

PAPER



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A transesterification–acetalization catalytic tandem process for the functionalization of glycerol: the pivotal role of isopropenyl acetate†

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At 30 °C, in the presence of Amberlyst-15 as a catalyst, a tandem sequence was implemented by which a pool of innocuous reactants (isopropenyl acetate, acetic acid and acetone) allowed upgrading of glycerol through selective acetylation and acetalization processes. The study provided evidence for the occurrence of multiple concomitant reactions. Isopropenyl acetate acted as a transesterification agent to provide glyceryl esters, and it was concurrently subjected to an acidolysis reaction promoted by AcOH. Both these transformations co-generated acetone which converted glycerol into the corresponding acetals, while acidolysis sourced also acetic anhydride that acted as an acetylation reactant. However, tuning of conditions, mostly by changing the reactant molar ratio and optimizing the reaction time, was successful to steer the set of all reactions towards the synthesis of either a 1 : 1 mixture of acetal acetates (97% of which was solketal acetate) and triacetin, or acetal acetates in up to 91% yield, at complete conversion of glycerol. To the best of our knowledge, a one-pot protocol with such a degree of control on the functionalization of glycerol via transesterification and acetalization reactions has not been previously reported. The procedure was also easily reproduced on a gram scale, thereby proving its efficiency for preparative purposes. Finally, the design of experiments with isotopically labelled reagents, particularly d_4 -acetic acid and d_6 -acetone, helped to estimate the contribution of different reaction partners (iPAC/AcOH/acetone) to the formation of final products.

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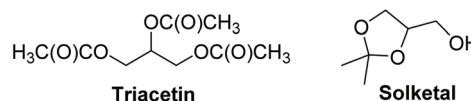
Introduction

Glycerol (Glyc) plays a preeminent role in the family of bio-based platform chemicals.¹ Several reasons concur to its chemical appeal, among which the most relevant are its versatility as a solvent and/or a reagent, the impressive number of applications of its derivatives, and its market availability as a co-product of biodiesel manufacture.^{2,3} These aspects have been highlighted by many recent extensive reviews on its reactivity, *e.g.* on its catalytic oxidation, hydrogenolysis, aqueous phase and steam reforming, dehydration, *O*-alkylation, oligomerization, and transcarbonation^{4–7} and the extension of such protocols to continuous-flow operation.⁸ Of particular significance in this context is also the conversion of glycerol into esters and acetals: both families of products have been and are largely investigated and used as renewable-based solvents, plasticizers, fuel additives, surfactants, flavorings, *etc.*^{9–11} Two

representative cases are triacetin (1,2,3-triacetoxypropane, TA) and solketal (2,2-dimethyl-1,3-dioxolane-4-methanol) derived from the triacetylation of glycerol and its condensation with acetone, respectively (Scheme 1).

With a global demand of 110 000 tonnes per year and an estimated CAGR (Compound Annual Growth Rate) of 4.4% for the next 8 years, TA alone accounts for *ca.* 10% of the worldwide glycerol market, while the current production of solketal amounts to 22 million USD.^{12,13}

Although both the esterification and acetalization of glycerol are apparently simple reactions, the implementation of such processes is not without issues. For example, the acetylation of glycerol with acetic anhydride (Ac_2O) is an excellent low energy-demanding transformation,¹⁴ but the high potential of explosion for acetic anhydride makes its application not



Scheme 1 Most common derivatives of esterification and acetalization of glycerol.

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suitable for large-scale manufacturing (vapour/air mixtures are explosive above 49 °C),⁹ not to mention the corrosivity of Ac₂O and the legislative restrictions to its use in many countries.¹⁵ The same reaction in the presence of acetic acid as an acetylating agent suffers from a poor selectivity since mixtures of mono-, di-, and tri-esters are often obtained, whose isolation and purification are complicated.¹⁶ Acetic acid may also induce undesired etherification and hydrolysis reactions, as observed during the acetylation of some glycerol derivatives.¹⁷ On the other hand, a major difficulty with the acetalization of glycerol is the formation of water as an equilibrium co-product, which not only weakens the acid strength of the catalyst involved in the process, decreasing the reaction conversion, but also entails corrosion and work-up problems.^{18,19}

As a part of our research program aimed at integrating our interest in eco-friendly synthetic protocols with the upgrading of glycerol and its derivatives,^{20,21} we recently discovered that the thermal (catalyst-free) transesterification of glycerol with isopropenyl esters was an effective option to prepare glyceryl esters.²² Isopropenyl acetate (iPac) emerged as a privileged reagent in this context: iPac is a non-toxic, commercially available and cheap compound, and its reaction with glycerol resulted in the rapid irreversible formation of the corresponding methyl esters accompanied by acetone (resulting from tautomerization of 2-propenol). It was demonstrated that when the process was carried out at $T = 180\text{--}300\text{ °C}$ and $p = 8\text{--}50\text{ bar}$, glycerol underwent an exhaustive acetylation producing triacetin (>99%) in the presence of excess iPac (20 molar equiv.; Scheme 2, top), while mixtures of mono-, di-, and triacetins were obtained under stoichiometric conditions (Glyc : iPac = 1 : 1 molar ratio; Scheme 2, bottom: path a). Intriguingly, at 180 °C, the formation of glyceryl mono- and diacetates was accompanied by the formation of non-negligible quantities of the cyclic acetals of glycerol (solketal and solketal acetate) derived from a tandem acetalization process promoted by acetone released during the transesterification step (Scheme 2 bottom: path b).

The tandem sequence provided a new route for the conversion of glycerol into either its acetins or its acetals, however the catalyst-free experiments did not allow the control of the distribution of products: the acetylation was clearly favored

over the acetalization reaction [compare paths (a) and (b) of Scheme 2]. These results prompted us to investigate the design of new conditions whereby the distribution of cascade products could be tuned.

