ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Article
Cite This: Org. Process Res. Dev. 2018, 22, 147−155
pubs.acs.org/OPRD

Microflow High-p,T Intensification of Vitamin D_3 Synthesis Using an Ultraviolet Lamp

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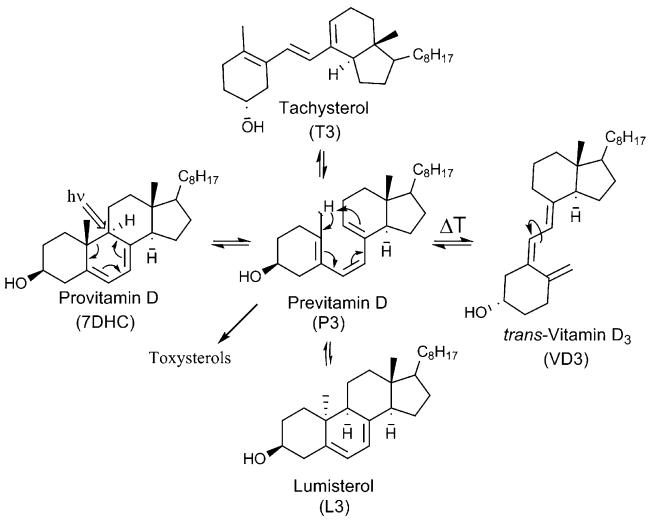
ABSTRACT: Herewith a new process concept for synthesis is presented which combines both UV-photoirradiation and high-p,T intensification (photo-high-p,T) in continuous flow. The application of this procedure to Vitamin D_3 synthesis promotes thermal shifting of the equilibrium from the reaction intermediate to the product. This is enabled by microreactors which allow operation under harsh conditions such as the high temperature used here. This provides, to our best knowledge, a new kind of process combination (novel process window). As a result, in less than 1 min, 42% conversion of 7-dehydrocholesterol can be achieved giving a 17% yield and 40% selectivity of Vitamin D_3. This approach enhances productivity by up to 2 orders of magnitude compared with the current capillary based vitamin D_3 synthesis, because, under the microflow conditions, photochemistry can be performed at fairly high concentration and up to 20 times faster.

1. INTRODUCTION

Recently, the FDA[1] as a regulatory authority pushed the manufacturers of the pharmaceutical and food industry (e.g., Novartis-MIT[2]) to promote use of continuous end-to-end processing. In a research environment, the use of microreactors and flow chemistry is an essential part of this goal, since they have proved the possibility to combine high pressure (p) and high temperatures (T) in a high-p,T fashion. This tandem gives the chance to achieve process intensification which derives in shorter reaction times.[3] Such chemical intensification is part of novel process windows (NPW).[4,5]

Following NPW, in this paper a fully continuous process intensification for the synthesis of Vitamin D_3 (VD3) is proposed. Therefore, the coupling of NPW with photochemistry gives the concept of photo-high-p,T intensification. The complex chemical synthesis of VD3 starts with 7-dehydrocholesterol (7DHC), commonly known as provitamin D, industrially produced from cholesterol obtained from the skin of animals. The irradiation of 7DHC with UV-B light most efficiently in the range 275−300 nm[6] (Scheme 1) gives a bond rearrangement resulting in an electrocyclic ring opening (Previtamin D), followed by an antarafacial [1,7] sigmatropic hydrogen rearrangement.[7] Dauben et al.[8] suggested that the VD3 productivity actually does not depend on the 7DHC excitation wavelength, but on P3's. Yet, in the first step, the reversible ring closure can also give the 7DHC isomer Lumisterol (L3),[9] but with low provability with high photon energy.[8] In the second, the rearrangement of previtamin D (P3) can give VD3 as a result in an equilibrium shifted thermally.[7] Unfortunately, the process must be stopped after short irradiations because of the synthesis of tachysterol (T3),[10] which has a more favorable quantum yield in this stage.[6] In addition, the conformation of P3 can also influence the equilibrium toward T3.[9] Besides T3, long irradiations can also give toxisterols.[9,11] Therefore, transferring the process into continuous flow means a short irradiation and high pressure in a temperature-dependent matter.

