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Research Article

Isopropenyl Acetate for the Continuous-Flow Synthesis of Triacetin, Solketal Acetate, and Allyl Acetate from Pure or Crude Glycerol

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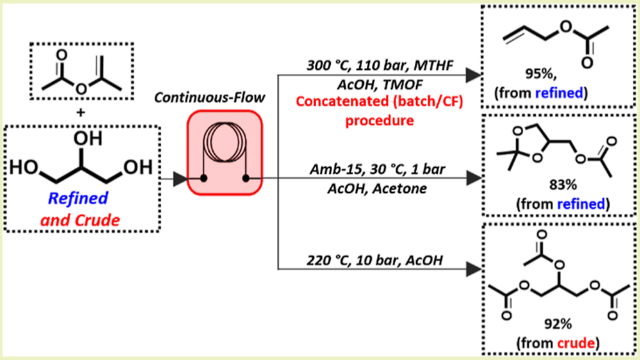
ABSTRACT: Isopropenyl acetate (iPAc) proved to be an effective green reagent for the chemical upgrading of refined and crude glycerol (CG) into valuable products, such as allyl acetate, triacetin (TA), and acetal acetates, under continuous-flow (CF) conditions. Two unprecedented tandem catalytic protocols of deoxydehydration (DODH)/acetylation and acetylation/acetalization were implemented to convert glycerol into allyl acetate and acetal acetates. These products were achieved in 95 and 78% yields, respectively, by combining a pool of innocuous compounds that acted with different roles: iPAc as an acetylating agent, triethylorthoformate as a DODH agent, acetone as an acetalization agent, and acetic acid and Amberlyst-15 as the homogeneous and heterogeneous catalysts, respectively. The parametric analysis of the process variables allowed us to reach the productivity (*P*) of 10.6 mmol·h^{-1} mL^{-1} at 300 °C and 110 bar and 37 mmol·$g_{cat}{}^{-1}$ h^{-1} at 30 °C and ambient pressure for the (DODH)/acetylation sequence and the acetylation/acetalization cascade reaction, respectively. Acetal acetates were obtained as a mixture of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate (solketal acetate) and 2,2-dimethyl-1,3-dioxan-5-yl acetate in a 97:3 ratio. A third protocol was designed for the peracetylation of CG as an industrial waste with iPAc: in the absence of any catalyst, TA (glycerol triacetate) was isolated in 92% yield with the productivity improved by more than 60 times compared to previous literature results. The performance of two of the target products (acetal acetates and TA) as biofuel additives was also investigated.



KEYWORDS: *tandem reactions, biofuel additives, process intensification, productivity, CHEM21 toolkit*

■ INTRODUCTION

Glycerol is obtained primarily as a co-product of biodiesel manufacture, and as such it is overabundant in the current market and available at a reasonably low cost. These features, along with its flexible reactivity, make glycerol an attractive biomass-derived platform chemical with a bright outlook for its industrial valorization.[1−4] Glycerol can be subjected to a plethora of synthetic transformations, thanks to the simultaneous presence of three −OH groups in its structure.[5−7] Its derivatives include acrolein,[8,9] divinyl glycol,[10] allyl alcohol,[11,12] glycerol carbonate,[13] glycidol,[14,15] 1,2-propanediol,[16,17] acetals, ketals,[18−23] triacetin (TA), solketal acetate (SA), and allyl acetate, all of which becoming increasingly popular building blocks.

TA, SA, and allyl acetate have been the targets of this work. These compounds find major applications as green solvents, plasticizers, excipients in formulations and drug delivery systems, flavors,[24−27] monomers for polymer synthesis,[28,29] and as intermediates for several reactions, including, for example, synthesis of *N*-aryl and *N*-alkyl pyrrolines[30] and Tsuji-Trost cross-couplings.[31−33] TA and SA also find applications as biodiesel additives to improve its flash point and oxidation stability, according to both American and European Standards (ASTM D6751 and EN 14214, respectively).[34]

Several routes have been reported for the synthesis of these three derivatives. In the case of TA, protocols for the acetylation of glycerol were achieved at 60−100 °C, by using acetic anhydride (Ac_2O) or acetic acid (AcOH) in the presence of zeolite beta, K-10 montmorillonite, and Amberlyst-15 or 36 as heterogeneous catalysts.[35−38] The desired product was obtained with up to 100% yield with Ac_2O, although the high explosion potential, the corrosivity, and the legislative restrictions on the use of Ac_2O made the procedure unsafe and not recommended for large-scale applications.[39,40] The acetylation was far less satisfactory with AcOH, not only for the slower kinetics but also for the selectivity issues since

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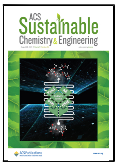

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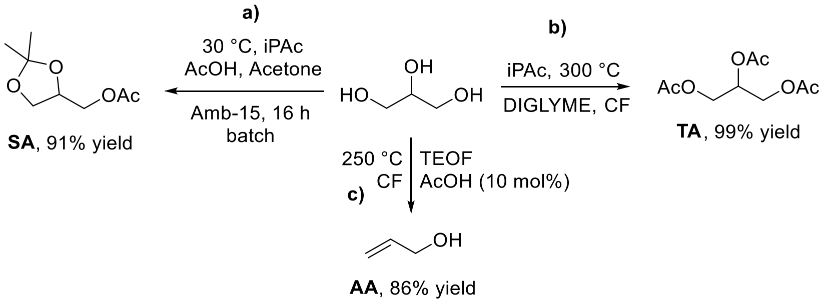
Scheme 1. Diversified Routes for the Upgrading of Glycerol: (a) Batch Tandem Synthesis of SA; (b) Selective CF Synthesis of TA; (c) High-Temperature CF DODH of Glycerol for the Preparation of Allyl Alcohol



mixtures of mono-, di-, and tri-acetylated products were observed.

Allyl acetate is most conveniently prepared starting from allyl alcohol as a precursor. Among the alternatives available for the synthesis of alcohol, deoxydehydration (DODH) of glycerol is emerging as one of the most economically viable options.[40,41] Both metal-catalyzed procedures based on Re-,[11,42−46] Mo-,[47] Fe,[48] and Mo/Fe/Ce-,[49] diverse transition metals,[50] and formic acid-assisted DODH strategies[51,52] have been reported in the literature.

The synthesis of SA has been described through a two-step process where glycerol was first subjected to a ring-closing acetalization with acetone providing solketal ((2,2-dimethyl-1,3-dioxolan-4-yl)methanol),[53] which in turn was acetylated by conventional agents such as Ac_2O.[24] The direct preparation of SA from glycerol has been, instead, less investigated. The reaction was attempted using a mixture of Ac_2O and acetone with H_2SO_4 as a catalyst, but the overall yield did not exceed 10%.[54] To the best of our knowledge, the most significant result was recently obtained by our group through the design of a one-pot tandem acetalization/acetylation of glycerol with the non-toxic isopropenyl acetate (iPAc). This sequence provided SA in up to 91% yield or, alternatively, a 1:1 mixture of TA and SA under very mild conditions (30 °C and ambient pressure), in the presence of AcOH as a solvent and a co-reagent, and Amberlyst-15 as a catalyst (Scheme 1, route a).[55]

In this scenario, continuous-flow (CF) procedures deserve a separate mention, wherein both TA and allyl alcohol were obtained through genuinely sustainable pathways. For example, some of us reported that at 300 °C and catalyst-free conditions, the CF acetylation of glycerol with iPAc afforded TA in a quantitative yield (Scheme 1, route b).[56] Other authors, instead, claimed that at 250−300 °C, the combined use of formic acid/AcOH as catalysts and triethyl orthoformate (TEOF) as a dehydrating agent allowed a highly selective CF DODH of glycerol. This provided allyl alcohol in an 86% yield (Scheme 1, route c).[57]

As part of our long-standing interest in the application of CF technologies in green organic synthesis,[58−61] this study was aimed at the design of original approaches for upgrading both pure and off-grade (crude) glycerol, the latter as received from the biodiesel production plant.