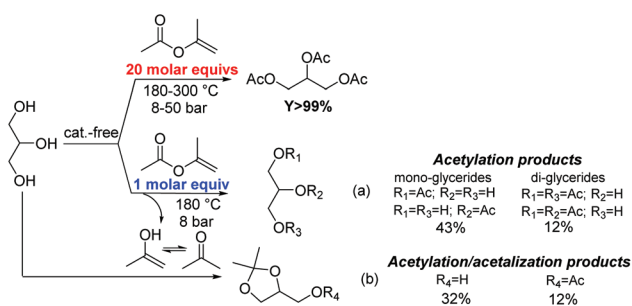
Based on the analysis of the literature and our previous inspection of the reactivity of 1,2-diols with iPac,^{23–25} the use of Amberlyst-15 as a heterogenous acid catalyst in the reaction of Scheme 2, along with acetic acid (AcOH) and acetone (Ace) as co-acetylation and co-acetalization reagents, respectively, was inspected. Albeit less effective than acetic anhydride, the greener features and also the solvency properties of AcOH prompted us to consider its use promising. We here report not only that the reaction of glycerol with iPac/AcOH in the presence of Amberlyst-15 proceeds with quantitative glycerol conversion at 30–70 °C and ambient pressure, but also that its selectivity can be tuned by optimizing T and the Glyc : iPac : AcOH : Ace molar ratio. The overall process can be steered either towards the formation solely of solketal acetate (up to 91%) or to a 1 : 1 mixture of solketal acetate–triacetin. Such a degree of control of the product distribution, triggered by the cooperative effect of the catalyst and the combination of an enol ester, acetic acid and acetone, demonstrates for the first time the potential of the strategy of Scheme 2 for preparative purposes *via* tandem (trans)esterification and acetalization of glycerol. Besides, this exemplifies an archetypal green protocol whereby innocuous reagents and solvents allow the selective upgrading of glycerol under mild catalytic conditions. Experiments with isotopically labelled reagents, specifically CD₃COOD and CD₃C(O)CD₃, have shed light on the mechanism and the role of each reaction partner, confirming the multiple roles of iPac for the success of the protocol. Notably, this analysis has also proved the intermediacy of acetic anhydride in the formation of glyceryl acetates and the unusual reactivity of iPac which assists the acetalization process even in the presence of excess acetone as the reagent.

Results and discussion

The tandem synthesis of solketal acetate and triacetin

The identification of the solvent and the catalyst was the first step in the design of experimental conditions for the reaction of glycerol (1) with isopropenyl acetate (2). Our previous study of such transformation proved that a polar solvent was necessary due to the very poor mutual solubility of the reagents.²² After screening several solvents, including diglyme that worked well in this reaction, we opted instead for acetic acid both for its solvent properties as well as for its non-toxicity and its acetylating reactivity that could be complementary to that of isopropenyl acetate.

A commercial Amberlyst-15 catalyst was selected based on the literature and for its comparatively better performance in terms of activity and stability for both acetylation and acetalization of glycerol compared to other heterogenous acids such as K-10, montmorillonite, niobic acid, and zeolites (H-beta, HZSM-5 and HUSY).^{9,11,23}



Scheme 2 The reaction of glycerol promoted by isopropenylacetate (iPac).

Effect of temperature, time and reactant molar ratio

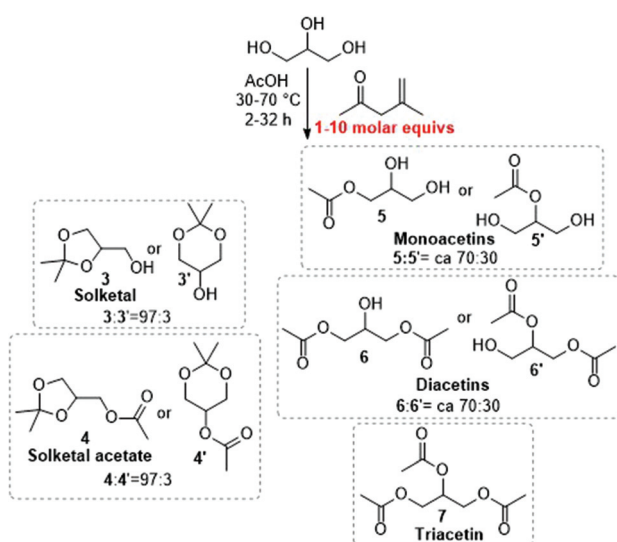
Reactions were carried out using a solution of glycerol (1; 1 mmol) in acetic acid (10 mL; 0.1 M), a variable amount of isopropenyl acetate (2; the molar ratio (Q) 2:1 = 1–10), and Amberlyst-15 (Amb15: 15 mg; 15 wt%) as the catalyst. Control experiments were performed over a range of temperatures 30–70 °C, and times varying between 4–24 h. In all cases, the observed products were: (i) solketal (3) and solketal acetate (4), along with trace amounts of the corresponding 6-membered ring isomers (3': 2,2-dimethyl-dioxane-5-ol, and 4': 2,2-dimethyl-1,3-dioxan-5-yl acetate); (ii) two regio-isomers of both glycerol monoacetate (monoacetins: 5/5') and glycerol diacetate (diacetins, 6/6'); and (iii) glycerol triacetate (triacetin, 7) (Scheme 3; compare also Scheme 2). The structures of derivatives 3–7 were assigned by GC/MS and NMR analyses and by comparison, when possible, with authentic commercial samples.

Under the above described conditions, blank tests were also carried out either without a catalyst or without iPAC.

The results of this screening are summarized in Table 1. The conversion of glycerol and the product distribution, both measured by calibration with standard solutions (details are in the Experimental section) are shown for the most representative experiments performed at 30, 50 and 70 °C for 4 h and at 30 °C for 24 h, respectively. In this work, given the interest in the tandem sequence, the selectivity (product distribution) for each of the binary mixtures 3 + 3', 4 + 4', 5 + 5', and 6 + 6' and compound 7 was defined according to the following expression:

$$S_i = [\text{mol } i / \text{conv. glyc.}] \times 100$$

where S_i is the selectivity (%) for compound i ($i = 3 + 3'$, $4 + 4'$, $5 + 5'$, $6 + 6'$ and 7), mol i stands for the total moles of com-



Scheme 3 Products of the reaction between glycerol and iPAC. The relative ratio 3 : 3', 4 : 4', 5 : 5', and 6 : 6' was determined by GC analyses and was constant regardless of reaction conditions.

pound i (by GC calibration) and conv. glyc. is the total conversion of glycerol for the combined transesterification and acetalization processes.