Scheme 1. Chemical Synthesis and Most Accepted Mechanistic Pathway for Vitamin D_3



In the current production of VD3, a solution of 7DHC in diethyl ether is shortly photoactivated up to 10% conversion using a high-pressure or medium-pressure mercury lamp in a quartz-made recirculation reactor,[12,13] where the upper temperature limit is strictly limited for photoreactions. Thompson[14] stated that the use of higher temperatures (than ambient, >20 °C) shifts the equilibrium toward higher amounts of P3, i.e. higher 7DHC conversion. From an initial solution at room temperature of 93:7 P3:VD3, after an equilibrium of just 30 min at 100 °C, the P3:VD3 isomeric proportion became 72:28. *Vice versa*, processing at temperatures below 20 °C can lead to the formation of side products (L3 and T3), and the portion of the latter increases with prolonged light exposure so that the

Received: October 8, 2017
Published: December 20, 2017

DOI: 10.1021/acs.oprd.7b00318
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net result is low reaction selectivity as well. From an industrial point of view, severe safety constraints are given due to the high photoenergy introduced and the highly reactive intermediates generated. The synthesis using the photoactivation of 7DHC is thus kept separate from the following isomerization to VD3 at medium temperature. Accordingly, the combined use of high light energy, pressure, and temperatures (photo-high-p,T) is not established and probably would be prohibited when using conventional equipment. This new kind of NPW is, however, made possible using photomicroreactors, and a major key is the much higher light penetration[15,16] due to the miniature characteristic dimension.[17] Microreactors are known to allow safe operation under classical harmful process conditions[18,19] and to achieve with all their process benefits a good sustainability profile.[20,21]

In this scenario, VD3 could be an ideal candidate, since it is known to be one of the most thermally stable vitamins.[22,23] In addition, operating under pressure has been demonstrated to be an efficient way to increase the VD3 productivity at room temperature.[24] Therefore, the combination of irradiation, pressure, and temperature in one photoreactor is a new approach to achieve control over the side product formation, while boosting conversion. The latter is also promoted by the high light penetration, common in microflow reactors, which allows operation at high concentrations close to solubility limits. Thus, finally the approach presented might be a new means to increase the productivity of vitamin D_3. Moreover, the advantageous surface-to-volume ratio of microflow reactors together with using modern lamps[25] allow both the photon transmission and energy efficiency to increase.

To date, very few continuous flow studies related to the synthesis of VD3 have been reported and none applying photo-high-p,T and NPW principles.[26,27] Fuse et al.[28,29] described a continuous process for the production of 1α,25-$(OH)_2$-vitamin D_3 operating in two steps. A first irradiation of a mixture of 7DHC analogues at 313−578 nm (high-pressure mercury lamp) achieved a mixture of VD3 analogues, which was irradiated again in a second step with 360 nm light at 100 °C. The flow rate was 0.3−0.6 mL·h^{-1} for a solution of a 0.03 M 7DHC analogue mixture at atmospheric pressure. The process gave a 28% yield of 1,25-$(OH)_2$-VD3 with a productivity of 1.9 mg/h and a residence time of 15 min. Other studies in UV-microflow[30,31] chemistry have been described successfully related to UV-photo Claisen rearrangement,[32] or for isomerization of cyclooctene derivatives,[33] using also inline packed bed reactors and operating at atmospheric pressure. Continuous-flow photochemistry with microreactors has been used in organic synthesis, material science, and water treatment.[34] Nevertheless, the need for UV-light for VD3 synthesis makes the use of quartz essential.

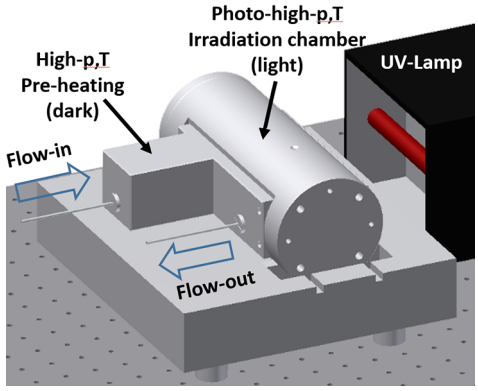
Inspired by these examples, a photo-high-p,T setup was developed with the capability of operating together, but during short times as demanded by VD3 chemistry, with high pressure, temperature, and irradiation conditions in a safe mode in one step, i.e. using the advantages common to microprocess engineering.[35] The setup allows operation at a reaction temperature above a solvent's boiling point (super heating), which is known to reduce the reaction time of a purely thermal reaction by several orders of magnitude compared with batch synthesis.[36] Due to the dangerous properties of ether peroxides generated by diethyl ether at high temperatures, in this study *tert*-butyl methyl ether (*t*-BME) is used to minimize as much as possible these inconveniences because of steric hindrance. The formation of *tert*-butyl radicals as a result of thermal and UV-irradiation is minimized due to the short residence times, and the absence of interfering compounds and oxygen inside the microchannels, which gives *t*-BME supplementary UV-stability.[37,38]

