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Title

A Robust and Scalable Continuous Flow Process for Glycerol Carbonate

Keywords

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Abstract

We report a robust continuous flow procedure for the synthesis of glycerol carbonate (2-GLC) from green reagents glycerol and dimethyl carbonate (DMC), mediated by an inexpensive polymer-supported base catalyst using methanol as co-solvent. High conversion and selectivity were obtained, while residence times were typically shorter than 10 minutes.

Introduction

There has been significant industrial interest in the valorisation of glycerol in recent years, mainly due to glycerol being a bulk waste product derived mainly from biodiesel production but increasingly from oleochemical manufacturing.[1,2] These industries accounted for over 2247 kilotons of glycerol in 2013 and the global glycerol market is expected to reach a value of $2.52 billion by 2020.[3] The conversion of glycerol as a waste stream into other value-added products has therefore received considerable attention.[4,5] Some illustrative examples are hydrogenolysis to 1,2-propanediol,[6] dehydration to allyl alcohol,[7] transformation to epichlorohydrin[8-10] and gasification to syngas.[11]

Glycerol carbonate (2-GLC; 4-(hydroxymethyl)-1,3-dioxolane-2-one; glycerol 1,2-carbonate) is another interesting product derived from glycerol, and is considered a renewable building block due to its versatility.[12,13] Applications of 2-GLC include usage as a curing agent,[14] surfactant,[15] chemical intermediate for polymer production[16] and electrolyte liquid carrier.[17] 2-GLC is also becoming increasingly popular as a safe bio-based alternative to several traditional organic solvents, possessing a high boiling point (115 °C at 0.1 mbar), low volatility (vapour pressure of 8 mbar at 177 °C) and high dielectric constant ($\varepsilon = 82.7$).[18,19] Moreover, 2-GLC is water-soluble, nontoxic, readily biodegradable and non-flammable.

The conversion of glycerol to 2-GLC has been extensively studied (Scheme 1).[12] Examples include the use of phosgene, carbon monoxide and carbon dioxide.[12] Other reagents such as organic carbonates and urea have also been used. Carbon dioxide is, of course, the most green reagent of choice for this reaction, but known processes for direct 2-GLC synthesis from CO_2 often include the use of toxic tin reagents and glycerol conversions are low (in the range of 30%). These processes are therefore less economically feasible for industrial scale preparation.[20] Dimethyl carbonate (DMC) is widely studied as a carbonyl source to synthesise 2-GLC since it is considered an environmentally benign chemical, and has also been used in industrial settings to synthesise 2-GLC.[21-26] Many catalysts are known for this transesterification, *eg*. inorganic bases,[27-30] tertiary amines,[31-34] lipases,[35-37] and *N*-heterocyclic carbenes.[38] However, to our surprise only a few continuous processes are known for this transformation,[39-42] while in general continuous processes more often meet the basic criteria for potential industrial feasibility and scale up. To the best of our knowledge, inorganic bases are the preferred catalysts of use for industrial preparation of 2-GLC prepared from glycerol and DMC mainly based upon cost.[23-26]

In this paper we report a robust and scalable continuous flow process transforming glycerol to 2-GLC using DMC as the carbonyl source, by making use of a cheap and easily recyclable polymer supported catalyst[43-48] in the presence of methanol as a co-solvent. When applying a temperature > 120 °C and high conversions and selectivity are obtained with residence times typically lower than 10 minutes and thus producing high space-time yields.

Results and discussion

As a starting point for our investigation, neat batch experiments with homogeneous catalysts were performed, in order to derive a better understanding of the transformation (Table 1). It quickly became clear that basicity was a crucial parameter. Strong bases gave rise to high yields, which was in accordance with the literature (entries 2, 3, 8-9).[12,13]