The reaction of an equimolar mixture of glycerol (1) and isopropenyl acetate (2) ($Q = 1$) showed that a quantitative conversion could be reached after 4 h even at the lowest investigated temperature (30 °C, entry 1). The increase of the temperature modified the product distribution. (i) At 30 °C the total of glyceryl acetals (3 + 4) was 71% compared to glyceryl esters (28%) that were mainly constituted by mono-acetins (5 + 5' = 25%) (entry 1). (ii) At 50 and 70 °C, the amounts of glyceryl acetals decreased in favor of glyceryl esters: mono-acetins became the major products (5 + 5' = 41–56%) along with diacetins (6 + 6' = 7–8%) and triacetin (7: 6–13%) (entries 2 and 3). The results were consistent with our previous studies on the competitive reactions of 1,2-diols with iPAC and acetone that had demonstrated that acetalization was faster than acetylation, though the latter became predominant by increasing the temperature.²⁵ The tandem acetylation–acetalization selectivity could however not be controlled, as confirmed by prolonging the reaction for 24 h at 30 °C: under such conditions, both the transesterification and acetalization reached equilibrium with an amount of glyceryl esters (6/6' + 7: 80%) significantly exceeding that of acetal products (3/3' + 4/4': 20%) (entry 4). The product distribution was not altered by doubling the reaction time to 48 h.

Blank experiments carried out in the absence of iPAC (entries 5 and 6) proved that AcOH acted not only as a solvent but also contributed to the formation of glyceryl esters. However, notwithstanding the large (175) molar excess of AcOH with respect to glycerol, only mixtures of mono- and diacetins were obtained with moderate conversions of 31% and 71% at 30 °C and 50 °C, respectively (cfr entries 1 and 5, and 2 and 6). Longer 24 h tests at 30–70 °C further proved that the reaction of glycerol with AcOH was in no way a selective process. Moreover, acetic acid was a far less active acetylating agent than iPAC (for details, see Fig. S1 in the ESI† section). This behaviour matched the results previously reported by Mota and coworkers for the same process run under similar conditions.¹⁶

The blank experiment in the absence of Amberlyst-15 demonstrated the need for an acidic catalyst since negligible conversion (1%) was observed after 24 h at 30 °C (entry 7).

Significantly better selectivity of the tandem sequence was finally achieved at 30 °C, by simultaneously increasing both the iPAC:glycerol molar ratio (Q) from 3 to 5 to 10, and the reaction time from 4 to 24 h. Indeed, this increase brought about a progressive and concurrent increase of acetal acetates (4/4') from 28 to 41% and triacetin (7) from 5 to 44%, at the expense of diacetins (6/6') whose amount dropped from 60 to 11% (entries 8–10). Thereafter, at $Q = 10$, a further control test prolonged for 32 h showed that compounds 4/4' and 7 could be obtained as sole products with a comparable selectivity of 51 and 49% *i.e.* in a 1 : 1 ratio (entry 11).

These results proved our concept demonstrating for the first time that through a cooperative effect between the electro-

Table 1 The reaction of glycerol (1) and isopropenyl acetate (2) catalyzed by Amberlyst-15 in the presence of AcOH as a solvent

Entry	iPac : Glycerol, Q (mol : mol)	Cat.	T/t (°C, h)	Conv. ^a (%)	Product distribution ^b (%)				
					Acetals		Esters		
					3 + 3' ^c	4 + 4' ^c	5 + 5' ^c	6 + 6' ^c	7
1	1	Amb 15	30, 4	≥99	20	51	25	1	3
2			50, 4	≥99	12	35	41	7	6
3			70, 4	≥99	2	21	56	8	13
4			30, 24	≥99	6	14		77	3
5	0 (iPac absent)	Amb 15	30, 4	31			81	19	
6			50, 4	71			68	30	2
7	1	None	30, 24	1	99				
8	3	Amb 15	30, 24	≥99	7	28		60	5
9	5		30, 24	>99	9	31		42	18
10	10		30, 24	>99	4	41		11	44
11	10		30, 32	>99		51			49

All reactions were carried out using a solution of glycerol (1: 1 mmol) in AcOH (10 mL; 0.1 M) in the presence of Amberlyst-15 (Amb15: 15 mg; 15 wt%) as the catalyst, except for entry 6 where the catalyst was absent. Entries 1–3: an equimolar mixture of glycerol and isopropenyl acetate was used (Q = 1). Entries 5 and 6: isopropenyl acetate was absent. Entries 7–11: an increasing amount of isopropenyl acetate (2) was used with 2:1 (Q) molar ratio in the range of 1–10. ^a Conversion of glycerol. ^b Selectivity towards products 3/3', 4/4', 5/5', 6/6' and 7. ^c Total amount of isomers.

philic reactivity of isopropenyl acetate, the solvent/acetylating properties of AcOH, and the use of an acid catalyst, conditions could be tuned to control the product distribution of the tandem sequence: glycerol was successfully upgraded into two derivatives by transesterification and acetalization reactions. An additional optimization study proved that the same (1:1) selectivity profile for compounds 4/4' and 7 was obtained at 30 °C by reducing the iPac excess from 10 to 7.5 equivalents with respect to glycerol, and the AcOH volume of up to 20 times, from 10 to 0.5 mL. The latter was the minimum volume to obtain a homogenous solution of reactants 1 and 2. This process intensification was not only beneficial to improve the carbon footprint and the safety of the procedure, but also to increase its overall efficiency since the higher reactant concentrations enhanced the rates of all the involved reactions. To gain a detailed insight into this aspect, the reaction mixture was monitored at intervals and the conversion of glycerol and the corresponding product distribution were measured against time for 24 h. Fig. 1 summarizes the results.