In particular, we wish to report herein the following: (i) a tandem DODH/transesterification sequence, where the use of TEOF and iPAc in the presence of AcOH as a catalyst allowed the conversion of glycerol into allyl acetate in a 95% yield; (ii) a parametric analysis of the exhaustive (triple) acetylation of crude glycerol (CG) with a mixture of iPAc and AcOH as reagents, which not only demonstrated the reaction feasibility, but also provided a productivity of TA up to 62.4 mmol h^{-1} mL^{-1}, suited to large scale preparations; (iii) the full implementation of the tandem acetalization/acetylation of glycerol with iPAc (Scheme 1, route a) from the batch- to the CF mode, with an overall 10 times increase of the productivity of SA.

In addition, this work investigated the performance of SA and TA as biofuel additives, demonstrating that both compounds, as such or as a mixture, improved the viscosity, density, and cloud and pour points of the fuel.

RESULTS AND DISCUSSION

General. The microfluidic CF apparatus used in this work was assembled in-house based on similar systems previously reported by us.[59,61,62] The apparatus is schematized in Figure 1. The reactant solution was delivered by an HPLC pump and conveyed to the CF reactor placed inside an oven for temperature control. If not otherwise specified, a coiled steel tubular micro-reactor (L = 5 m, Ø = 0.5 mm) was used in all CF experiments for improved mass/heat transfer and mixing.[63,64] A back-pressure regulator maintained a constant operating pressure throughout the system and allowed the depressurization and recovery of the reaction mixture. The samples collected at the reactor outlet were directly analyzed by GC, GC−MS, and NMR to determine the reaction conversion and product distribution. All reactions were run in duplicate to ensure reproducibility. Unless otherwise stated, conversions, selectivity, and yields differed by less than 5% from one test to another.

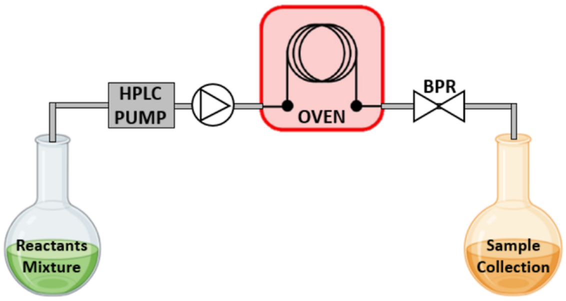
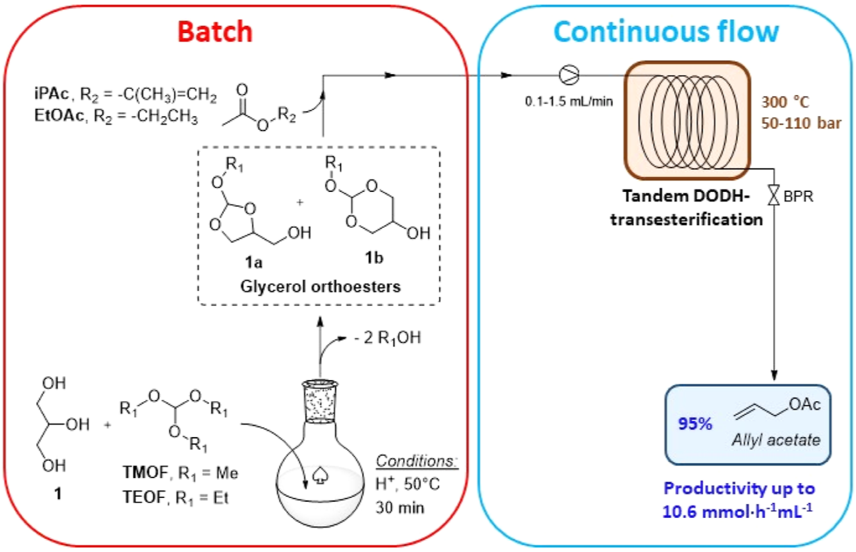


Figure 1. Microfluidic CF setup for the upgrading of glycerol.

Synthesis of Allyl Acetate by a Batch-CF Concatenated Procedure. This study was aimed at accomplishing a three-step cascade sequence: (i) the conversion of glycerol into glycerol orthoesters; (ii) the deoxydehydration of the orthoesters to allyl alcohol; and (iii) the transesterification of the alcohol with different esters as acetyl donors, to produce

Scheme 2. Concatenated Procedure for the Cascade Conversion of Glycerol to Allyl Acetate. (a) Batch Synthesis of Glycerol Orthoesters (Left); (b) Tandem DODH-Transesterification of Glycerol Orthoesters to Allyl Acetate (Right)



allyl acetate (Scheme 2). Reaction conditions were adapted from a previously reported work on the preparation of allyl alcohol.[57] It should be noted that, due to their viscosity, neither glycerol nor glycerol orthoesters **1a**/**1b** could be fed into the CF system of Figure 1 without the use of a solvent. Experiments were therefore carried out using a 1 M solution of glycerol in methyl tetrahydrofuran (MTHF), which was chosen as a renewable green reaction medium,[65] in the presence of TEOF or trimethyl orthoformate (TMOF) (1 equiv) as a DODH agent and AcOH (0.5 equiv) as a catalyst. This solution was placed in a glass flask and set to react at 50 °C under magnetic stirring until glycerol was completely converted into the corresponding glycerol orthoesters **1a** and **1b** (in a 97:3 ratio, respectively) (Scheme 2, red box, left). Such derivatives were typically obtained after 30 min. Without any further treatment, the solution of **1a**/**1b** was conveyed to the CF reactor at 0.1 mL min^{-1} at 300 °C and 50 bar. These conditions proved robust and gave reproducible results for the CF deoxydehydration (DODH) of the orthoesters of glycerol: the desired product, allyl alcohol, was achieved in a yield variable between 68 and 78%, depending on the dehydration agent used. TEOF was a comparatively better reagent than TMOF (details of this study are in Table S1 of the Supporting Information section).

The CF tandem DODH-transesterification sequence was then explored. Based on our previous investigations that demonstrated the superior acetyl donor ability of iPAc compared to methyl or ethyl acetate,[56,66] initial tandem CF tests were carried out by adding iPAc to the mixture of glycerol orthoesters **1a** and **1b** (prepared as described above). The resulting solution was delivered to the CF reactor at a temperature (T) and a flow rate (F) set to the values used for the synthesis of allyl alcohol, 300 °C and 0.1 mL min^{-1}, respectively (Scheme 2, blue box, right). Both T and F were never modified throughout the study. Different sets of experiments were performed by changing the pressure from 50 to 80 and 110 bar and the amount of iPAc from 2 to 5 and 10 equiv with respect to glycerol.

