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Continuous-flow preparation of γ-butyrolactone scaffolds from renewable fumaric and itaconic acids under photosensitized conditions

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KEYWORDS

Platform molecules, Photochemistry, Continuous-flow chemistry, Metal-free generation of radicals, Paraconic acids, In-line NMR monitoring

ABSTRACT

The method and results described herein concern the photosensitized addition of various alcohols to renewable platform fumaric and itaconic acids under scalable continuous-flow conditions in glass micro- and mesofluidic reactors. Alcohols were used both as reagents and as solvents, thus contributing to a reduced environmental footprint. Process parameters such as the temperature, light intensity, as well as the nature and amount of the photosensitizer were assessed under microfluidic conditions, and next transposed to a lab-scale mesofluidic reactor connected with an in-line NMR spectrometer for real-time reaction monitoring. Substituted γ -butyrolactones, including spiro derivatives with unique structural features, were obtained with quantitative conversion of the starting materials and in 47-76% isolated yields. The model photoaddition of isopropanol to fumaric acid was next successfully transposed in a pilot-scale continuous-flow photoreactor to further demonstrate scalability.

INTRODUCTION

Carboxylic acids are abundant in Nature, and have been widely utilized as renewable and sustainable building blocks.¹⁻⁴ Among them, fumaric (1) and itaconic (2) acids are listed in the top 12 value-added chemicals from biomass by the U.S. Department of Energy.⁵ Although 1 is still manufactured from fossil resources, fumaric acid can also be synthesized by fungi through fermentation of sugars.⁶ By contrast, 2 is already produced on the industrial scale using a mature biotechnology based on fungi to transform carbohydrates.⁶ Fumaric and itaconic acids have thus a bright forecast as sustainable chemical building blocks.⁵ The presence of an alkene moiety in 1,2 is an asset for designing sequences of reactions towards more complex molecular architectures, such as reactions with carbon radicals.

Photochemistry can be advantageously exploited for metal-free radical generation.⁷ For instance, terebic acid (**3a**) was synthesized by Schenck and colleagues using a photochemical addition of isopropanol-derived radicals to maleic or fumaric acid, followed by *in situ* lactonization in a conventional macroscopic batch reactor. In the report, irradiation of the medium over 18 h was necessary to obtain 4.56 g of **3a**, and benzophenone was utilized as a photosensitizer (PS).⁸ The scope of the methodology was later broadened to other alcohols, and the corresponding radicals were generated by thermal or photolytic treatment of peroxides, giving various γ -butyrolactone scaffolds, *i.e.* paraconic acids **3a-c** or the corresponding esters (Scheme 1).⁹⁻¹¹ Phenylglyoxylic acid was also recently reported as an effective PS for the preparation of **3a-c** benzyl esters in batch.¹² Paraconic acids are synthetic or naturally occurring, and many of them are endowed with promising biological activities.¹³⁻¹⁴ Compounds **3a-c** are nowadays commercially available, and are reported as building blocks for the preparation of biologically relevant molecules.¹⁵⁻¹⁶



 $R=-CH_3(a), -(CH_2)_5-(b), -H(c)$

Scheme 1. Addition of alcohol radicals to maleic or fumaric acid.

Most batch photochemical processes are limited to small scale as a consequence of superficial light penetration. Long irradiation times are often required, hence triggering side-reactions due to overexposure. The combination of photochemistry and continuous-flow micro-and mesofluidic reactors is a blooming research area since it enables efficient and scalable photochemical processes.¹⁷⁻¹⁸ The acetone-photosensitized addition of isopropanol (*i*PrOH) to maleic acid was reported in continuous microfluidic setups, as well as in a batch reactor, but only the influence of the residence time was studied, and the scalability was not addressed.¹⁹ The most performant microflow reactor (800 μ m internal diameter) sustained a low productivity for **3a** (1.5 g d⁻¹), but emphasized the superiority of continuous-flow reactors for such photochemical processes.¹⁹ The scope was later extended to the photoaddition of *i*PrOH to furanones.²⁰⁻²³