With respect to Table 1, the reduction of the reaction volume highly impacted the kinetics. The conversion of glycerol was quantitative within the first 30 minutes and in the same time interval, the multiple transesterification of glycerol favored the formation of triacetin (7: 28%; green profile). Almost simultaneously, the onset of the acetalization reaction gave rise to a steep increase of acetals (3/3': black profile), mostly solketal that reached a maximum (45%) after 25 min and then dropped with the parallel increase of acetal acetates (4/4') up to ca. 30% (red curve). These derivatives (4/4') were plausibly obtained by the direct esterification of acetals (3/3') and the acetalization of monoacetins (5/5'), thereby explaining the decline of the blue profile from 62% to zero in less than 20 min. Indeed, once formed, monoacetins (5/5') were consumed to feed both the transesterification process and the par-

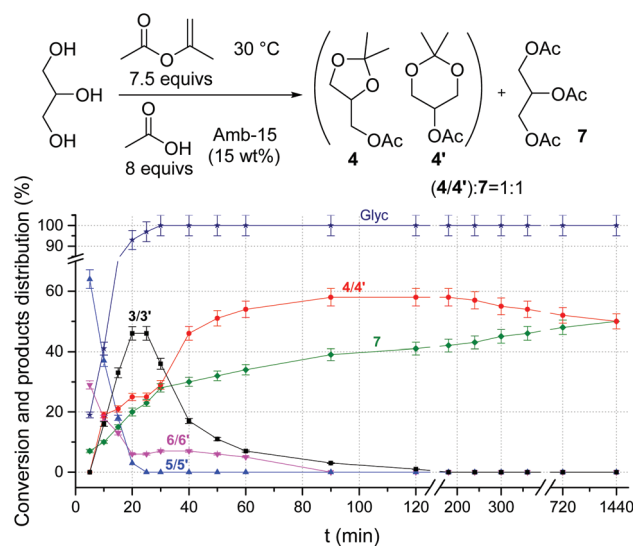


Fig. 1 The product distribution of the reaction of a mixture of glycerol (1.1 mmol), iPac (7.52 mmol) acetic acid (0.5 mL; 8.75 mmol), and Amberlyst-15 (15.0 mg; 15 wt%), $T = 30$ °C. (–★–) Glycerol (1) conversion; (–■–) solketal (3/3') selectivity; (–●–) solketal acetate (4/4') selectivity; (–▲–) monoacetin (5/5') selectivity; (–▼–) diacetin (6/6') selectivity; (–◆–) triacetin (7) selectivity.

allel acetalization reaction. In the next 90 min, competitive reactions proceeded with the gradual decrease of acetals (3/3') and diacetins (6/6', magenta curve) until their disappearance in favor of the acetal acetates (4/4') and triacetin that increased to 58 and 41%, respectively (after 120 min from the start). The final part of the sequence was a slow interconversion of (4/4') into triacetin (7) until the mixture reached the thermodynamic equilibrium distribution after 24 h with the final products

present in equal quantities. From that moment on, the relative proportions of (4/4') and (7) did not change anymore.

Further results on the effect of the catalyst amount are given in the ESI section (Table S1†). Under the conditions of Fig. 1, changing the glycerol : catalyst weight ratio altered the kinetics of the different reactions, without however affecting the selectivity of the formation of acetal acetates and triacetin.

The overall picture was consistent with the reactions in Scheme 4.

The transesterification pathways (blue) mediated by iPac/AcOH release acetone which is consumed in the acetalization pathways (red). Both processes form water as a co-product. Glycerol yields first mono-acetins (5/5') and as soon as acetone is made available, acetals (3/3'). Mono-acetins (5/5') undergo either transesterification to di-acetins (6/6') or acetalization to acetal acetates (4/4'). Di-acetins (6/6') react further to form triacetin (7). In the last part of the sequence, acetal acetates (4/4') undergo slow hydrolysis to mono-acetins (5/5') and slowly equilibrate to a 1 : 1 thermodynamic mixture of (4/4') and (7).

The reaction of Fig. 1 involved a simple and safe experimental setup as well as an equally convenient procedure for the work-up and purification of the products. Once the reaction was complete (24 h), the catalyst was filtered off and the mixture of 4/4' and 7 could be isolated by vacuum distillation (5 mBar, 50–80 °C) of the oily residue in nearly quantitative yields of 47% and 48%, respectively (based on glycerol as the limiting reagent). Moreover, the procedure could be scaled up by a factor of 10 without any appreciable variation in terms of product distribution, yields, and time.

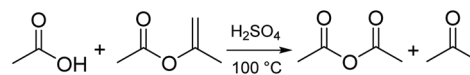
The role of iPac and acetic anhydride

Curiously, from Fig. 1, although the acetylating mixture of iPac/AcOH was in a very large excess compared to acetone, the amount of acetal acetates was higher than that of triacetin in the initial stages of the reaction (red and green profiles). Since the direct acetalization of glycerol by iPac was not plausible, the results led us to hypothesize that (excess) iPac acted not only as a transesterification agent, but also as a source of acetone for acetalization through some kind of parallel reaction. The inspection of the literature indicated that at 100 °C,

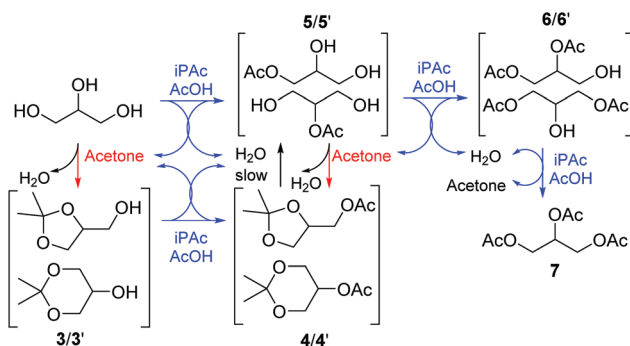
in the presence of H₂SO₄ as a catalyst, an equimolar mixture of AcOH and iPac underwent an acyl nucleophilic substitution (acidolysis of iPac) to provide acetone and acetic anhydride in almost quantitative yields (Scheme 5).²⁶

Presuming that the same reaction took place under the conditions of Table 1 and Fig. 1, the desired tandem sequence could be assisted by both acetone and acetic anhydride (Ac₂O) for the acetalization and acetylation reactions, respectively. Additional experiments were therefore carried out aiming at investigating the acidolysis of iPac at 30 °C with Amberlyst 15 as a catalyst. The first test was performed by replicating the conditions of Fig. 1. The complexity of the product mixture did not allow satisfactory GC/MS or NMR analyses to resolve signals of acetone and iPac, but the presence of acetic anhydride was nonetheless verified and quantified. Since Ac₂O was obtained from iPac as an excess reactant, the anhydride amount was conveniently calculated as a percentage with respect to the total number of products obtained from glycerol (3/3', 4/4', 5/5', 6/6' and 7; Fig. 2).