At intervals, the solution sampled at the outlet of the reactor was analyzed by GC and GC/MS to determine both the conversion and composition. All tests were prolonged for at least 3 h until the composition of the effluent mixture was steady over time, with variations within ±5% between one analysis and the other. Results are shown in Figure 2.

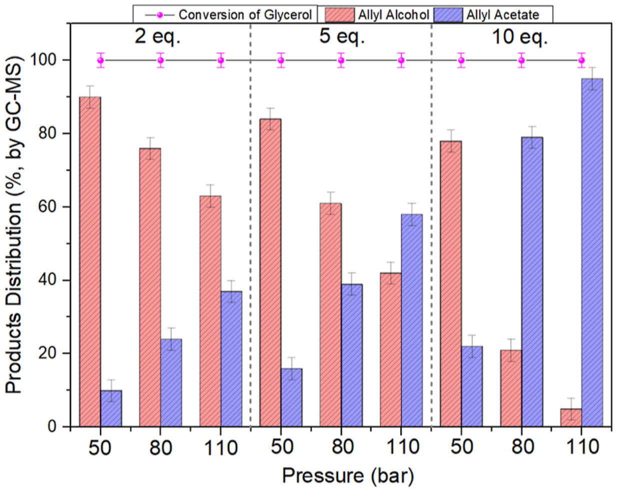
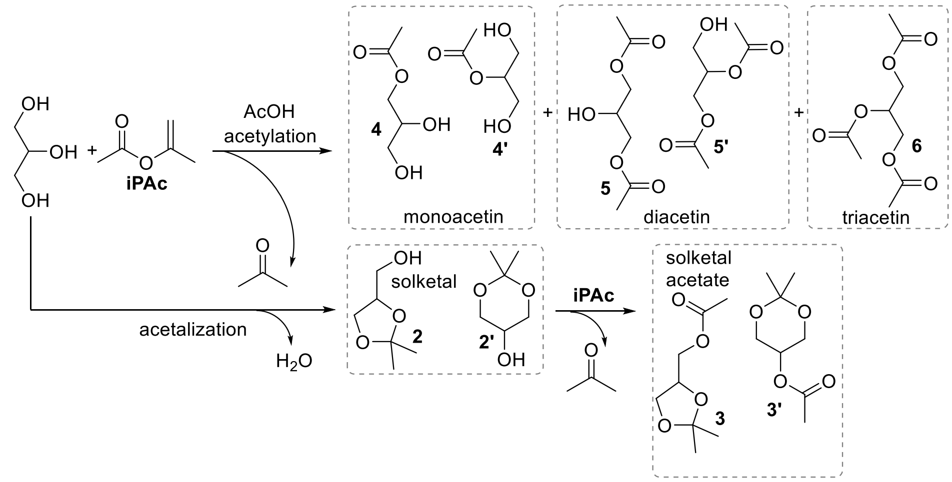


Figure 2. Effect of iPAc equivalents and pressure on the product distributions of the tandem DODH-transesterification sequence. Reaction conditions: glycerol (1 M in MTHF), TEOF (1 equiv with respect to glycerol), and AcOH (0.5 equiv with respect to glycerol), 300 °C, 0.1 mL min^{-1}; Conversion and product distributions were determined by GC–MS.

All experiments proceeded with the complete conversion of the glycerol orthoesters, no other products except allyl alcohol and allyl acetate were detected in the reaction mixture. This demonstrated that the desired DODH-transesterification tandem process was feasible. However, the relative quantities of the ester and the alcohol [Q ratio = allyl acetate (%, by GC): allyl alcohol (%, by GC)] were highly dependent on both the pressure and the iPAc amount.

In the pressure range of 50–80–110 bar, the increase of the amount of iPAc from 2.0 to 5.0 and 10 equiv, brought about a gradual and significant increase of the Q ratio from 0.10 to

Scheme 3. Products Observed in the CF Reaction of CG with iPAc/AcOH



0.61, 0.18 to 1.4, and 0.25 to 19.0, respectively (Figure 2, left to right). In other words, at 110 bar and with the highest investigated amount of iPAc, the tandem process was favored to the point that allyl acetate was almost the only product (95%). Very selective reactions took place, notwithstanding the high reaction temperature and the reactivity of the enol ester; acetone released as a co-product did not induce any side reactions from the acetalization of allyl alcohol (see also the following sections in this work). The beneficial effect of the pressure on the tandem product was ascribed to a favorable partitioning of the reagents and the catalyst in a condensed (liquid) phase within the reactor, where their mutual contact was improved and so were the reaction kinetics.

Encouraged by these results, a different approach for the tandem process was conceived by replacing iPAc with ethyl acetate. The acetylation of allyl alcohol with AcOEt would have originated in ethanol, the same co-product of the DODH process (from TEOF, Scheme 2), thereby minimizing/avoiding interferences with the overall sequence. Moreover, ethyl acetate is far cheaper than iPAc, and like the enol ester, it is a nontoxic compound.

CF experiments were carried out under the conditions of Figure 2 (300 °C, 110 bar), except for the substitution of iPAc with AcOEt in 10, 20, and 30 equiv with respect to glycerol. Experiments demonstrated that the DODH/transesterification tandem sequence was feasible with 10% AcOEt as well, albeit with a lower yield relative to iPAc, yielding allyl acetate in 62% yield. Only with 30% AcOEt was 93% allyl acetate observed. The results are reported in Table S2 in the Supporting Information section.

Overall, the study proved the concept of the selective conversion of glycerol into allyl acetate. The sequence combined multiple concatenated reactions: the batch transesterification of glycerol with TMOF or TEOF, followed by a CF tandem reaction sequence involving the DODH of the orthoesters to allyl alcohol and the transesterification of allyl alcohol with acetate esters. iPAc as a reactive enol ester was more suited for the last step compared to conventional acetates, although by tuning the conditions, e.g., increasing the amount of ester, ethyl acetate could be used as well.