Increasing the temperature also furnished improved results (Table 1, entry 8-9). Since we were initially also interested in developing a continuous synthesis for glycidol, the recent work of Tao *et al.* seemed of high relevance.[49] Tetraethyl ammonium amino acid ionic liquids were reported as efficacious catalysts for the one-pot neat synthesis of glycidol, starting from glycerol and dimethyl carbonate under reflux conditions. When replicating their experiments however, we were unable to achieve selectivity towards glycidol. Instead, a high selectivity towards 2-GLC was obtained (Table 1, entries 10-11). It should be noted that potentially glycerol can be derivatized to form different isomers involving either a five- or six-membered cyclic carbonate. The five membered derivative is the kinetic product whilst under alternative reaction conditions the six-membered cyclic glycerol carbonate (3-GLC, 5-hydroxy-1,3-dioxan-2-one, glycerol 1,3-carbonate) can be prepared as the thermodynamic product.[50] Intrigued by the initial results generated by the ammonium catalyst, a selection of related catalysts was also examined for the transformation (Table 1, entries 12-14). The low yields obtained in these instances could suggest that both an NH-moiety and carboxylate are required for efficient catalysis; entry 12 indicates acetate alone is not a sufficient catalyst.

Tetraethylammonium pipecolinate was the catalyst of choice for homogeneous catalysis flow experiments, using a Vapourtec® R-series system which was equipped with a FEP (fluorinated ethylene propylene) heated coil reactor. Since DMC and glycerol are immiscible at room temperature, a two stream setup was used as depicted in Table 2. The relative flow rate was adjusted in such a way as to provide 3.5 equivalents of DMC. Initially we adopted the protocol from the de Souza group,[40] using neat glycerol with catalyst, preheated at 70 °C (Table 2, entry 1). However, it was immediately apparent that pumping this viscous mixture would not be easily achieved. A solvent which is able to dissolve both glycerol and DMC was desired, *eg.* aliphatic alcohols. Therefore the glycerol and catalyst were dissolved in ethanol for these explorative experiments. It quickly became clear that 2-GLC formation increased with temperature. Applying a temperature of 140 °C yielded a 90% conversion and 85% selectivity (Table 2, entry 4).

When repeating these conditions in the absence of the pipecolinate catalyst, almost no 2-GLC formation was observed (Table 2, entry 5). Variation of residence time resulted in small conversion differences, while a slight decrease in selectivity was observed with increasing residence time (Table 2, cf. entry 6 with entries 4 and 7). It is worth noting that diethyl carbonate formation was observed in small amounts by ^{1}H-NMR in these experiments. In a final experiment, water instead of ethanol was used as solvent (note crude glycerol is often sourced as an aqueous mixture) but only a low conversion of 2-GLC was obtained (Table 2, entry 8). This might be due to poor mixing as a biphasic segmented flow was seen whilst a homogeneous flow was observed when ethanol was used as the solvent.

The easy separation of the catalyst after performing the reaction is one of the key requirements for industrial applicability and we therefore wanted to see if these results could also be generated when making use of a heterogeneous catalyst system. Therefore, additional batch experiments were carried out, this time using a polymer supported catalysts (Table 3). Pipecolic acid was immobilised by a simple neutralisation reaction with Ambersep® 900 hydroxide a high performance macroreticular polystyrene resin (Dow Chemical Company, 2.4 mmol g^{-1}, see Supporting Information). To our delight, a nearly quantitative conversion towards 2-GLC was obtained under neat conditions when using the immobilised catalyst (Table 3, entry 1). Since one could argue that this result might be due to remaining strongly basic sites on the polymer, a blank experiment was performed using fresh Ambersep® 900 hydroxide as the catalyst (Table 3, entry 2). However, a low conversion was obtained and confirmed that the hydroxide anion was replaced by pipecolic acid. Note that this result differs greatly from using potassium hydroxide as catalyst (79% GC yield, Table 1, entry 2), but is in accordance with the result for NEt_4OH (16% GC yield, Table 1, entry 7) with the difference explained due to mass transport limitations. Only a slight increase in yield was observed when methanol was used as co-solvent (Table 3, entry 3) or when the reaction was carried out at 120 °C in a microwave reactor (Table 3, entry 4). These results strongly suggest that a different mechanism takes place when using weakly basic catalysts of this type rather than strongly basic catalysts (*t*BuOK, KOH).