The gradual increase of Ac₂O throughout the process offered convincing, albeit indirect, proof for the corresponding formation of an increasing amount of acetone which could in turn feed the acetalization of glycerol and monoacetins (Scheme 5). Additional evidence for this mechanism of acetone formation was then gathered by the reaction of an equimolar mixture of isopropenyl acetate (5.00 mmol) and acetic acid in the presence of Amb-15 as a catalyst (14.8 mg; 15 wt%). At 30 °C, after 24 h, acetic anhydride was observed in 80% yield (by GC). It was excluded that Ac₂O was obtained from the catalytic dehydration of AcOH since this reaction was reported only at temperatures above 500 °C.²⁷ The process also allowed to identify minor amounts of by-products (≤10% with respect to Ac₂O), the mass spectra of which was consistent with the formation of acetylacetone plausibly derived from an acid-promoted rearrangement of iPac,²⁸ and the aldol conden-



Scheme 5 The reaction of acetic acid with iPac.



Scheme 4 Reactions involved in the selective formation of (4/4') and (7).

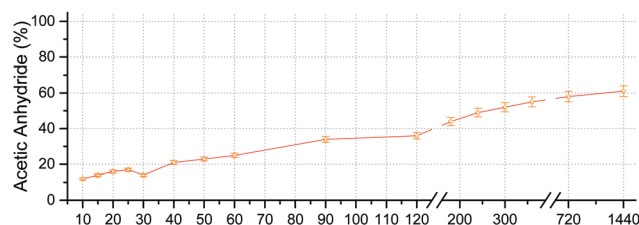


Fig. 2 The formation of Ac₂O during the reaction of a mixture of glycerol (1.1 mmol), iPac (7.52 mmol), acetic acid (0.5 mL; 8.75 mmol), and Amberlyst-15 (15.0 mg; 15 wt%), at = 30 °C. (-☆-) Amount calculated as the % of acetic anhydride with respect to other products (3/3', 4/4', 5/5', 6/6' and 7) observed during the reaction.

sation of acetone (see Fig. S2† for details). A not optimal resolution of acetone and iPac prevented their quantification also in this case.

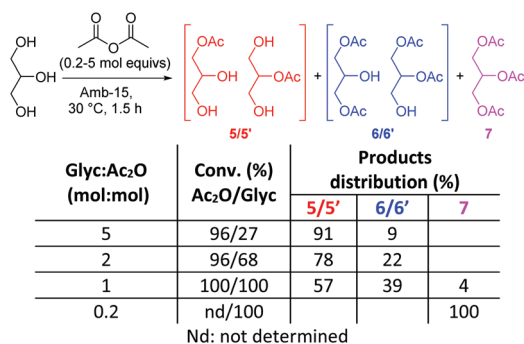
The *in situ* formation of Ac₂O during the reactions of both Table 1 and Fig. 1 allowed us also to envisage another consequence: the involvement of the anhydride as an acetylating reagent in parallel with iPac and AcOH. In this respect, a detailed study was carried out on the acetylation of glycerol with acetic anhydride under conditions as close as possible to those of Table 1, in which iPac was replaced by Ac₂O. Experiments were performed at 30 °C, using a solution of glycerol (1 mmol) in acetic acid (0.1 M, 10 mL: conditions of Table 1) and a glycerol : Ac₂O molar ratio variable in the range from 5 to 0.2. Amberlyst-15 (15 mg, 15 wt% with respect to glycerol) was the catalyst. The most representative results, reported in the ESI section (Fig. S3†) and briefly summarized in Scheme 6 suggested that the esterification of glycerol occurred much faster with Ac₂O than with AcOH alone, and the higher the anhydride amount, the higher the formation of products of multiple (double and triple) acetylation. The reaction, however, was effective even with sub-stoichiometric Ac₂O.

The emerging picture confirmed the multiple roles of iPac and indicated that the investigated sequence was even more complicated than that shown in Scheme 4. In addition to the competitive (parallel or consecutive) processes there described, the occurrence of the acidolysis of iPac provided an extra supply of acetone and acetic anhydride, the latter serving as a co-acetylating agent. A limited hydrolysis of iPac and glyceryl esters could also not be ruled out.^{17,29}

Nonetheless, the combined relative kinetics and equilibria of such a network of transformations led towards the selective formation of a 1 : 1 mixture of 4/4' and 7. It should be noted that our attempts to achieve the same result by replacing iPac with a mixture of Ac₂O and acetone (in variable proportions) were unsuccessful. Not to mention dangers and possible regulatory constraints associated with the direct use of Ac₂O.

Insights into the tandem mechanism

The complexity of a system in which different components (the enol ester, the acid and the anhydride) could simultaneously



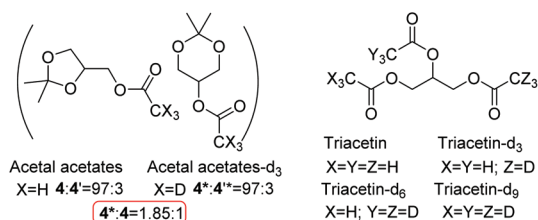
Scheme 6 The acetylation of glycerol with acetic anhydride at 30 °C, over Amberlyst-15.

express the same reactivity as acetylating agents made it rather challenging to discriminate the contribution of each single partner. To shed light on this aspect, additional experiments were devised using D-isotope labelled acetic acid.

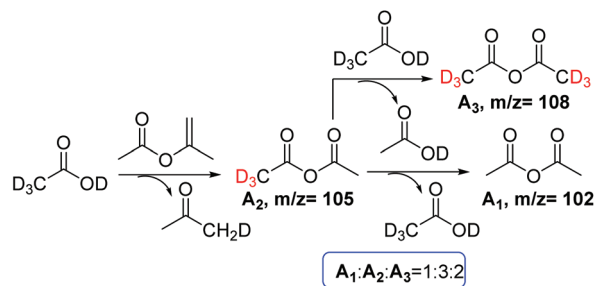
A control experiment was carried out under the conditions of Fig. 1 by replacing AcOH with its perdeuterated analogue, CD₃COOD (glycerol: 1 mmol, iPac: 7.5 mmol; CD₃COOD: 0.5 mL, 8.75 mmol); Amberlyst-15: 15 mg, 15 wt%; 30 °C; 24 (h). The GC/MS analysis of the reaction mixture allowed the identification of the expected products. Acetal acetates were detected as two species per isomer: the non- and the tri-deuterated compounds, 4/4' and 4*/4*' respectively. Triacetin was detected in the form of four species, the non-, the tri-, the hexa-, and the nona-deuterated products, respectively (Scheme 7).