CF Synthesis of TA from Crude Glycerol. The design of protocols to upgrade CG as obtained from the biodiesel manufacturing process is becoming more and more attractive to limit the costs and carbon footprint associated with the refining of glycerol, which is often far more energy-demanding compared to the refining of glycerol derivatives.[62] However, the presence of contaminants, such as metals, salts, organics, and water, makes the reactions of CG challenging because catalyst(s) may deactivate, selectivity may be hard to control, and yield can be limited. This investigation was inspired by a protocol previously reported by us for the CF alkylation of glycerol derivatives with alkyl and enol esters.[56]

CG, employed as received from a biodiesel producer, was composed of a mixture of glycerol, ash, MONG (matter organic non-glycerol), and water in 80, 5%, ca. 3, and 12% amounts, respectively. The synthesis of TA was studied using a solution of iPAc as an acetylating agent and AcOH as the solvent, which could also aid the esterification of glycerol.[55] CF experiments were carried out in the micro-reactor of Figure 1 by feeding CG, iPAc (3−10 equiv with respect to glycerol), and AcOH (10 equiv with respect to glycerol) at a flow rate (*F*), *T*, and *p* in the range of 0.1−2 mL·min^{-1}, 180−240 °C, and 10−30 bar, respectively. All reactions were prolonged for at least 2 h until the composition of the effluent mixture was steady over time. The test proved that the desired transesterification of CG was feasible under the investigated CF conditions. However, a variety of products, shown in Scheme 3, were detected.[55]

The acetylation of CG with iPAc provided mono-, di-, and tri-acetin along with the enol of acetone, making the overall transformation irreversible (Scheme 3, top). Mono- and diglyceryl acetates were obtained as a mixture of two isomers, **4**/**4′** and **5**/**5′**, with a 2.3:1 preference toward the monoacetin **4** and the diacetin **5** due to the higher reactivity of the primary hydroxyl groups (**4**:**4′** and **5**:**5′** = 70:30). AcOH probably contributed only to the mono-acetylation of glycerol, as observed previously.[55,67−69]

The stoichiometric formation of acetone promoted competitive acetalization of glycerol to cyclic acetals **2** and **2′**. These derivatives, in turn, underwent subsequent acetylation with iPAc to provide acetal acetates **3** and **3′** (Scheme 3, bottom). Indeed, only compounds **3** and **3′** were detected. The greater thermodynamic stability of the five-membered ring isomer **3** explained its preferential formation over the 6-membered ring analogue **3′** (**3**:**3′** = 97:3). Isomers were therefore grouped together, and their amounts were reported as the totals **3** + **3′**, **4** + **4′**, and **5** + **5′**. The conversion of glycerol and the product distribution (selectivity) were

Table 1. Catalyst-Free CF Reaction of Crude Glycerol with iPAc and Acetic Acid[a]

entry	T (°C)	p (bar)	F (mL min^{-1})[b]	Q (mol/mol)[c]	products distribution (%)[d]				P (mmol$_6$·h^{-1}mL^{-1})[f]
					acetal acetates	acetins			
					3 + **3′**[e]	**4** + **4′**[e]	**5** + **5′**[e]	**6**	
1	240	10	0.5	3	1	1	36	62	20.8
2				4	3	2	9	86	25.6
3				5	4	1	1	94	25.3
4				10	6		3	91	16.4
5	220	10	0.5	5	3	1	1	95	26.1
6		20			5		2	93	25.0
7		30			5	1	1	92	24.7
8		10	0.7		7	1	7	85	32.0
9			1		6	3	10	81	43.5
10			2		7	2	33	58	62.4
11	200	10	0.5	5	8	3	9	80	21.5
12	180	10	0.5	5	11	2	30	57	15.3
13[g]	300	50	0.1	20				99	1

[a] Reactions were carried out using a mixture of CG (1 equiv of glycerol), iPAc (3−10 equiv), and AcOH (10 equiv). Equivalents were referred to with respect to glycerol. Tests were prolonged for at least 2 h. [b] F = flow rate. [c] Q = iPAc/Glycerol molar ratio (mol/mol). [d] Amount of products **3**−**3′**, **4**−**4′**, **5**−**5′**, and **6** in the mixture collected at the reactor outlet. [e] Total amount of isomers. [f] Productivity of TA (**6**). [g] Taken from ref 56.

evaluated by calibration with standard solutions. In particular, the selectivity for both the transesterification products and acetal acetates was calculated for each of the binary mixtures **3** + **3′**, **4** + **4′**, and **5** + **5′** and compound **6** according to the following expression

$$S_i = [\text{mol i/conv. glycerol}] \times 100 \quad (1)$$

where S_i is the selectivity (%) for compound i (i = **3** + **3′**, **4** + **4′**, and **5** + **5′** and **6**) and mol i stands for the total moles of compound i (by GC calibration) and conv. Glycerol is the total conversion of glycerol for the combined transesterification and acetalization processes (Scheme 3).

Results are reported in Table 1, where Q and P represent the iPAc/glycerol molar ratio and the productivity of TA, respectively. P was calculated as the mmoles of **6** obtained per time unit (h) and volume unit (mL) of the CF reactor (P = mmol·h^{-1}·mL^{-1}).[67] The conversion of glycerol was not indicated since it was ≥99% in all experiments.

The effect of the amount of iPAc was highlighted from reactions carried out at constant T, p, and F of 240 °C, 10 bar, and 0.1 mL min^{-1}, respectively (entries 1−4). Under such conditions, the increase of the Q ratio from 3 to 4 and 5 brought about a progressive increase of TA, the product derived from the exhaustive (tri-)acetylation of glycerol, that was achieved with an excellent selectivity up to 94% and a productivity of 25.3 mmol·h^{-1}·mL^{-1} (entry 3), at the expense of mono- and diacetins. The formation of acetal acetates **3**/**3′** remained substantially steady and almost negligible (1−4%).

A further increase to Q = 10, however, did not significantly change the product distribution, though P dropped to 16.4 mmol·h^{-1}·mL^{-1} (entry 4). This behavior was confirmed by an additional experiment in which CG was replaced by a lab-made crude substrate comprised of a mixture of glycerol, MeOH, H_2O, and NaCl in a 50:23:26:1 wt % ratio, respectively. This composition mimicked that of other types of off-grade glycerol available on the biodiesel market.[70] At 240 °C (10 bar, 0.5 mL min^{-1}, Q = 10), a total conversion was reached, and the selectivities toward TA **6** and acetal acetates **3**/**3′** were 96 and 4%, respectively.

The results indicated that the whole sequence of Scheme 3 could be steered toward the formation of TA on the condition that iPAc was present in an over-stoichiometric quantity (Q > 3) with respect to that required for the triple transesterification of glycerol. This was consistent with partial hydrolysis of iPAc[71] due to the water (12%) present in the starting CG. It was known from the literature that iPAc could also undergo an acyl nucleophilic substitution (acidolysis) with AcOH to provide acetone and Ac_2O.[66,72] This further reaction, however, was ruled out under the investigated conditions since acidolysis required a strong acid catalyst (e.g., H_2SO_4). Moreover, not even traces of Ac_2O were detected during the CF tests of Table 1.

At Q = 5, the amount of iPAc was sufficient to ensure the selective synthesis of TA (>90%). CF conditions were then fine-tuned to explore the effects of temperature and pressure and to improve reaction productivity by changing the flow rate. The decrease of T to 220 °C, leaving other parameters unaltered (p = 10 bar, F = 0.5 mL·min^{-1}, and Q = 5), did not appreciably vary the product distribution, particularly the TA selectivity, which continued to be very high (95%, entry 5). The product (**6**) was isolated by fractional distillation in a 92% yield (10.8 g after 2 h of time-on-stream), thereby confirming the robustness of the protocol for gram-scale synthesis. Likewise, the change in pressure did not induce any significant modification; at 220 °C, comparable results were achieved in the range 10−30 bar (entries 6−7). The flow rate, instead, dramatically affected productivity. By quadrupling F from 0.5 to 2 mL min^{-1}, P increased by a factor of 2.4, reaching 62.4 mmol·h^{-1}·mL^{-1} (entries 5 and 8−10). This value was more than 60 times higher than that previously reported by us for the same reaction (entry 13).[56]

Lowering the temperature to 200 and 180 °C at p = 10 bar, F = 0.5 mL·min^{-1}, and Q = 5, lowered the yield of TA while promoting the formation of diacetins **5**/**5′** and acetal acetates **3**/**3′** (11 and 30%, respectively) (entries 11−12).