When translating this to a continuous flow process, a column reactor was filled with catalyst (see Experimental Section below) and heated to the appropriate temperature while the reagents were pumped through. The results are summarised in Table 4. *[It should be noted that the quoted residence times might be slightly underestimated since the polymers beads have the tendency to contract when heated!]* Methanol was the solvent of choice for dissolving glycerol, albeit a more concentrated solution than previously used (Table 2), since minimisation of solvent volume is desired for industrial applicability. Moreover, methanol is more easily removed than ethanol and results in less complex mixtures as methanol is generated as a by-product in the reaction. In a first trial, a residence time of 15 minutes at 100 °C yielded 85% conversion and 89% selectivity (Table 4, entry 1). Raising the temperature allowed higher conversions with essentially equivalent selectivity (Table 4, entries 2-3). Although showing improved overall conversions the general trend emulated the results originally obtained using the homogeneous catalyst (Table 2, entries 2-4). Of particular interest was that when repeating the reactions with the strongly basic Ambersep 900 hydroxide catalyst, a 73% conversion and 93% selectivity were obtained (Table 4, entry 4). This in stark contrast to the results obtained in batch (Table 3, entries 1-2), where the difference in efficacy between both catalysts was far more pronounced. By comparison in this continuous flow setup, the differences in results are relatively small.

Of note, previously several polymer supported basic catalysts have been trialled for the solvent free batch synthesis of 2-GLC but interestingly without much success.[30] It was however immediately evident that the Ambersep® 900 hydroxide resin is an ideal catalyst for flow scale up of this process being a low cost and commercially available material prepared at scale for use in water treatment. It was therefore decided to further optimise this process based upon its use.

High conversion and selectivity were obtained when raising the reactor temperature to 120 °C (Table 4, entry 5). To our delight, when further increasing the temperature to 140 °C the residence time could be lowered to 3 minutes without significant differences in 2-GLC formation (Table 4, entry 6). It was observed that a higher excess of DMC resulted in higher glycerol conversion, but decreased the selectivity due to formation of diglycerol tricarbonate, in accordance with the literature (Table 4, entry 7).[51] We also attempted to use neat glycerol by employing peristaltic pumps (Vapourtec E-series system) to deliver the more viscous solution (preheated glycerol at 70°C, Table 4, entry 8) but a conversion of only 30% was obtained. It appears that methanol as co-solvent enhances the homogeneity of the liquid phase and therefore ensures better mixing and catalyst interaction (less channelling of the viscous solution in the packed bed[52,53]). Ochoa-Gómez *et al.* have postulated that formation of 2-GLC occurs only if the glyceroxide anion is formed.[30] Therefore, close contact between the catalytic sites and glycerol is required, which is of course enhanced by homogeneity and reduced viscosity. According to the Ochoa-Gómez group, mass transport limitations also explain why their results are poor when using heterogeneous strongly basic ion exchange resins Amberlyst® 26 OH form and Amberjet® 4400 OH in batch.[30] Likewise, in our hands, we did not manage to achieve high conversion in batch under reflux conditions with our heterogeneous, strongly basic catalyst, Ambersep® 900 hydroxide resin (Table 3, entry 2). It was hypothesised that these formerly low conversions were greatly enhanced in our case by (a) using higher temperatures, (b) inducing a homogeneous liquid phase by adding methanol and (c) performing the reaction in a continuous column reactor, thus inducing more turbulence (convection and diffusion to the catalyst sites) than conventional batch stirring.

One final question was regarding the speciation of the Ambersep® 900 hydroxide resin specifically if under the column conditioning or during the reaction an anion exchange was occurring to form a more active catalyst. Considering that the hydroxide resin is potentially capable of exchanging with the methanol co-solvent a methoxide may be the active species (also accounting for the batch differences with water inhibiting the process). Consequently an appropriately functional methoxide resin was prepared and tested in the flow process giving essentially identical results to the formal hydroxide resin (Table 4, entries 5 & 9). As the trifluoroethanolate anion had shown a profound counter ion enhancement when utilised as part of a guanidinium based ionic liquid system for 2-GLC synthesis we elected to also prepare such a resin.[54] When tested we were pleased to see an enhancement in both conversion and selectivity (Table 4, entry 10). However, as anticipated after 35 min of use the output returned to a composition equivalent to parent methoxy resin. Despite offering an option of potentially using 2,2,2-trifluoroethanol as a co-solvent this was not pursued further due to the issue of cost.

Motivated by these findings, it was decided to maintain methanol as the co-solvent. Since conversion and selectivity were quite similar for both homogeneous and heterogeneous flow catalysis, but residence time was longer for the former, attempts to demonstrate the scalability of the heterogeneous flow setup were performed. As depicted in Scheme 2, the use of single, parallel as well as sequentially sequenced columns was tested to examine different aspects of the scale up process.