We report herein on the development of a scalable continuous-flow photosensitized addition of alcohols to renewable platform molecules such as fumaric and itaconic acids. Substituted γ butyrolactones, including paraconic acids with unique structural features, were prepared accordingly in commercial glass micro- and mesofluidic reactors. Fast optimization of the process parameters was ensured by in-line NMR spectroscopy. Screening of the reaction parameters revealed a positive impact of an increase in temperature, as well as a moderate effect of light intensity. Under optimized conditions, γ -butyrolactones were prepared on an unprecedented scale (up to ~12 g day⁻¹) with short residence time (10 min) and moderate to high isolated yields (47-76%) in a lab-scale mesofluidic reactor. The model photoaddition of *i*PrOH onto fumaric acid (1) was eventually translated in a pilot-scale glass mesofluidic reactor, which sustained a productivity of 83 g day⁻¹. This work is part of our ongoing research program dedicated to the continuous-flow upgrading of biomass-derived platform molecules²⁴ and to the preparation of valuable scaffolds under photosensitized continuous-flow conditions.²⁵

RESULTS AND DISCUSSION

 Assessing feasibility. This investigation started with a preliminary study using a commercial glass microfluidic photoreactor (FutureChemistry[®] FlowStart EvoTM, 92 μ L internal volume) equipped with a photochemical module comprising 2 LEDs (365 nm) mounted on a thermoregulated support (Supporting Information). The photoaddition of *i*PrOH onto fumaric acid (1) under irradiation at 365 nm was selected as a model reaction, and process parameters including the residence (irradiation) time, the concentration in 1 ([1]) and in PS as well as the temperature (Supporting Information for details) were assessed. Promising results were collected, and the process was translated to a commercial glass mesofluidic photoreactor (Corning[®] Advanced-Flow Lab Photo ReactorTM, Figure 1).



Figure 1. a. Photograph of a lab-scale Corning[®] Advanced-Flow Lab Photo ReactorTM. **b.** Details of the hub hosting the compact glass mesofluidic module integrated with a high capacity

heat-exchanger and the thermoregulated LED panels (2 x 20×365 nm LEDs). **c**. Side view of the glass module upon irradiation at 365 nm. Corning proprietary.

The increase in scale facilitated the integration of in-line NMR spectroscopy, which in turn drastically accelerated the optimization of the photoaddition under continuous-flow conditions. A thorough screening of process parameters such as the temperature, residence (irradiation) time, light intensity, as well as the nature of the PS and the substrate/PS ratio was performed, and dozens of experimental data points were generated within one day. The reactor configuration included a thermoregulated glass fluidic module (2.6 mL internal volume) sandwiched between two 365 nm LED panels (Figure 2, see also Experimental Section and Supporting Information). A dome-type back-pressure regulator (Zaiput Flow Technologies[®]) was inserted after the reactor (pressure set at 2 bar), and the reactor effluent was redirected towards a bench-top in-line NMR spectrometer (43 MHz SpinsolveTM Carbon NMR spectrometer from Magritek[®]).



Figure 2. Simplified flow chart for the continuous-flow preparation of γ -butyrolactones 3,4a-c through a photosensitized addition of alcohols to renewable platform fumaric (1) and itaconic acids (2). PS stands for photosensitizer (R = H, benzophenone; R = OMe, 4,4'-

dimethoxybenzophenone). Compounds 3(4)a, 3(4)b and 3(4)c were obtained in *i*PrOH, CyOH/MeOH (9:1) and MeOH, respectively, from 1(2). Heat exchangers are omitted for clarity.

A solution containing both 1 and the PS in *i*PrOH was subjected to irradiation at 365 nm in the continuous-flow setup. Various residence (irradiation) times ranging from 1 to 20 min were screened using 0.2 equiv. of either dimethoxybenzophenone (DMBP) or benzophenone (BP) as PS (Figure 3). The residence time was adjusted by changing the set point of the HPLC pump. Faster reactions and higher conversions were observed for the photoaddition of *i*PrOH on 1 (0.05 M) with DMBP as PS than with BP, in agreement with previous literature reports.²³ Despite these promising results, the lower solubility of DMBP affected negatively the productivity of the continuous-flow process since it imposed low concentrations of 1. The higher solubility of BP in *i*PrOH (up to 0.04 M) enabled more concentrated feed solutions (up to 0.2 M for 1). With a low concentration feed solution (0.05 M in 1) and with 0.2 equiv. in BP, the photoaddition of *i*PrOH on 1 plateaued at 67% for the longest residence time (20 min). Upon increasing the concentration in 1 to the limit of solubility in *i*PrOH (0.2 M) and keeping the BP/1 ratio at 0.2, the conversion increased with the residence time, and reached 88% after 20 min irradiation. BP can undergo photoreduction and photopinacolization in the presence of a hydrogen donor such as *i*PrOH, leading to its deactivation.²⁶ It was suggested that in the case of diluted solutions, the larger amount of *i*PrOH induced PS deactivation to a greater extent. A 0.2 M solution of **1** in *i*PrOH containing benzophenone as a photosensitizer was thus selected for further optimization.