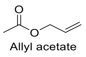
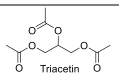
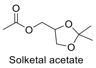
Overall, a successful benign-by-design CF protocol was implemented for the synthesis of TA via the acetylation of glycerol with iPAc. The study exemplified clear benefits in terms of process intensification yielding a high-quality product, improved process safety, and, to the best of our knowledge, one of the highest reported productivities amenable to scale-up

Table 2. CF Reaction of Glycerol with iPAc and Acetone, Catalyzed by Amb-15[a]

entry	flow (F) (mL min^{-1})	products distribution (%)[b]					productivity (mmol$_{3/3'}$ g$_{cat}$$^{-1}$h^{-1})[d]
		acetals		esters			
		2 + 2′[c]	3 + 3′[c]	4 + 4′[c]	5 + 5′[c]	6	
1	0.1		62			38	5
2	0.3		81			19	18
3	0.6	4	83		2	12	37

[a] Conversion of glycerol. [b] Selectivity toward products **2**/**2′**, **3**/**3′**, **4**/**4′**, **5**/**5′**, and **6**. [c] Total amount of isomers. [d] Productivity of acetal acetates **3**/**3′**. Data referred to reactions carried out for 2 h.

Table 3. Comparison of Different Routes to Allyl Acetate, TA, and SA Based on the CHEM21 Metrics Toolkit and the *E*-Factor

Entry	Target compound	Procedure	Zero Pass		First Pass						E-factor (g/g)		Ref.
						Conditions			Health and Safety	Reaction mode			
			Yield (%)	AE, RME (%)	PMI (g/g)	Cat.	E (T, °C)[a]	Work-up	Reagents/solvent	Batch/CF	sEF[b]	cEF[c]	
1	 Allyl acetate	**A** concatenated	🟩 95	29.4, 7.7	22.7	🟩 AcOH	🟩 Batch: 50 🟥 Flow: 300	🟩	🟩 TEOF 🟩 iPAc 🟨 MeTHF	🟨 Batch 🟩 CF	12.4	21.4	This work
2		**B** Two steps	🟩 Step 1: 97 🟩 Step 2: 91 🟨 Overall: 88	27.4, 14.3	206.1	🟩 Step 1: AcOH 🟥 Step 2: ZnO	🟥 Step 1: 300 🟩 Step 2: rt	🟨	🟩 Step 1: TEOF, HCOOH Step2: EtOAc, H_2O 🟨 Step 2: AcCl	🟩 Step 1: CF 🟨 Step 2: Batch	8.9	-[d]	57,80
3		**C** Two steps	🟩 Step 1: 91 🟩 Step 2: 91 🟨 Overall: 83	58.7, 48.9	373.1	🟨 Step 1: $ReOx·Al_2O_3$ 🟥 Step 2: ZnO	🟥 Step 1: 148 🟩 Step 2: rt	🟨	🟩 Step 1: 2-hexanol, MeOH Step 2: EtOAc, H_2O 🟨 Step 2: AcCl	🟨 Step 1: Batch 🟨 Step 2: Batch	3.2	33.4	80,81
4	 Triacetin	**D**	🟩 95	55.6, 35.0	5.9	🟩 none	🟥 220	🟩	🟩 iPAc, AcOH	🟩 CF	2.4	5.3	This work
5		**E**	🟩 >99	55.6, 10.4	31.1	🟩 none	🟥 300	🟩	🟩 iPAc, 🟨 Diglyme	🟩 CF	9.2	29.5	57
6		**F**	🟥 41	80.2, 5.8	112.1	🟩 Amb-15[e]	🟩 100	🟩	🟩 AcOH, CO_2	🟩 CF	16.1	27.3	36
7	 Solketal acetate	**G**	🟨 83	69.7, 18.5	6.6	🟩 Amb-15	🟩 30	🟩	🟩 iPAc, Ace, AcOH	🟩 CF	4.8	6.0	This work
8		**H**	🟩 91	69.7, 14.8	7.9	🟩 Amb-15	🟩 30	🟩	🟩 iPAc, Ace	🟨 Batch	6.2	7.3	56
9		**I** Two steps	🟥 25	69.1, 10.3	19.5	🟥 *p*-TsOH	🟩 Step 1: 80 🟩 Step 2: 50	🟩	🟩 Ace 🟥 Benzene, Ac_2O	🟨 Step 1: Batch 🟨 Step 2: Batch	10.3	15.0	55

[a] *E*: energy consumption. [b] sEF: simplified *E*-factor. [c] cEF: complete *E*-factor. [d] cEF was not determined because of missing (experimental) data in procedure **B**. [e] Amb-15: Amberlyst 15.

development for commercial applications. All this starts with off-grade glycerol as the feedstock.

CF Synthesis of Acetal Acetates (3/3′). The study continued with the aim of achieving the synthesis of acetal acetates **3**/**3′** (Scheme 3) via a selective tandem acetalization/transesterification process. This sequence was successfully reported by our group under batch conditions[55] in the presence of Amberlyst-15 (Amb-15) and AcOH as the catalyst and the solvent, respectively. To the best of our knowledge, however, no investigations were available in the continuous mode or with CG as the substrate.

An extensive analysis was carried out using 6 different types of off-grade glycerol,[73,74] under a variety of conditions, including batch-flow and CF experiments in the presence of excess AcOH and with and without an acid catalyst (details are reported in the Supporting Information section, Tables S3−S5, and Figure S2). All attempts, however, were unsuccessful. Among the (multiple) reasons responsible for this result, the presence of water and residual salts as impurities in the starting substrate played a role in weakening the acid strength of the catalyst and/or in catalyst poisoning. The study proved that Amberlyst-15 inexorably deactivated with time, and even though tandem acetalization/transesterification reactions were observed, the selectivity toward acetal acetates (**3**/**3′**) was very unsatisfactory, not exceeding 30%.

This conclusion prompted us to study the viability of the CF reaction using pure glycerol. The most representative results were obtained with a homogeneous solution of glycerol, iPAc, acetone, and AcOH in a 1:4:5:3 molar ratio, respectively. This mixture was continuously delivered to a tubular reactor (70 × 5 mm, length × internal diameter) filled in with a catalytic bed of Amberlyst-15 (0.8 g). Experiments were carried out at T = 30 °C and atmospheric pressure by varying the flow rate (F) in the range 0.1−0.6 mL min^{-1}. Results are reported in Table 2. All reactions were run for at least 2 h until the composition of the effluent mixture was steady over time.

