (m, 2H), 3.38 (s, 3H); **2b** 4.83 (d, 1H, *J* = 6.1 Hz), 4.73 (d, 1H, *J* = 6.1 Hz), 4.02 (dd, 2H, *J*₁ = 11.6 Hz, *J*₂ = 3.5 Hz), 3.71 (dd, 2H, *J*₁ = 11.6 Hz, *J*₂ = 6.1 Hz), 3.40 (s, 3H), 3.32–3.26 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): **2a** 95.3, 74.3, 68.9, 66.9, 56.8; **2b** 93.6, 72.9, 71.3, 54.8.

4-(Methoxymethyl)-2,2-dimethyl-1,3-dioxolane (2c).^{9c–e,41}

Compound **2c** was isolated at the end of the reaction reported in Table 2 (entry 2). The final mixture was filtered (Gooch #4) to remove K₂CO₃, and the solid was washed diethyl ether (3 × 50 mL). The resulting solution was concentrated by rotary evaporation (40 °C, 600 mbar), and then vacuum distilled (56 °C, 3 mmHg) to give product **2c** in a 66% yield (2.47 g, purity 98% by CG).

GC-MS (relative intensity, 70 eV) *m/z*: 146 (M⁺, <1%), 131 ([M–H₃C]⁺, 26), 101 ([M–H₂COCH₃]⁺, 4), 71 (24), 59 (8), 58 ([M–H₃C–(H₂CO)–(H₂CCO)], 100), 45 ([CH₂=OCH₃]⁺, 4), 43 ([H₃CCO]⁺, 48), 42 (11), 41 (11). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 4.28–4.22 (m, 1H), 4.03 (dd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 6.4 Hz), 3.67 (dd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 6.5 Hz), 3.44 (dd, 1H, *J*₁ = 9.8 Hz, *J*₂ = 6.1 Hz), 3.38 (dd, 1H, *J*₁ = 9.8 Hz, *J*₂ = 5.1 Hz), 3.37 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 109.3, 74.5, 73.7, 66.6, 59.2, 26.6, 25.3.

4-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolane (4c).^{9c–e,41}

Compound **4c** was isolated at the end of the reaction reported in Table 3 (entry 5). The final reaction mixture was filtered (Gooch

#4) to remove K₂CO₃, and the solid was washed diethyl ether (3 × 50 mL). The resulting solution was concentrated by rotary evaporation. The residual oil was purified by FCC (flash column chromatography) over silica gel, using a mixture of petroleum ether (PE)/diethyl ether (Et₂O)/ethyl acetate (EA) as eluant solution [PE:Et₂O:EA = 4:1:1 v/v]. Isolated yield of **4c** was of 80% (2.58 g). Product **4c** was fully characterized by GC-MS, ¹H and ¹³C NMR.

GC-MS (relative intensity, 70 eV) *m/z*: 222 (M⁺, <1%), 207 ([M–H₂C]⁺, 12), 105 (11), 101 ([M–H₂COCH₂Ph]⁺, 28), 92 (12), 91 ([CH₂Ph]⁺, 100), 65 (11), 43 ([H₃CCO]⁺, 35). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.40–7.27 (m, 5H), 4.62–4.53 (m, 2H), 4.34–4.26 (m, 1H) 4.05 (dd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 6.4 Hz), 3.74 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 6.3 Hz), 3.55 (dd, 1H, *J*₁ = 9.8 Hz, *J*₂ = 5.7 Hz), 3.47 (dd, 1H, *J*₁ = 9.8 Hz, *J*₂ = 5.5 Hz), 1.42 (s, 3H), 1.36 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 138.0, 128.4, 127.7, 109.4, 74.7, 73.5, 71.1, 66.9, 26.8, 25.4.

Synthesis, isolation and characterization of carboxyalkyl products

Carboxyalkyl products were prepared by adjusting a conventional method for base-catalyzed transesterification reactions.²¹

(1,3-Dioxolan-4-yl)methyl methyl carbonate (3a) and 1,3-dioxan-5-yl methyl carbonate (3b). A 250 mL glass flask equipped with a condenser was charged with GlyF (**1a+1b**, 10 g, 0.096 mol), DMC (162 mL, 173 g, molar ratio, *W*, DMC : GlyF = 20) and K₂CO₃ (15.9 g, molar ratio, *Q*, K₂CO₃ : GlyF = 1.2). The flask was immersed in a thermostated oil bath, heated to the reflux temperature of DMC (90 °C) and kept under magnetic stirring. The reaction was monitored by GC. After 55 h, the mixture was cooled to rt, and filtered to remove K₂CO₃ (Gooch#4). The solid was washed with diethyl ether (3 × 30 mL). The resulting solution was concentrated by rotary evaporation (30 °C, 600 mbar), and then vacuum distilled. Compounds **3a** and **3b** were isolated (65 °C, 3 mmHg) as a mixture of isomers in approximately the same ratio of the starting isomers of GlyF. Yield of **3a–3b** was 79% (12 g, purity 98%, by GC). The products were fully characterized by GC-MS, ¹H and ¹³C NMR.