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Figure 3. Conversion of **1** as a function of the residence time (lab-scale experiments performed in a Corning[®] Advanced-Flow Lab Photo ReactorTM). Conditions: fumaric acid (**1**) + 0.2 equiv. of PS in *i*PrOH, temperature = 25 °C, LED power (365 nm) = 100%. BP = benzophenone, DMBP = dimethoxybenzophenone.

The influence of the temperature, light intensity and substrate/PS ratio were studied at a residence time of 10 min (Table 1). The conversion was improved from 35% at 25 °C to 69% at 55 °C, and plateaued at 68% at higher temperature (entries 1-4). A similar positive impact of temperature for a photosensitized electron-transfer deoxygenation reaction²⁷ and for an analog photosensitized addition of *i*PrOH to furanones were previously noticed.²⁸ As the latter did not involve a lactonization step, the radical addition is most likely the rate limiting step. Temperature-dependent rates were also reported for the addition of carbon radicals to alkenes and alkynes.²⁹⁻³⁰ Decreasing the LED intensity to 60% had a minimal impact on the conversion, but it dropped from 35% to 22% conversion when the intensity was further diminished to 40% (entries 1, 5-7). The BP/1 ratio had a dramatic impact on the conversion: it increased from 12% with a BP/1 ratio of 0.05 to 78% with a BP/1 ratio of 0.4 (entries 1, 8-11).

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Table 1. Conversion of 1 as function of the temperature, LED power and PS amount (lab-scaleexperiments performed in a Corning[®] Advanced-Flow Lab Photo ReactorTM).

Entry	Temperature	LED	Benzophenone	Conv.
	(°C)	Power (%)	(equiv.)	(%)
1	25	100	0.2	35
2	40	100	0.2	54
3	55	100	0.2	69
4	70	100	0.2	68
5	25	80	0.2	36
6	25	60	0.2	35
7	25	40	0.2	22
8	25	100	0.05	12
9	25	100	0.1	18
10	25	100	0.3	49
11	25	100	0.4	78

Conditions: 0.2 M fumaric acid + BP in *i*PrOH, res. time = 10 min.

Substrate scope. This set of results clearly emphasized the positive impact of increasing both the temperature and the BP/1 ratio. The scope of this continuous-flow procedure was next broadened to the addition of *i*PrOH, cyclohexanol (CyOH) and methanol (MeOH) to fumaric (1) and itaconic (2) acids (Figure 2). To keep the process as efficient as possible, the conditions were further optimized to reach maximal conversion while balancing temperature and reaction time. Actually, the BP/1 ratio appeared as a powerful leverage to reach quantitative conversion under mild process conditions (T = 40 °C, res. time = 10 min). The most representative results are summarized in Table 2 (Supporting Information for full details of the optimization).

The addition of *i*PrOH and CyOH to **1** required 0.4 equivalent of BP to reach quantitative conversion. To avoid crystallization of CyOH and to improve the solubility of the substrate, a 9:1 v/v mixture of CyOH/MeOH was utilized as solvent in the CyOH feed. Terebic acid (**3a**) and its spiro derivative **3b** were obtained in 76% and 75% isolated yields, respectively (entries 1-2). The addition of MeOH was more challenging:^{11,12} a larger excess of BP (3 equiv.) gave only 64% conversion. At higher temperature (55 °C) and longer irradiation time (20 min), quantitative reaction of **1** with MeOH was observed, and the simplest paraconic acid **3c** was isolated in 47% yield (entry 4). Alternatively, some of these compounds could be purified by recrystallization. Quantitative conversion of compounds **1** and **2** was obtained for the photoaddition of MeOH, *i*PrOH and CyOH (entries 1,2,4,6, and 10, Table 1), in which case only the desired γ -butyrolactones were formed. Material loss occurred upon chromatography on silica gel.