A satisfactory GC resolution was achieved only for the acetal acetates, particularly solketal acetate (4 and 4*), while signals of the different triacetins were substantially superimposed (further details in the ESI section, Fig. S4–S7†). Comparison of the analytical data recorded in the full scan (TIC) and the SIM mode (set at the most abundant fragment ions, *m/z* = 159 and 162 for 4 and 4*, respectively) indicated that the relative amounts of 4* and 4 were 65% and 35%, meaning that the quantity of the tri-deuterated product was approximately twice that of the non-deuterated derivative (Fig. S5 and S6†).

Relevant to this study was also the evidence of the formation of three differently deuterated acetic anhydrides, *i.e.* the non-, the tri-, and hexa-deuterated products which were present in a 1 : 3 : 2 ratio (by GC/MS) in the reaction mixture. These results were consistent with Scheme 8 in which



Scheme 7 D-Isotope labelled products observed in the reaction of glycerol with iPac/CD₃COOD.



Scheme 8 Plausible pathways for the formation of the three observed species of acetic anhydride.

CD_3COOD mediated the acidolysis not only of iPac, but also of the produced (deuterated) anhydride.³⁰

As a first approximation, excluding kinetic and equilibrium isotope effects,³¹ the relative contributions of CD_3COOD and iPac as acetylating agents could be inferred from the observed 2 : 1 ratio for products **4*** and **4**, respectively (Scheme 7). The deuterated acid acted directly or indirectly (*via* the formation of **A₂** and **A₃**) to produce twice the amount of **4*** with respect to **4**. The latter instead was obtained from iPac as such or its derivative **A₁**. From the stoichiometry of acidolysis and the 1 : 3 : 2 ratio of **A₁** : **A₂** : **A₃** in Scheme 8, one could also estimate that about 54% of the total mixture of anhydrides was sourced from the deuterated acid.

An additional experiment was then carried out by doubling the amount of CD_3COOD , keeping all the other conditions unaltered (glycerol: 1 mmol, iPac: 7.5 mmol; CD_3COOD : 1 mL, 17.5 mmol); Amberlyst-15: 15 mg, 15 wt%, 30 °C, 24 (h). GC/MS analyses carried out using the above-described procedure in full scan and sim mode indicated that the relative quantities of products **4*** and **4** were 73 and 27%, respectively. Albeit with a modest increase, the higher the amount of CD_3COOD , the higher the formation of the labelled acetal ester with respect to the corresponding non-labelled derivative.

The tandem synthesis of acetal acetates

The reaction of glycerol with the mixture iPac/AcOH was further investigated with the aim to steer the overall process towards the selective formation of the products deriving from a single acetylation and acetalization step, *i.e.* the solketal acetate (**4**) and its 6-membered ring isomer (**4'**) couple. To this end, several new experiments were carried out by modifying the conditions of Fig. 1, particularly by changing the reactant molar ratio and by adding a large excess of acetone (20 molar equiv. with respect to glycerol) as a co-acetalizing agent. Although acetone (alike iPac) was scantily soluble with glycerol,³² in the presence of AcOH a homogeneous solution of reactants was achieved. The salient aspects of this study are summarized in Fig. 3, which shows the product distribution obtained during the reaction of a mixture of glycerol (1.0 mmol), acetic acid (0.5 mL, 8.75 mmol), and acetone (0.9 mL, 20.0 mmol), in the presence of Amberlyst-15 (15.0 mg; 15 wt% with respect to glycerol) as a catalyst and variable amounts of isopropenyl acetate (1–4 mmol), at 30 °C, after 24 h. Conversion of glycerol is not reported since it was quantitative in all tests.

The product distribution mirrored the intrinsic reactivity of acetone and iPac. In the presence of equimolar amounts of glycerol and iPac ($Q = 1$, left), acetals (**3/3'**) were the predominant products (60%, black profile) followed by acetal acetates (**4/4'**: 37%, red profile) and traces of glyceryl esters implying that excess acetone favored acetalization *versus* acetylation. The result was comparable when the amount of IPA was doubled ($Q = 2$). Instead, for $Q = 3$ the formation of acetals dropped strikingly from 60% to 6% and the acetal acetates **4/4'** increased from 37% to 88%. The greater availability of iPac and acetic anhydride (from the acidolysis of the enol ester)

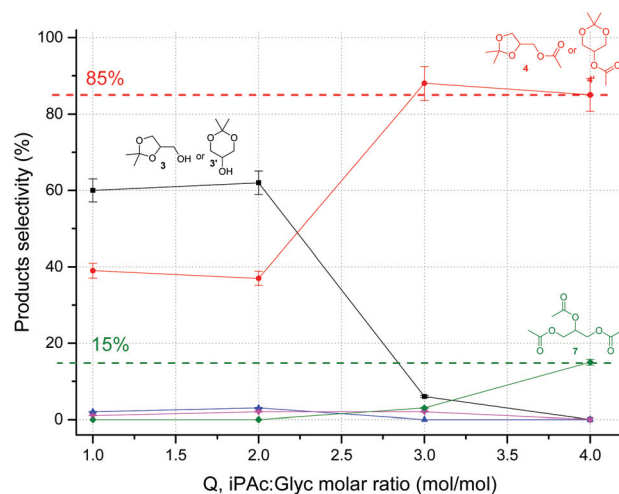


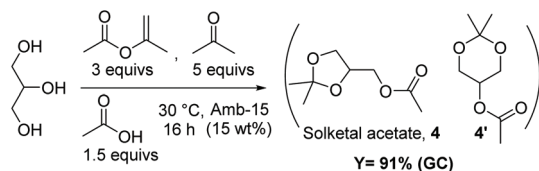
Fig. 3 The reaction of glycerol with a mixture of iPac/AcOH and acetone: the effect of increasing amounts of iPac. Conditions: glycerol (1.0 mmol), isopropenyl acetate (1.0–4.0 mmol), acetic acid (8.75 mmol), acetone (20.0 mmol), Amberlyst-15 (15.0 mg; 15 wt%), 30 °C, 24 h. Selectivity towards: (—■—) acetals (**3/3'**); (—●—) acetal acetates (**4/4'**); (—▲—) mono-acetins (**5/5'**); (—▼—) di-acetins (**6/6'**); (—◆—) triacetin (**7**). Glycerol conversion was $\geq 99\%$ in each test.

brought about a significant improvement of the transesterification reaction which, however, involved mainly the OH function of the acetals and not of glycerol. Indeed, the total amount of glyceryl esters remained low at *ca.* 6%. The results were consistent with the higher electrophilicity of acetone compared to esters and anhydrides that favored acetalization of glycerol to yield acetals (**3/3'**), which in turn underwent transesterification with iPac/ Ac_2O to the corresponding acetal acetates (**4/4'**). A further increase of the iPac : glycerol molar ratio ($Q = 4$) caused complete disappearance of the acetals (**3/3'**), albeit with slightly lower selectivity towards acetal acetates (**4/4'**: 85%) due to the formation of triacetin (15%) by exhaustive acetylation of glycerol.