The conversion of glycerol was ≥99% in all cases. The use of pure glycerol (ACS grade, >99%) greatly improved the formation of derivatives **3**/**3′**. At the lowest investigated flow rate, F = 0.1 mL min^{-1}, acetal acetates were obtained with a selectivity (62%, entry 1) more than double compared to that achieved with the crude substrate (20−30%; Tables S4 and S5 and Figure S2). Interestingly, the **3**/**3′** selectivity was further enhanced to 81% when F was tripled to 0.3 mL min^{-1} (entry 2). The result was consistent with the reduction of the contact time (τ from 6.2 to 2.1 min) induced by the increase of F, which favored the kinetic products (acetals) with respect to glyceryl esters, in analogy to our previous findings on competitive acetalization/acetylation reactions.[60] This was confirmed when F was set to 0.6 mL min^{-1} (τ = 1 min): the selectivity toward **3**/**3′** increased to 83%, and, at the same time, a small but significant formation of non-esterified acetals (**2**/**2′**: 4%) and glyceryl esters with a lower esterification degree (diacetins **5**/**5′**: 2%) was observed (entry 3). Highly relevant under such conditions was the reaction productivity for derivatives **3**/**3′**, P = 37 mmol·g$_{cat}$$^{-1}$·h^{-1}, which was improved by a factor of 9.3 compared to the best result achieved by us for the same reaction in the batch mode (P = 4 mmol·g$_{cat}$$^{-1}$·h^{-1},[55]). The isomer mixture **3**/**3′** was isolated by fractionated distillation in an 78% yield (10.6 g after 2 h of time-on-stream). This result not only proved that the CF protocol was suited to the tandem reaction, but it demonstrated the potential of the CF technique for process intensification.

The parametric analysis was not further optimized, but an additional experiment was performed to investigate the stability of the catalyst over time under the conditions of entry 3 and prolonged for 12 h showed that the performance of Amb-15 was totally preserved: the mixture sampled at the reactor outlet at intervals of 2 h showed negligible variations of its composition within ±5% between one analysis and the other (Figure S3).

Comparison of the CF Procedures in This Work to Literature Results. A comparative assessment of the CF protocols proposed in this work against other methods available for the synthesis of allyl acetate, TA, and acetal acetates was carried out by selecting papers from the literature that were sufficiently detailed to provide experimental conditions, yields of the products and allowed the calculation of green metrics with the aid of the CHEM21[75] metrics toolkit (CMT) and the *E*-factor (sEF and, when possible, cEF) associated with the described procedures.[76] Only the first two passes (zero and one) of CMT were considered. At the present stage of development of this work, further passes 2 and 3, intended for applications with reactions/pathways at pilot scale and beyond, were not explored. Accordingly, yield, atom economy (AE), and reaction mass efficiency (RME) were included in the zero pass, while process mass intensity (PMI), along with considerations on health and safety hazards of chemicals and solvents, energy demand, and use of endangered elements/metals, were analyzed for the first pass. The conversion was not considered since all the examined procedures were based on quantitative reactions (conversion >99%). The system described by CMT and based on green, amber, or red flags as visual indicators to mark the acceptability of a given variable was used, with green denoting "preferred", amber denoting "acceptable-some issues", and red denoting "undesirable".

Results are reported in Table 3. Further details of the calculations, together with some examples of the CHEM21 toolkit, are reported in the Supporting Information section.

Allyl Acetate. Except for the concatenated (batch + flow) approach of Scheme 2 (entry 1, procedure **A**), no other direct methods were found for the preparation of allyl acetate. Two representative sequences (procedures **B** and **C**) were therefore considered, each obtained by the combination of a reaction reported for the conversion of glycerol to allyl alcohol (step 1),[56,77] with a second process for the acetylation of the alcohol to the corresponding acetate derivative (step 2).[78] For the most difficult reaction, the synthesis of allyl alcohol, two methods were examined that operated under batch or flow conditions (entries 2 and 3; ref 55 was already quoted in a previous section).

The banding established by CMT for yield indicated that only the concatenated protocol (procedure **A**, entry 1, this work) was enabled to the green flag for the Zero Pass, as it showed a 95% yield vs the total values of 88 and 83% in procedures **B** and **C** (both amber flags, entries 2−3), respectively. However, the comparison of AE and RME showed a preference for method **C** (entry 3: 58.7 and 48.9%, respectively) because of a favorable stoichiometry and a lower reactant mass input due to the absence of any deoxydehydration agent. The poorest RME for procedure **A** was determined by the iPAc excess, up to 10 molar equiv (entry 1: 7.7%). The trend of metrics based on mass flow was reversed in the first pass when all mass-based inputs were considered through the calculation of the process mass intensity (PMI total). Indeed, PMI was significantly minimized by procedure **A** to a value of 22.7 g/g, which was 9 and 7 times lower than that of methods **B** and **C**, respectively (206.1 and 373.1). The advantageous PMI of **A** was mostly due to the convenient work-up that did not require additional solvents.

The First Pass of CMT also covered several other aspects that were grouped under the columns "Conditions", "Health and Safety", and "Reaction mode" in Table 3. These included (i) the nature and recyclability of the catalyst (Cat, conditions). In this respect, a green flag was awarded only to method **A** promoted by a recyclable and not endangered catalyst as AcOH, while a combination of green/red or amber/red flags were attributed to methods **B** and **C**, respectively, because of the use of Zn and Re, whose availability/reserve is at risk of depletion within the next 5−50 and 50−100 years; (ii) the energy consumption (*E*, conditions). This showed red flags assigned in all cases because the reaction temperature was above the limit of 140 °C defined as acceptable by CMT, in at least one step of the three examined methods; (iii) the evaluation of common workup techniques (work-up, conditions). The purification of the product carried out by a low-temperature distillation gave a green flag to procedure **A**, which made it preferred over methods **B** and **C**, whose work-up required at least one liquid/liquid extraction with an amber flag; (iv) H-statements as defined by CMT (Reagents and Solvents and Health and Safety). The assessment of H codes for compounds used in procedures **A**−**C** provided combinations of green and amber flags in all cases, thereby not helping in differentiating/selecting a method over the others; (v) the reaction mode (CF/batch). CMT favored continuous vs batch processes for their potential to avoid or minimize solvent use and improve energy management. Procedures **A** and **B** were then preferable over **C**. Moreover, **A** as a concatenated procedure was further advantageous in terms of step economy and process intensification,[78] for it was the only protocol where the intermediate allyl alcohol was not isolated, compared to two-step sequences.

The analysis of the *E*-factor was based on both the simplified and the complete metric, sEF and cEF, respectively. The latter (cEF) was not determined for method **B** due to missing (experimental) data. By definition, sEF did not consider non-hazardous water (if used) and all solvents that could be recovered and recycled.[79] sEF (12.4) was higher for method **A** than for methods **B** (8.9) and **C** (3.2), respectively, thereby indicating that procedure **C** was the most convenient. The recovery of iPAc or AcOEt, both used in up to 30 equiv with respect to glycerol, left room for improvement in the case of procedure **A** (our protocol). If the excess acetylating agent was recycled, the corresponding sEF was reduced to 1.9. However, the intrinsic limit of the sEF metric in the evaluation of the actual amount of waste produced, appeared clear from the calculation of the complete *E*-factor (cEF) for procedures **A** and **C**, which were 21.4 and 33.4, respectively. These values reversed the trend obtained from the sEF comparison.