GC-MS (relative intensity, 70 eV) *m/z*: **3a** 162 (M⁺, <1%), 161 ([M – H]⁺, 4), 103 ([M–CO₂CH₃]⁺, 14), 102 (34), 86 ([M–H–OCO₂CH₃]⁺, 49), 77 (14), 73 ([M–CH₂OCO₂CH₃]⁺, 44), 59 ([CH₂OC≡O]⁺, 40), 58 (43), 57 (38), 55 (11), 45 ([CH=OCH₃]⁺, 100), 44 (36), 43 (50), 31 (52), 30 (10), 29 ([CH=O]⁺, 98), 28 (34), 27 (25); **3b** 162 (M⁺, <1%), 161 ([M – H]⁺, 4%), 102 ([M–(H₂CO)₂]⁺, 72), 86 ([M–H–CO₂–OCH₃]⁺, 49), 59 ([CH₂OC≡O]⁺, 41), 58 ([M–(H₂CO)₂–CO₂]⁺, 65), 57 (33), 55 (16), 45 (63), 44 (21), 43 ([M–(H₂CO)₂–CO₂CH₃]⁺, 72), 31 (59), 30 (14), 29 ([CH=O]⁺, 100), 28 (44), 27 (27). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): **3a** 5.03 (s, 1H), 4.89 (s, 1H), 4.32–4.25 (m, 1H), 4.21 (dd, 1H, *J*₁ = 11.3 Hz, *J*₂ = 5.7 Hz), 4.16 (dd, 1H, *J*₁ = 11.3 Hz, *J*₂ = 5.2 Hz), 3.97 (m, 1H), 3.79 (s, 3H), 3.72 (dd, 1H, *J*₁ = 8.5 Hz, *J*₂ = 5.5 Hz); **3b** 4.89 (d, 1H, *J* = 6.3 Hz), 4.81 (d, 1H, *J* = 6.2 Hz), 4.60–4.57 (m, 1H), 4.03 (dd, 2H, *J*₁ = 12.2 Hz, *J*₂ = 2.9 Hz), 3.96 (dd, 2H, *J*₁ = 12.1 Hz, *J*₂ = 4.2 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): **3a+3b** 155.5, 155.1, 95.5, 95.4, 72.5, 67.2, 66.6, 54.9, 54.9.

Methyl (2,2-dimethyl-1,3-dioxolan-4-yl)methyl carbonate (3c).

A 100 mL glass flask equipped with a condenser was charged with solketal (**1c**, 3.0 g, 0.023 mol), DMC (39 mL, 41 mL, molar ratio, W , DMC:**1c** = 20) and K_2CO_3 (3.9 g, molar ratio, Q , K_2CO_3 :**1c** = 1.2). The flask was immersed in a thermostated oil bath, heated to the reflux temperature of DMC (90 °C) and kept under magnetic stirring. The reaction was monitored by GC. After 95 h, the mixture was cooled to rt, and filtered to remove K_2CO_3 (Gooch#4). The solid was washed with diethyl ether (3 × 30 mL). The resulting solution (~100 mL) was concentrated by rotary evaporation (30 °C, 600 mbar), and then vacuum distilled. Product **3c** was isolated by distillation under reduced pressure (63 °C, 3 mmHg), in 88% yield (3.85 g, purity 98% by GC). The product was fully characterized by GC-MS, 1H and ^{13}C NMR.

GC-MS (relative intensity, 70 eV) m/z : 190 (M^+ , <1%), 175 ($[M-H_3C]^+$, 18), 115 ($M-OCO_2CH_3]^+$, 2), 101 ($M-CH_2OCO_2CH_3]^+$, 8), 71 (19), 59 ($[CH_2OC\equiv O]^+$, 16), 57 (11), 43 ($[H_3CCO]^+$, 100), 41 (17). 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.36–4.31 (m, 1H), 4.19–4.15 (m, 2H), 4.08 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 6.4$ Hz), 3.78 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 5.8$ Hz), 3.79 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.5, 190.8, 73.2, 67.9, 66.2, 54.9, 26.6, 25.3.

Benzyl(2,2-dimethyl-1,3-dioxolan-4-yl)methyl carbonate (5c).

A 50 mL glass flask equipped with a condenser was charged with solketal (**1c**, 0.94 g, 7.1 mmol), DBnC (3.6 g, molar ratio, W , DBnC:**1c** = 2), K_2CO_3 (1.3 g, molar ratio, Q , K_2CO_3 :**1c** = 1.2) and dimethoxyethane (glyme, 20 mL) as the solvent. The flask was immersed in a thermostated oil bath, heated to the reflux temperature of glyme (85 °C) and kept under magnetic stirring. The reaction was monitored by GC-MS. After 12 h, the mixture was cooled to rt, and filtered to remove K_2CO_3 (Gooch#4). The solid was washed with diethyl ether (3 × 10 mL). Compound **5c** was purified by FCC (flash column chromatography) over silica gel, using gradient petroleum ether (PE)/diethyl ether (Et_2O) elutions [initial PE: Et_2O = 1:0 v/v, final PE: Et_2O = 1:1 v/v], and isolated in a yield of 65% (1.2 g). Product was fully characterized by GC-MS, 1H and ^{13}C NMR.

GC-MS (relative intensity, 70 eV) m/z : 266 (M^+ , <1%), 101 ($[M-H_2COCO_2CH_2Ph]^+$, 11), 91 ($[CH_2Ph]^+$, 100), 65 (10), 59 (10), 43 ($[H_3CCO]^+$, 64). 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.39–7.33 (m, 5H), 5.17 (s, 2H), 4.35–4.31 (m, 1H), 4.21 (dd, 1H, $J_1 = 9.2$ Hz, $J_2 = 3.2$ Hz), 4.16 (dd, 1H, $J_1 = 9.2$ Hz, $J_2 = 3.9$ Hz), 4.07 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 6.4$ Hz), 3.78 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 5.9$ Hz), 1.42 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 149.7, 129.8, 123.4, 123.2, 104.7, 68.1, 64.6, 62.7, 61.1, 21.4, 20.1.

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