Table 2. Optimization of isopropanol, cyclohexanol and methanol photoaddition to fumaric and itaconic acids (lab-scale experiments performed in a Corning[®] Advanced-Flow Lab Photo ReactorTM).

Entry	Substrate	Solvent	Benzophenone	Product	Conv. ^a	Yield ^b	Productivity
			(equiv.)		(%)	(%)	$(g day^{-1})$
1	1	iPrOH	0.4	3 a	>99	76	9.7
2^{c}	1	СуОН	0.4	3b	>99	75	11.6
3	1	MeOH	3	3c	64	-	-
4 ^d	1	MeOH	3	3c	>99	47	2.6
5	2	<i>i</i> PrOH	0.4	4 a	64	-	-
6	2	<i>i</i> PrOH	0.7	4 a	>99	52	7.2
$7^{\rm c}$	2	СуОН	0.4	4b	85	-	-
8 ^c	2	СуОН	0.5	4b	95	72	11.5



Conditions: 0.2 M substrate + BP in alcohol, res. time = 10 min, T = 40 °C, LED power = 100%. ^a Off-line ¹H NMR. ^b Isolated yield after purification by column chromatography. ^c The solvent was a 9:1 v/v mix of CyOH/MeOH. ^d Res. time = 20 min, T = 55 °C. ^e 0.1 M substrate. ^f Traces of compound **4c** in the crude, no purification attempted.



Scheme 2. Photosensitized addition of alcohols to itaconic acid.

The unprecedented radical addition of alcohols to **2** potentially leads to two plausible products, after either 5-*exo-trig* or 6-*exo-trig* lactonization (Scheme 2). Under these conditions, only γ -butyrolactones **4a-b** were detected in the crude NMR spectra, in accordance with Brown's postulate.³¹ Previous literature ¹H NMR data for **4a** did not match those reported in the present study.³² The structural features of compounds **4a-b** were unambiguously confirmed by 2D NMR experiments, and by X-ray diffraction on a single crystal (Figure 4 and Supporting Information). The photoaddition of alcohols to **2** required an increased amount of BP, as expected from its lower electrophilicity.⁹ With a BP/**2** ratio of 0.4 to mediate the photoaddition of *i*PrOH, only 64% conversion was reached (entry 5). With a BP/**2** ratio of 0.7, quantitative conversion was observed, and the corresponding product **4a** was isolated in 52% yield (entry 6). Similarly, the

photoaddition of CyOH onto **2** required a BP/**2** ratio of 0.5 to proceed with near quantitative conversion, and the desired compound **4b** was isolated in 72% yield (entries 7-8). CyOH appeared thus slightly more reactive than *i*PrOH for the photoaddition onto **2**. The addition of MeOH was attempted with the same conditions as used in entry 4. However, clogging occurred downstream the reactor (entry 9). The concentration of substrate **2** was reduced to 0.1 M, and quantitative conversion was reached at larger BP/**2** ratio of 3.5. However, a complex mixture was obtained and only traces of compound **4c** were observed in the crude. No further purification was attempted (entry 10). Experiments were also conducted using cinnamic acid as substrate in an *i*PrOH feedstock, but low conversion (<5%) was obtained in each cases, emphasizing its poor electrophilicity as substrate.



Figure 4. Single crystal X-Ray diffraction structure of 4a.

Scaling-out. Finally, the model photoaddition of iPrOH onto **1** was implemented in a pilot-scale mesofluidic photoreactor (41 mL internal volume, Corning[®] Advanced-Flow G1 Photo ReactorTM, see Figure 5) (Supporting Information). The reactor configuration included 5 thermoregulated glass fluidic modules (8.2 mL internal volume) fluidically connected in series. The G1 photo reactor used for assessing the scalability was not fully optimized, and the LED

density was decreased by 53% compared to the Lab Photo Reactor utilized in the preliminary lab-scale trials. Each fluidic module was irradiated on both sides by a thermoregulated LED panel (365 nm, 30 LEDs per panel, 300 LEDs in total). With such design, the conditions are comparable in terms of light intensity to an experiment run in an Advanced-Flow Lab Photo ReactorTM (see lab-scale experiments above) at 47% of LED power.



Figure 5. a. Pilot-scale Corning[®] Advanced-Flow G1 Photo ReactorTM composed of 5 thermoregulated glass fluidic modules connected in series. **b.** Details of the glass fluidic modules (left) (8.2 mL internal volume) that are surrounded by 2 thermoregulated LED panels (30 LEDs@365 nm per panel, right). Corning proprietary.