Overall, the concept was proven: not was only a tandem sequence for the synthesis of allyl acetate from glycerol accomplished, but the analysis of (green) metrics and the application of CMT suggested that the procedure was competitive vs other methods. A further improvement, however, could be considered through an engineering optimization aimed at a more efficient delivery/handling of

Table 4. Effect of Additives on the Characteristics of Soybean Oil-Derived Biodiesel[a]

entry	additive	density (g mL^{-1})	viscosity (cS)	cloud point (°C)	pour point (°C)
1	none	$0.8789 \pm 1 \times 10^{-4}$	3.70 ± 0.03	1.7 ± 0.7	-0.6 ± 0.1
2	**3**/**3′**+ **6** (5 wt %, each)	$0.8871 \pm 1 \times 10^{-4}$	3.59 ± 0.03	0.3 ± 0.2	-1.7 ± 0.6
3	**3**/**3′** (10 wt %)	$0.8849 \pm 1 \times 10^{-4}$	3.48 ± 0.01	-0.4 ± 0.2	-2.3 ± 0.1

[a] **3**/**3′**: mixture of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate (**3**: SA, 97%) and 2,2-dimethyl-1,3-dioxan-5-yl acetate (**3′**); **6**: TA.

viscous solutions through the CF apparatus, able to minimize/avoid the use of solvents and favor the reaction kinetics (at a lower *T* and *p* than in entry 1).

Triacetin. In the Zero Pass, the yield comparison based on CMT awarded a green flag to procedures **D**−**E** (entries 3−4), while method **F** was scored red (yield 41%, entry 6). Other metrics indicated that method **C** displayed a favorable stoichiometry (AE: 80.2%; only water as a co-product), but **D**−**E** were the preferred options from the analysis of RME, particularly **D,** whose RME (35.0%) was 6 and 3.3 higher than that of **F** and **E**, respectively. The result was due to the amount of the acylating reagent, either iPAc or AcOH, which was used in a 5, 20, and 24 molar excess in procedures **D**, **E**, and **F**, respectively. A more efficient design of the reaction mass inputs in procedure **D** was also confirmed by the assessment of the process mass intensity (PMI = 5.9 g/g), which was 19- and 5-fold lower than those of the other two methods. The PMI trend was accounted for by the volumes of the solvents (AcOH and diglyme) and CO_2 that were used as carriers.

The further evaluation of conditions attributed red flags to both procedures **D** and **E** in the energy consumption (*E*) because the reaction temperatures were above 140 °C. CMT, however, did not consider the operating pressure and costs associated with compression and equipment; the integration of this detail indicated that conditions of procedure **D**, particularly *T* and *p* of 220 °C and 10 bar, respectively, were on average more accessible than those of procedures **E** (300 °C, 50 bar) and **F** (100 °C, 200 bar). A green flag was assigned to all the other metrics based on the analysis of conditions, health and safety, and reaction mode of both methods **D** and **F**. Only for procedure **E,** an amber warning occurred due to the use of diglyme as the solvent.

The comparative evaluation of the *E*-factor indicated that procedure **D** (current work) afforded by far the lowest values for both sEF and cEF (2.4 and 5.3, respectively; entry 4) with respect to methods **E** and **F** (entry 5 and 6). cEF was ca 5.5 lower compared to the other two methods, not only for the very modest amount of (recyclable) waste of procedure **D** but also because the non-reacted iPAc and AcOH could be isolated by fractionated distillation and reused.

These considerations, together with the high productivity shown in Table 1 and the valorization of a crude starting material, made the green credentials of method **D** promising. The CMT analysis attributed an alert to the reaction temperature, but the low working pressure was a significant mitigating factor in the energy demand. We believe that for a complete view, upstream and downstream energy requests, including that expended on the work-up, the solvent recovery, the waste treatment, and any other input, need to be examined. To this end, studies aimed at the implementation of the reaction at a pilot scale are under progress in our lab, and a techno-economical assessment based on the second and possibly the third passes of the CHEM21 toolkit will be the object of future investigations.

Acetal Acetates. For simplicity, only SA was considered since it was the almost exclusive component (97%) of the isomer mixture **3**/**3′**. From the analysis of Table 3, considerations similar to those highlighted for TA emerged for SA. A green flag was awarded to all the metrics examined for the procedure **G** proposed in this work, except for the product yield (83%, amber flag; entry 7). The reaction enjoyed the advantages of the CF techniques, specifically: (i) the easier recycling of the non-reacted reagents as acetone and iPAc; and (ii) thanks to the mild conditions (30 °C and ambient pressure), the preservation of the catalyst (Amberlyst-15, Figure S3) that could be used/recycled virtually indefinitely without deactivation and without removal from the reactor. Notably, our previously reported method for the synthesis of SA received the same total score from the CMT analysis, with all green flags on zero and first pass except for an amber warning due to the batch reaction conditions (procedure **H**; entry 8). Procedure **I**, instead, was seriously compromised by three red flags attributed to the very low yield (25%), the use of dangerous/not recyclable catalysts, reagents, and solvents (entry 9).

Finally, metrics based on the mass inputs (RME and PMI) and the *E*-factor, both sEF and cEF, indicated a moderate preference for **G** compared to **H**, while **I** was confirmed as the least convenient method.

The overall scenario led us to conclude that the design/implementation of method **G** were more than encouraging, though a room for improvement persisted in the product yield. Future efforts should therefore be focused in this direction by optimizing the reactant ratio (Glycerol, iPAc, and acetone) and the flow rate before any further consideration through the second and third passes of CMT and any transfer of this knowledge/process to a large scale.

Biofuel Additive Tests. TA and acetal acetates (mainly solketal) are among the most attractive derivatives of glycerol, and one of their most studied applications is as additives for biofuels.[80,81] This prompted us to investigate the performance of products **3**/**3′** and **6** achieved in this work as additives for a commercial soybean oil-derived biodiesel. Compounds **3**/**3′** and **6** were tested as single components (10 wt % in the biodiesel) or as a 1:1 mixture (5 wt % each) to explore their effects on the biofuel density, viscosity, cloud point, and pour point. Experiments were carried out according to standard methodologies reported elsewhere, particularly cloud and pour points, which were measured following the ASTM D97-17b and ASTM D2500-17a standard test methods, respectively.[34] Table 4 summarizes the results. The reported data are the mean value of three repeated measurements, and the error has been calculated as the standard deviation of the obtained values.

Both products, **3**/**3′** and **6**, improved the biofuel characteristics, particularly **3**/**3′** which was mostly comprised of solketal (97%) was more effective at decreasing the viscosity, the pour point, and the cloud point (entry 3). This result was consistent with previously reported studies where the properties of solketal as an additive were explained through increased atomization and a more complete combustion of biodiesel.[82]

EXPERIMENTAL SECTION

General. Reagents and solvents were commercially available and used as received. Glycerol, AcOH, MeOH, acetone, iPAc, Me-THF, and Amberlyst-15 were sourced from Sigma-Aldrich (now Merck). NaCl, TMOF, and TEOF were sourced from Fluka. CG was supplied by Eco Fox s.r.l., and soybean biodiesel was commercially available. GC−MS (EI, 70 eV) analyses were performed on a HP5-MS capillary column (L = 30 m, Ø = 0.32 mm, film = 0.25 mm). GC (flame ionization detector; FID) analyses were performed with an Elite-624 capillary column (L = 30 m, Ø = 0.32 mm, film = 1.8 mm). ^{1}H and ^{13}C NMR spectra were recorded in the Bruker Advance III HD 400 WB equipped with a 4 mm CP/MAS probe at 400 and 101 MHz, respectively. Chemical shifts were reported downfield from tetramethylsilane (TMS), and $CDCl_3$ was used the solvent. All reactions were performed in duplicate to verify reproducibility. All the CF experiments were performed using the apparatus described in Figure 1.