In the first scale up experiment (Flow process 1; Scheme 2a) a total flow rate of 1 mL min^{-1} was used at 140 °C and employing 4 equivalents of DMC, which resulting in a residence time of ~4 min by passage through a single packed column of Ambersep® 900 hydroxide (4.5 g). A satisfying conversion of 96% and selectivity of 82% was obtained. To examine the linear scalability a second equivalent packed bed column was appended to the flow path (Flow process 2, Scheme 2b) and the flow rate was raised to 2 mL min^{-1} again maintaining the reactor temperatures at 140 °C. A consistent conversion of 95% and associated selectivity of 81% was achieved and maintained over 4 hours of additional processing without loss of efficiency, consuming 82 grams of glycerol. The 2-GLC was isolated in a 75% yield resulting in a space-time yield of 3.38 kg 2-GLC per L reactor per hour. When repeating this experiment (Flow process 3; Scheme 2b) but lowering the residence time to 2 minutes (4 mL min^{-1} total flow rate), a slightly reduced 62% isolated yield of 2-GLC was obtained but resulting in a higher space-time yield of 5.60 kg 2-GLC per L reactor per hour.

Next, we performed the flow process using two parallel reactor cartridges (Flow process 4, Scheme 2c). It should be acknowledged that although distribution of a flow stream to two parallel linked reactors should theoretically give equal flows and hence equivalent contact times (residence times) in practice this approach can give different results especially when using heterogeneous inline reactors. This can be rationalized by the changes in hydrodynamic loading which effects aspects of mixing, diffusion and convection through the packed columns.[55-59] This can be particularly problematic at very low flow rates but was not significant in our scenario. Indeed using a combined flow rate of 2 mL min^{-1} and reactor temperature setting of 140 °C a conversion of 97% and higher selectivity of 91% was attained.

To validate the long term stability of the catalyst it was used in 5 consecutive runs of 5 h each performed at 140 °C (with cooling and methanol washing between cycles). A total 10% decrease in conversion was observed by the fourth usage which was also associated with a slight browning of the resin bead colour from its original ivory shade (Figure 1).

This decrease in activity could be compensated for by simply decreasing the flow rate as shown in run 5, however deactivation in further runs was again observed. It appears that the catalyst is robust and air-stable but does suffer from some long term thermal degradation. This would be expected given the nature of the functionality (benzyltrimethyl ammonium) and the benzylic linker which may be expected to undergo substitution/elimination reactions at elevated temperature.[60] By comparison an equivalent process run at 120 °C maintained activity even after 8 cycles (76-79% conversion).

Reflecting on the resin stability findings we set out to create a more sustainable flow process whilst attempting to decrease the equivalents of DMC and increasing the concentration of glycerol. As the parallel reactor configuration (Flow process 4 using the reactor depicted in Scheme 2c) had shown slightly improved processing characteristics we continued to employ this set-up in our optimization study. The experimental parameters were interrogated through a central composite design (CCD) using JMP Statistical Software (see experimental for configuration design). From this profiling a new reaction concentration of glycerol at 6.2 M was predicted, using 2.45 equivalents of DMC and a 115 °C with a 10 min residence time (Flow process 5). A stock solution of glycerol (6.2 M in MeOH) was pumped at 375 µL min^{-1} to combine in a 270 uL Uniqsis mixer chip with a flow stream of DMC (410 µL min^{-1}) before being distributed over the two parallel packed bed reactors distributed using a PEEK T-piece connector. After passing through the heated reactor columns (115 °C) a second T-piece connector was used to recombine the flow streams and the material then collected after passing a back pressure regulator (250 psi). As an extension to the process we took the exiting reaction solution and used it as a direct feedline to a rotary evaporator fitted with a 3 L collection flask. The heating bath was at set at 50 °C and the pressure fixed at 40 mbar. This enabled a continuous evaporation of the less volatile methanol and DMC which was shown could be recycled. Next standard vacuum distillation of the residual crude 2-GLC gave an 80% yield (3.5 h collection) equating to a productivity of 13.2 g/h with a reactor space-time yield of 0.84 kg 2-GLC per L reactor per hour.