In all cases the binary mixtures of compounds **3/3'** and **4/4'** maintained a 97 : 3 ratio between 5- and 6-membered ring products.

Additional tests demonstrated that the selectivity of the tandem sequence towards **4/4'** could be further optimized by reducing the quantities of acetone and AcOH to 5 and 1.5 equivalents with respect to glycerol, respectively. After 16 h under these conditions the acetal acetates (**4/4'**) were obtained in up to 91% yield (Scheme 9). Co-products were acetals (**3/3'**: 3%) and di- and triacetins (**5/5'**: 2% and **7**: 4%).

With respect to Fig. 2, decreasing the reaction volume allowed to reduce the reaction time to 16 hours and at the same time, to slightly increase the yield of (**4/4'**). Under such conditions, the reaction was scaled up by a factor of 10. Once the experiment was complete (16 h), the catalyst was filtered and vacuum distillation (5 mBar, 50–80 °C) of the oily residue allowed us to isolate **4/4'** in an 87% yield (1.51 g, 8.7 mmol; based on glycerol as the limiting reagent), thereby further vali-



Scheme 9 The tandem synthesis of acetal acetates. The amounts of iPAC, AcOH, and Ace and the catalysts are referred to glycerol. Other conditions were those of Fig. 3 (glycerol: 1.00 mmol, iPAC: 3.00 mmol, Amberlyst-15: 15.0 mg).

dating the mass balance and the synthetic efficiency of the process.

The results of Fig. 2 and Scheme 9 proved the second major novelty of this paper and the originality of the approach used. The strategy based on the cooperative reactivity of multiple compounds, pivoted on isopropenyl acetate, could be fine-tuned to yield a one-pot tandem acetalization and acetylation sequence of glycerol that produced the binary mixture of isomers 4/4' with high selectivity.

To the best of our knowledge, the direct synthesis of acetal acetates 4/4' from glycerol has no precedent in the literature. Although in the presence of Amberlyst-15 the acetylation of solketal with acetic anhydride was reported with >90% conversion and >80% selectivity towards solketal acetate,¹⁷ earlier studies on the reaction of glycerol with mixtures of acetone and Ac₂O under reflux conditions yielded at best solketal (3) and its acylated derivative (4) in a 9 : 1 ratio (with no mention of isomers 3' and 4').³³ This reaction system was further examined by us under the conditions of Fig. 3. Experiments showed that reactants (glycerol, Ac₂O and acetone) were not mutually miscible. AcOH was used as a solvent. At complete conversion, acetal acetates (4/4') were obtained in a maximum 82% selectivity along with triacetin (18%). Compared to iPAC, not only the selectivity was lower, but acetone and Ac₂O had to be used in a significantly large excess of 20 and 5 equiv., respectively, with respect to glycerol (details are shown in Table S2†).

Additional experiments to confirm the role of iPAC further demonstrated that the tandem selectivity was elusive also by reacting glycerol with different mixtures of AcOH and acetone, in the presence of Amberlyst 15 as a catalyst: the amount of 4/4' did not exceed 32% (further details are shown in Table S3†). In no way could the use of iPAC be replaced.

Acetal acetates with d₆-acetone

With the aim to investigate the relative role of iPAC and acetone as acetalization agents, the tandem formation of acetal acetates (4/4') was explored by replacing acetone with its d₆-isotope labelled analogue, CD₃COCD₃. An experiment was carried out under the same conditions of Scheme 9 (glycerol: 1 mmol; isopropenyl acetate: 3 mmol; acetic acid: 1.5 mmol; Amberlyst-15: 15 mg; *t* = 16 h; d₆-acetone: 5 mmol). The GC/MS analysis of the reaction mixture allowed us to identify the expected acetal acetates as two species (per isomer), the non-

and the hexa-deuterated compounds, respectively (4/4' and 4_{d6}/4'_{d6}).

Data analysis was focused on the most abundant isomer solketal acetate (4) and its d₆-labelled derivative (4_{d6}). The comparison of the analytical data recorded in the full scan (TIC) and the SIM mode (set at the most abundant fragment ions, *m/z* = 159 and 162 for 4 and 4_{d6}, respectively) indicated that their relative amounts were 35% and 65%, *i.e.* the hexa-deuterated species was approximately twice as much the non-deuterated one (further details in the ESI section, Scheme S1 and Fig. S8†).

Noteworthy is the correspondence between the ions analyzed in SIM mode both for the tests with labelled acetic acid and acetone. Although ions with *m/z* = 159 and 162 were selected for both the investigations, the comparison of mass spectra proved that different fragmentation pathways occurred: (i) using d₄-acetic acid the isotopic marking of the considered ion regarded the acetyl group; (ii) when d₆-acetone was used, the marking was set on the acetalized portion of acetal acetates.

Although the apparent contribution of CD₃COCD₃ to the acetalization reaction was almost double that of acetone released by iPAC, the acetalizing capability of the enol ester was still remarkable considering the excess d₆-acetone used. Even more so considering the inverse secondary deuterium isotope effect described for the formation of ketals from the reaction of methanol and acetone/d₆-acetone, the measured *K_H/K_D* (equilibrium constants for non-deuterated and deuterated ketals) ratio was ~0.7.³⁴

Experimental

General

Reagents and solvents were commercially available compounds and were used as received unless otherwise stated. Glycerol, acetic acid, acetic anhydride, acetone, isopropenyl acetate, Amberlyst-15, d₄-acetic acid, and d₆-acetone, were sourced from Sigma Aldrich (now Merck).