Tandem Synthesis of Allyl Acetate from Glycerol. In a typical procedure, a mixture of glycerol (1 equiv), TEOF (1 equiv), and AcOH (0.5 equiv) (with or w/o Me-THF) was set to react at 50 °C under magnetic stirring for 30 min in order to convert glycerol into glycerol orthoesters (**1a** and **1b**). A desired amount of iPAc or EtOAc was added, and the so-achieved homogeneous solution was continuously delivered at a flow rate of 0.1 mL min^{-1}, to a stainless steel capillary coiled microreactor (L = 5 m and Ø = 0.5 mm) heated at 300 °C. The CF system was pressurized at p in the range of 50−110 bar. Before use, the CF apparatus was conditioned with AcOH (30 mL at 1 mL·min^{-1}). Aliquots (0.3 mL) of the reaction mixture were sampled at the outlet of the reactor every 30 min and analyzed by GC−MS to determine the conversion and the product distribution. The GC−MS analysis of the products was performed by comparison with standard solutions of the product, and the yield of allyl acetate was determined by NMR with mesitylene as an internal standard (more details in Supporting Information Section). Reactions were allowed to proceed, usually for 2 h; though, some prolonged tests were carried out for up to 12 h.

Synthesis of TA from Crude Glycerol. CG [composition: 80% glycerol, 5% ash, >3% MONG (matter organic non-glycerol), 12% water] supplied by the Eco Fox s.r.l. company was used without any purification. In a typical procedure, the CF apparatus was conditioned with AcOH (30 mL at 1 mL·min^{-1}). Thereafter, a homogeneous solution of the reactants (CG, iPAc, and AcOH in the relative molar ratio indicated in Table 1) was continuously delivered to a stainless-steel capillary coiled microreactor (L = 5 m, Ø = 0.5 mm) at a temperature, pressure, and flow rate of 180−240 °C, 10−50 bar, and 0.1−2 mL·min^{-1}, respectively. Aliquots (0.3 mL) of the reaction mixture were sampled at the outlet of the reactor every 30 min and analyzed by GC-FID. The GC-FID analysis of the products was performed by comparison with standard solutions, and the conversion of glycerol and product selectivity were determined upon calibration. Reactions were allowed to proceed, usually for 2 h, though some prolonged tests were carried out for up to 12 h.

Under the conditions of entry 5 in Table 1 [CG/iPAc molar ratio (Q) = 5, AcOH (10 equiv), T = 220 °C, p = 10 bar, F = 0.5 mL·min^{-1}], an experiment was performed for 2 h. The mixture collected at the reactor outlet was subjected to vacuum distillation (p = 10 mbar), and compound **6** (propane-1,2,3-triyl triacetate) was isolated in a 92% yield (10.8 g, 49.5 mmol). The product was characterized by ^{1}H NMR, ^{13}C NMR, and GC−MS analyses (see Supporting Information). The data were in agreement with those reported in the literature.[55]

Synthesis of Acetal Acetates from the Tandem Acetalization/Esterification of Glycerol. In a typical procedure, the CF apparatus of Figure 1 was conditioned with AcOH (30 mL at 1 mL·min^{-1}). The reactor (70 × 5 mm, length x internal diameter) was filled with a catalytic bed comprising Amberlyst-15 (0.8 g) Thereafter, a homogeneous solution of the reactants (glycerol, iPAc, AcOH, and acetone in the relative molar ratio indicated in Table 2) was continuously delivered to the reactor at T, p, and flow rates of 30 °C, 1 bar, and 0.1−0.6 mL·min^{-1}, respectively. Aliquots (0.3 mL) of the reaction mixture were sampled at the outlet of the reactor every 30 min and analyzed by GC-FID. The GC-FID analysis of the products was performed by comparison with standard solutions, and the conversion of glycerol and product selectivity were determined upon calibration. Reactions were allowed to proceed, usually for 2 h though some prolonged tests were carried out for up to 12 h.

Under the conditions of entry 3 in Table 2 (glycerol/iPAc/Ace/AcOH = 1:4:5:3, T = 30 °C, p = 1 bar, F = 0.6 mL·min^{-1}), an experiment was performed for 2 h. The mixture collected at the reactor outlet was subjected to vacuum distillation (p = 10 mbar), and compound **3**/**3′** was isolated in an 83% yield (10.6 g, 60.9 mmol). The isomer mixture **3**/**3′** was characterized by ^{1}H NMR, ^{13}C NMR, and GC−MS analyses (see Supporting Information). The data were in agreement with those reported in the literature.[55]

Cloud and Pour Point Measurements. Cloud point (CP) and pour point (PP) were measured according to ASTM D97-17b and ASTM D2500-17a standard test methods, respectively. The sample was cooled in a glass tube under prescribed conditions and inspected at intervals of 1 °C until a cloud or haze appeared. This temperature was recorded as CP. For the determination of PP, the sample was cooled in a glass tube under prescribed conditions and inspected at intervals of 1 °C until it no longer moved when the surface was held vertical for 65 s; the PP was then taken as 3 °C above the temperature of cessation of flow. The procedure was performed three times for each sample.

CONCLUSIONS

This study reports the design of CF methodologies for converting both pure and off-grade glycerol into valuable products such as allyl acetate, TA, and glycerol acetal acetates. The latter derivatives have been obtained as isomer mixtures mostly comprised of SA (97%). All protocols rely on the unique reactivity of iPAc as the key non-toxic mediator of the transesterification and acetalization reactions of glycerol. Three original sequences have been implemented: (i) a tandem DODH/acetylation procedure by which allyl acetate is synthesized in a 95% yield using TEOF, iPAc, and AcOH as a dehydration agent, an acetylating reagent, and a catalyst, respectively; (ii) a catalyst-free method for the per-acetylation of (crude) glycerol as received from the biodiesel manufacture, which provides TA in a 92% isolated yield and with a productivity improved by more than 60 times with respect to the literature benchmark; (iii) a tandem acetylation/acetalization cascade that, albeit not yet optimized for the product yield not exceeding 83%, paves the way for the preparation of SA through a new catalytic route with improved safety and mild operating conditions.

A comparative analysis carried out with the aid of the CHEM21 toolkit and the evaluation of both simplified and complete E-factors demonstrates that the procedures proposed here are competitive with respect to representative literature works, with emphasis on the synthesis of TA from CG. The latter is likely the most promising method among those explored in this work, and it is currently under investigation for a large (pilot)-scale development.

ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.3c02197.

CF synthesis of allyl alcohol, determination of NMR yield of allyl acetate, tests for the synthesis of acetal acetates (**3**/**3′**) from CG, calculation of the E-factor and the use of the CHEM21 Toolkit, and NMR and MS spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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