Although the space-time yield was much lower in this process than previously achieved (Flow process 1-4) we were able to run the system uninterrupted for over 6 days (152 h) producing a consistent output and generating >2.0 Kg of isolated material equating to a catalyst TON of 981 and TOF of 6.46 h^{-1}.[61] It is also worth contrasting the different scale-up processes developed by applying additional processing metrics (i.e. Mass Intensity – MI and Reaction Mass Efficiency - RME) in which case the latter flow process becomes much more competitive in terms of its green credentials (Table 5).[62] Furthermore taking into account the requirement for reduced heating (115 vs 140 °C) this makes the latter run even more compelling. In addition as we have shown that columns can be run in parallel this would enable a simple numbering up approach to scaling especially with having demonstrated the long term stability of the catalyst. Alternatively if throughput is critical, we have shown that an automated switching value system could be easily installed to rapidly exchange the catalyst reaction cartridge, for example, on loosing activity, without interruption to the flow process.[63-66] This would thus enable the process to be run at a higher temperature and the eventually depleted columns to be replaced allowing a higher overall throughput albeit with the continual sacrifice of the catalyst, noting in this case its low cost.

Overall we feel this work acts as a powerful proof of concept study using a small laboratory set-up which could be utilized for further scale up towards a production level manufacture of 2-GLC using a combination of a simple reactor design and a low cost catalyst.

Conclusions

In summary, we have developed a scalable and robust continuous flow process for the synthesis of glycerol carbonate (2-GLC), starting from two green reagents, glycerol and dimethyl carbonate (DMC). The reaction has been shown to be efficiently mediated by Ambersep® 900 hydroxide functional resin, a bulk low cost polymer supported basic catalyst. High conversion and selectivity were obtained and residence times were typically short. In a series of scale up experiments we have demonstrated that the continuous production of 2-GLC can be achieved in high throughput and with improved processing metrics creating the foundations for a production level process.

Experimental Section

Materials

All purchased materials were used with further purification unless otherwise noted. Glycerol (glycerin) was purchased from Sigma Aldrich, and dimethyl carbonate (DMC) was purchased from Fluorochem. Methanol was purchased from Fisher Scientific UK (analytical reagent grade) and was used as such. Ambersep® 900 hydroxide was purchased from Fluka and rinsed with 1 M solution of aqueous NaOH, deionised water and dry methanol before use (see below). For column chromatography silica gel 60 (0.015-0.040 mm) was used (CAS No. 7631-86-9, EC Number 231-545-4) purchased from Merck Millipore.

Flow equipment

A Vapourtec® R2+ R4 unit was used for all flow reactions. An exception to this was when using neat glycerol: a Vapourtec E-series system with peristaltic pumps was used. Omnifit® glass columns (10 mm i.d. x 100 mm) were used as reactors for the heterogeneous catalysis experiments.

CCD optimisation

A central composite design (CCD) for optimization of the flow process (Flow process 3) was performed using JMP Pro 12.1.0 software optimized for conversion. The predicted test condition sets were derived from a 4 factors 4 levels Full Factorial Design and Least Square Fit model (2 replicates). Factors addressed were temperature (105, 110, 115, 120 °C), residence time – which equated to a flow rate (5, 7.5, 10, 12.5 min), glycerol concentration (5.8, 6, 6.2. 6.4 M) and stoichiometry (2.0, 2.2, 2.4, 2.6 M) generating surface plots from which the optimised conditions were sampled.