Similar processing conditions were used as for the optimized reaction in the 2.6 mL mesofluidic reactor (Table 2), and **3a** was obtained accordingly with a daily productivity of 83 g (60% conversion, 10 min residence time), demonstrating the scalability of the photosensitized addition of alcohols to fumaric and itaconic acids. Based on the findings at lab and pilot level, an optimized production scale photo reactor (Advanced-flow G3 Photo ReactorTM) would have an expected daily productivity of 547 g.

CONCLUSION

This work reports an efficient photosensitized addition of isopropanol, cyclohexanol and methanol to renewable fumaric and itaconic acids under scalable continuous-flow conditions. The implementation of in-line NMR spectroscopy enabled fast optimization of the reaction parameters. The positive impact of both the temperature and the substrate/photosensitizer ratio was demonstrated on the model photoaddition of isopropanol to fumaric acid. Upon optimization, various γ -butyrolactones, including novel spiro derivatives, were prepared within short residence times and in 47-76% isolated yields. This continuous-flow procedure is amenable to the preparation of libraries of structurally unique building blocks, including spiro derivatives and, most importantly, the method is scalable.

EXPERIMENTAL SECTION

Continuous-flow setup.

The feed solution was conveyed to the photoreactor with a FLOM HPLC pump (0.01 – 100 mL min⁻¹; wetted-parts: PTFE, PCTFE, FFKM and ruby) through a section of 1/8" PFA tubing (Swagelok[®]). The feed solution was installed on a precision scale for accurate flow rate monitoring. The reactions were conducted in a commercial continuous-flow reactor (Corning[®] Advanced-FlowTM Lab Photo Reactor). The photoreactor included a compact glass mesofluidic module (0.4 mm channel height, 2.6 mL internal volume) sandwiched in a high capacity heat-exchanger (2 layers, 22 mL, 1 W mL⁻¹ K⁻¹). LED panels were mounted on both sides of the fluidic module (40 mm from the center of the reactive layer), and each LED panel was equipped with 20 × 365 nm LEDs and a heat exchanger (T = 10 °C). The thermoregulation of both the glass fluidic module and the LED panels was carried out with LAUDA[®] Proline RP 845 thermostats. The reactor effluents were conveyed through PFA capillaries (1/8" O.D.) towards an

inline 43 MHz Spinsolve[™] Carbon NMR spectrometer from Magritek[®] equipped with the flowthrough module, and collected. A Zaiput Flow Technologies[®] dome-type back-pressure regulator (BPR) was inserted between the photoreactor and the in-line NMR spectrometer and connected to a cylinder of compressed argon (set point: 2 bar).

Typical experimental procedure (lab mesoscale). A solution of the substrate (1 or 2, 0.2 M) and the appropriate amount of benzophenone in 250 mL of an alcohol (*i*PrOH, CyOH or MeOH) was prepared under sonication, and degassed with argon for 15 min. For the cyclohexanol solution, a 9:1 v/v mixture of CyOH/MeOH was used as solvent. The feed solution was loaded in a brown glass feed tank and kept under an argon atmosphere. The solution was delivered to the glass mesofluidic reactor under irradiation at 365 nm through a HPLC pump set at the appropriate flow rate, and the reaction was monitored by in-line NMR spectroscopy (Supporting Information). After equilibration and collection, the solvent was removed under reduced pressure and the sample was analyzed by off-line high field NMR. Analytical samples were obtained after column chromatography on silica gel (ethyl acetate/petroleum spirit 40-60/acetic acid 10:10:1).

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge. Details of the equipment, microfluidic and mesofluidic (pilot scale) procedures, additional experimental data, structural assignments (NMR and X-ray diffraction) and characterization of compounds **3a-c** and **4a,b**. (PDF).

Accession Codes

CCDC 1554500 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge

 Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk). AUTHOR INFORMATION Corresponding Author * jc.monbaliu@ulg.ac.be (Jean-Christophe M. Monbaliu)

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

NMR, nuclear magnetic resonance; PS, photosensitizer; BP, benzophenone; DMBP, dimethoxybenzophenone; LED, light emitting diode; CyOH, cyclohexanol; MeOH, methanol; *i*PrOH, isopropanol; BPR, back pressure regulator

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