GC/MS (EI, 70 eV) analyses were performed on a HP5-MS capillary column (*L* = 30 m, \varnothing = 0.32 mm, film = 0.25 mm), and GC analyses (CG/FID) were performed on an Elite-624 capillary column (*L* = 30 m, \varnothing = 0.32 mm, film = 1.8 mm). ¹H and ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts were reported downfield from tetramethylsilane (TMS), and CDCl₃ was used as the solvent.

General procedure for the tandem synthesis of solketal acetate and triacetin

Experiments were carried out under different conditions (Table 1 and Fig. 1) which can be summarized as follows: in a 25- or 50-mL round-bottomed flask equipped with a condenser and a magnetic stir bar, a mixture of glycerol (1 mmol), isopropenyl acetate (1–10 mmol), acetic acid (0.5–10 mL) and Amberlyst-15 (5–15 mg) as a catalyst (5–15 wt%) was set to react at the temperature of choice (30–70 °C) and atmospheric pressure, for 24–32 h. Conversion of glycerol and product

selectivity were determined by GC/FID analysis upon calibration.

Compounds **4/4'** ((2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate and 2,2-dimethyl-1,3-dioxan-5-yl acetate, respectively) and **7** (propane-1,2,3-triyl triacetate) were isolated from a reaction scaled up by a factor of 10, using 10 mmol of glycerol (other conditions: $T = 30\text{ }^{\circ}\text{C}$; $p = 1\text{ atm}$; molar ratio Glyc : iPac : AcOH = 1 : 7.5 : 8.75; Amberlyst 15 = 15 wt%; $t = 24\text{ h}$). Once the experiment was complete, the solid catalyst was filtered off, and the liquid solution was distilled under vacuum (5 mBar, 50–80 °C). Isolated yields were 47% and 48% for **4/4'** and **7**, respectively. Products were characterized by both ^1H and ^{13}C NMR and GC/MS analyses. Data were in agreement with those reported in the literature.^{22,35}

General procedure for the selective tandem synthesis of acetal acetates

Experiments were carried out under different conditions (Fig. 3 and Scheme 9) which can be summarized as follows: in a 25- or 50-mL round-bottomed flask equipped with a condenser and a magnetic stir bar, a mixture of glycerol (1 mmol), isopropenyl acetate (1–4 mmol), acetic acid (0.5 mL), acetone (1–20 mmol) and Amberlyst-15 as a catalyst (15 wt%) was set to react at the temperature of choice (30–70 °C) and atmospheric pressure, for 16–24 h. Conversion of glycerol and product selectivity were determined by GC/FID analysis, upon calibration.

Acetal acetates **4/4'** ((2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate and 2,2-dimethyl-1,3-dioxan-5-yl acetate, respectively) were isolated from a reaction scaled up by a factor of 10, using 10 mmol of glycerol (other conditions: $T = 30\text{ }^{\circ}\text{C}$; $p = 1\text{ atm}$; molar ratio Glyc : iPac : AcOH : Ace = 1 : 3 : 1.5 : 5; Amberlyst 15 = 15 wt%; $t = 16\text{ h}$). Once the experiment was complete, the solid catalyst was filtered off, and the liquid solution was distilled under vacuum (5 mBar, 50–80 °C). The isolated yield of **4/4'** was 87%. Products were characterized by both ^1H and ^{13}C NMR and GC/MS analyses; data were in agreement with those reported in the literature.^{22,35}

The reactions with D-labelled compounds

Experiments with labelled reagents were carried out by replacing AcOH or acetone with the same quantity of the perdeuterated analogues, CD_3COOD or CD_3COCD_3 . In the case of d_4 -acetic acid, a mixture of glycerol (1 mmol), iPac (7.5 mmol), CD_3COOD (0.5 mL, 8.75 mmol), and Amberlyst-15 (15 mg, 15 wt%) was set to react in a 25 mL round-bottomed flask at $T = 30\text{ }^{\circ}\text{C}$ and atmospheric pressure, under stirring for 24 h. In the case of d_6 -acetone, a mixture of glycerol (1 mmol), isopropenyl acetate (4 mmol), d_6 -acetone (5 mmol), acetic acid (1.5 mmol), and Amberlyst-15 (15 mg; 15 wt%) was set to react in a 25 mL round bottomed flask, at $T = 30\text{ }^{\circ}\text{C}$ and atmospheric pressure, under stirring for 16 h.

The mixtures of labelled products were analyzed by GC/MS both in the full scan mode (TIC, 70 eV) and in the SIM mode on the characteristic fragment ions $m/z = 159$ and 162 (other details are in the ESI† section).

Conclusions

This study reports for the first time a one-pot tandem catalytic acetalization–acetylation sequence of glycerol where the presence of multiple reagents allows one to control the product distribution. Crucial to this result is the cooperative reactivity of isopropenyl acetate, acetic acid and acetone in the presence of Amberlyst-15. The major role is played by the enol ester that acts as the acetylating agent of glycerol and at the same time, it undergoes acidolysis with AcOH. Both these processes release acetone which in turn triggers the acetalization of glycerol. Moreover, acetic anhydride co-generated during the acidolysis of iPac further contributes to the acetylation of glycerol. Notwithstanding the complex network of reactions, this investigation demonstrates that the experimental conditions can be tuned to obtain the selective conversion of glycerol to either a 1 : 1 mixture of acetal acetates (**4/4'**: 97% of which is solketal acetate) and triacetin, or solely acetal acetates **4/4'** in up to 91% yield. The latter result is achieved simply by supplying extra acetone to the iPac/AcOH mixture. Experiments using d_4 -acetic acid and d_6 -acetone suggest that acetic acid, mostly through the formation of acetic anhydride, is the major contributor (for about 65%) to the final products, while curiously acetone released by iPac provides *ca.* 35% of acetal acetates (**4/4'**) even when excess acetone is sourced externally. Acetic acid, along with acidolysis, also serves as a solvent to overcome the issue of poor mutual solubility of iPac and acetone with glycerol.

The approach used is original and genuinely green. The synthetic potential of the tandem sequence for the upgrading of glycerol takes advantage from the use of a pool of innocuous reactants (glycerol, iPac, acetic acid and acetone) and mild/simple reaction conditions (30 °C and atmospheric pressure) which make the scale-up of the protocol safe and easy. This study has also proved that intensification of the process can be achieved by controlling (reducing) the reactant molar ratio. In this respect, studies are currently in progress to transfer the procedure from batch to continuous flow to further enhance its productivity.

Conflicts of interest

There are no conflicts to declare.

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