General experimental procedure for flow preparative scale synthesis

An Omnifit® glass column (10 mm i.d. x 100 mm) was filled with Ambersep® 900 hydroxide resin beads (4.5 g). The ends of the column were sealed using adjustable PTFE flow adaptors and the resin washed by passing an aqueous 1 M solution of NaOH (10 min), water (20 min) and MeOH (40 min) through at a flow rate of 1 mL min^{-1} (A Knauer K120 pump was used for the washing sequence). After the initial 10 min of MeOH washing, the temperature was gradually increased to 140 °C over the remaining 10 minute period (heating of the column reactors was conducted by placing the Omnifit columns into individual cartridge heaters attached to the Vapourtec® R4 unit). Next a solution of glycerol (5 M – Pump A on the Vapourtec® R2+ system) in MeOH was pumped at 366 µL min^{-1} and combined via a PEEK T-piece connector with a second stream containing DMC (neat, 4 equivalents - Pump B on the Vapourtec® R2+ system) at 634 mL min^{-1}. The combined stream was directed into the reactor column (residence time of approximately 4 min) and finally passing through an in-line backpressure regulator of 17 bar. The output was collected for analysis (calibrated GC-MS see SI for additional details) and after evaporation of MeOH and DMC (rotary evaporation at 50 °C and 40 mbar), 2-GLC was purified via either vacuum distillation (145-148 °C at 0.2 mmHg) or column chromatography on silica (DCM:MeOH 95:5). 2-GLC: ^{1}H NMR (d_6-DMSO; 400 MHz): 5.26 (t, J = 5.7 Hz, 1H), 4.84-4.74 (m, 1H), 4.49 (t, J = 8.1 Hz, 1H), 4.28 (dd, J = 8.1, 5.7 Hz, 1H), 3.66 (ddd, J = 12.6, 5.7, 2.8 Hz, 1H), 3.50 (ddd, J = 12.6, 5.7, 3.4 Hz, 1H). ^{13}C NMR (d_6-DMSO; 101 MHz): 155.16 (C), 77.01 (CH), 65.86 (CH$_2$), 60.59 (CH$_2$).

Flow scale up procedure, Flow process 1 (Scheme 2a):

A glass column (Omnifit® 10 mm i.d. x 100 mm) was filled with Ambersep® 900 hydroxide resin (4.5 g) and the ends sealed using adjustable PTFE flow adaptors before being placed into a cartridge heater attached to the Vapourtec® R4 unit. The catalyst bed was washed with aqueous 1 M NaOH (10 min), deionised water (20 min) and MeOH (20 min) was pumped through at a flow rate of 1 mL min^{-1}. After the initial 10 min of MeOH washing, the temperature was gradually increased to 140 °C. A stock solution of glycerol in MeOH (5 M – Pump A on the Vapourtec® R2+ system) was pumped at 366 µL min^{-1} and combined at a PEEK T-piece connector with a second stream containing DMC (neat, 4 equivalents - Pump B on the Vapourtec® R2+ system) at 634 µL min^{-1}. The combined flow stream (total flow 1 mL min) was directed into the column reactor (residence time of approximately 4 minutes), finally passing through an in-line backpressure regulator of 17 bar resistance. The flow output was collected as a batch and analysed by calibrated GC-MS (see SI for additional details) and showed a conversion of 96% and selectivity towards 2-GLC of 82%. The system was run uninterrupted for 4 h to validate steady state operation and to test the system for stability.

Flow scale up procedure, Flow process 2 (Scheme 2b):

Two Omnifit® glass columns (10 mm i.d. x 100 mm) were filled with Ambersep® 900 hydroxide resin beads (4.5 g). Both ends of the columns were sealed using adjustable PTFE flow adaptors and after linking in series a 1 M aqueous solution of NaOH (10 min), deionised water (10 min) and MeOH (20 min) was pumped through at a flow rate of 1 mL min^{-1}. After the initial 10 min of MeOH washing, the temperature was gradually increased to 140 °C over the remaining a 10 minute period (heating of the column reactors was conducted by placing the Omnifit columns into individual cartridge heaters attached to the Vapourtec® R4 unit). Next a solution of glycerol (5 M – Pump A on the Vapourtec® R2+ system) in MeOH was pumped at 740 µL min^{-1} and combined via a PEEK T-piece connector with a second stream containing DMC (neat, 4 equivalents - Pump B on the Vapourtec® R2+ system) at 1.25 mL min^{-1}. The combined stream was directed into the two linked columns and a finally passing through an in-line backpressure regulator of 17 bar. The flow output was collected and analysed by calibrated GC-MS (see SI for additional details) and showed a conversion of 95% and selectivity of 81%. The process was run uninterrupted for 4 hours processing 82 g of glycerol. Following evaporation of MeOH and DMC under reduced pressure using a rotary evaporator (50 °C and 40 mbar) the 2-GLC was purified by vacuum distillation in a 75% isolated yield.

Flow scale up procedure, Flow process 3 (Scheme 2b):

The set up employed was identical to the sequence described above – Flow process 2. The solution of glycerol (5 M – Pump A on the Vapourtec® R2+ system) in MeOH was pumped at 1.5 mL min^{-1} and the second stream containing DMC (neat, 4 equivalents - Pump B on the Vapourtec® R2+ system) at 2.5 mL min^{-1} (total flow rate of 4 mL min^{-1} and a residence time of 2 minutes). The flow output was collected and analysed by calibrated GC-MS (see SI for additional details). A standard 4 h run time was used to validate system stability. The output from the reactor was tested at 30 minutes, 1 h, 2 h, 3 h and 4 h giving a 84%±1.2% conversion. Following batch evaporation of the MeOH and DMC under reduced pressure using a rotary evaporator (50 °C and 40 mbar) the 2-GLC was purified by vacuum distillation in a 62% isolated yield.

Flow scale up procedure, Flow process 4 (Scheme 2c):

Two Omnifit® glass columns (10 mm i.d. x 100 mm) were filled with Ambersep® 900 hydroxide resin beads (4.5 g) and placed in the column heaters of the Vapourtec® R4 unit. The columns were sealed using adjustable PTFE flow adaptors and arranged inline in a parallel mode using a T-piece connector. The resin beds were washed with in sequence with 1 M aqueous solution of NaOH (10 min), water (10 min) and MeOH (20 min) pumping at a flow rate of 1 mL min^{-1}. After the initial 10 min of MeOH washing, the temperature was gradually increased to 140 °C over the remaining 10 minute period. A stock solution of glycerol (5 M – Pump A on the Vapourtec® R2+ system) in MeOH was pumped at 740 µL min^{-1} and combined via a PEEK T-piece connector with a second stream containing DMC (neat, 4 equivalents - Pump B on the Vapourtec® R2+ system) at 1.25 mL min^{-1}. The combined stream was directed into the two linked columns before finally passing through an in-line backpressure regulator of 17 bar. The flow output was collected and analysed by calibrated GC-MS (see SI for additional details) and showed a conversion of 97% and selectivity towards 2-GLC of 91%. No further purification was performed on the bulk sample.

Flow scale up procedure, Flow process 5 (Scheme 2c):

Two Omnifit® glass columns (10 mm i.d. x 100 mm) were filled with Ambersep® 900 hydroxide resin beads (4.5 g) and placed in the column heaters of the Vapourtec® R4 unit. The columns were sealed using adjustable PTFE flow adaptors and arranged inline in a parallel mode using a T-piece connector. The resin beds were washed with in sequence with 1 M aqueous solution of NaOH (10 min), water (10 min) and MeOH (20 min) pumping at a flow rate of 1 mL min^{-1}. After the initial 10 min of MeOH washing, the temperature was gradually increased to 115 °C over the remaining 10 minute period. A stock solution of glycerol (6.2 M – Pump A on the Vapourtec® R2+ system) in MeOH was pumped at 375 µL min^{-1} and combined via a 270 uL Uniqsis mixer chip with a second stream containing DMC (2.45 equivalents - Pump B on the Vapourtec® R2+ system) at 410 µL min^{-1}. The combined stream was split via a PEEK T-piece and directed into the two reactor columns before being reunited via a second PEEK T-piece and then passing through an in-line backpressure regulator of 17 bar. The output was connected as the feedline to a rotary evaporator fitted with a 3 L collection flask. The heating bath was at set at 50 °C and the pressure at 40 mbar facilitating continuous evaporation of volatiles. Vacuum distillation of the crude 2-GLC gave an 80% yield.

Analysis

GCMS experiments were carried out on a Shimadzu QP2010-Ultra located in CG43 EI is carried at 70 ev and the working mass range is 35 – 650 u for all experiments. The samples were prepared by dissolving 10 µL of collection volume in 1 mL of methanol. 0.5 µL of this sample was split injected (25:1) into the Shimadzu QP2010-Ultra equipped with a Rxi-17Sil MS column using helium as carrier gas (0.41 mL min^{-1}). The temperature of the oven was increased from 30 to 300 °C with a 50 °C min^{-1} rate. Finally, the oven was maintained at 300 °C for 5 min. It was found that glycerol and 2-GLC have the same response when plotting peak area in function of concentration (see Supporting Information). Therefore the following terms are defined as follows: conversion as the relative peak area of glycerol with all other peaks, selectivity as the relative peak area excluding the glycerol signal and GC yield as the relative peak area ratio of 2-GLC with glycerol.

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