2. MATERIAL AND METHODS

In order to perform experiments in a small statistically relevant fashion, three reaction variables were taken into account: temperature, concentration, and irradiation time. For each variable, at least three levels were considered, and each experiment was carried out at least three times. The levels of each variable are described in the corresponding section.

For each experiment, a solution of the desired concentration of 7DHC (>90% Cayman Chemical Company) in *t*-BME (99% Alfa Aesar) was pumped using an ISCO pump (100D series). All chemicals were used as received. The pressure was monitored by the pressure sensor of the ISCO pump. IDEX PEEK Ora 0.55 mm (1/16″) ID tubing and the corresponding fittings were used for the connections. Quartz (HOQ: 90% transparency at 280 nm) coil 0.5 mm ID and 3.2 mm ED was used in the thermally controlled (photo-high-p,T) irradiation chamber (Scheme 2) made of reflective aluminum in order to enhance internal reflections and therefore the irradiation from all sides of the coil. A Phillips HOK 4/120 mercury lamp was used to produce light energy during the reaction, which was carried out at different temperatures above the boiling point of the solvent (55 °C). The spectrum of the lamp is provided in Figure 1. The HOK lamp was placed on one side, 6 mm out of the reactor. The light reflection was previously evaluated

Scheme 2. Design View of the Photochemical and Thermal Microflow System



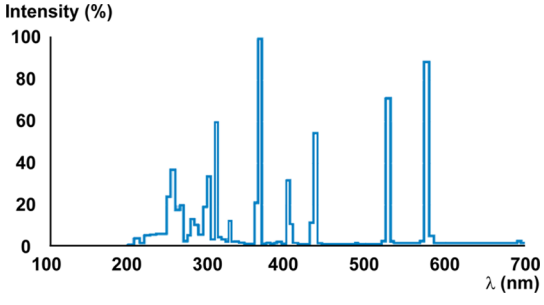


Figure 1. Full spectrum of Phillips HOK 4/120 mercury lamp (provided by Phillips).

DOI: 10.1021/acs.oprd.7b00318
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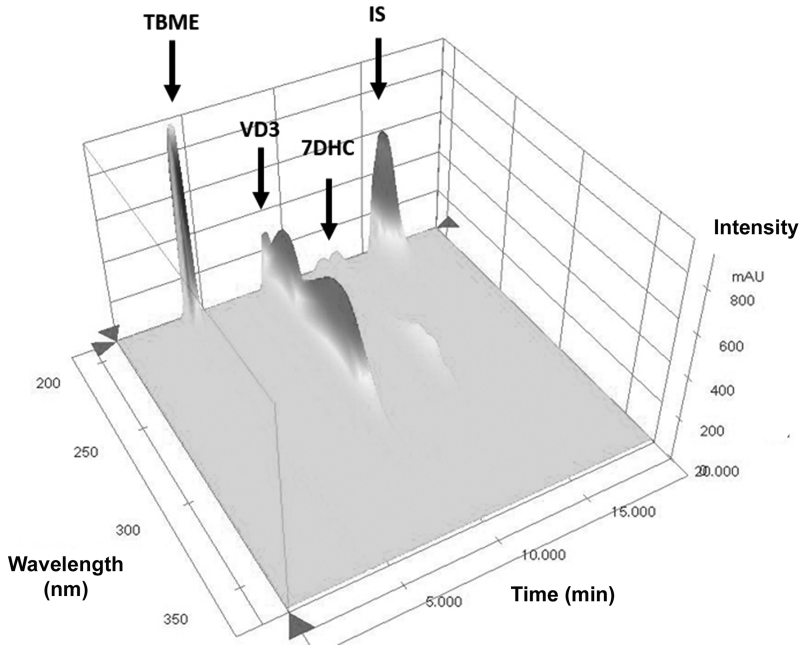

Figure 2. Absorption spectra of most of compounds involved.

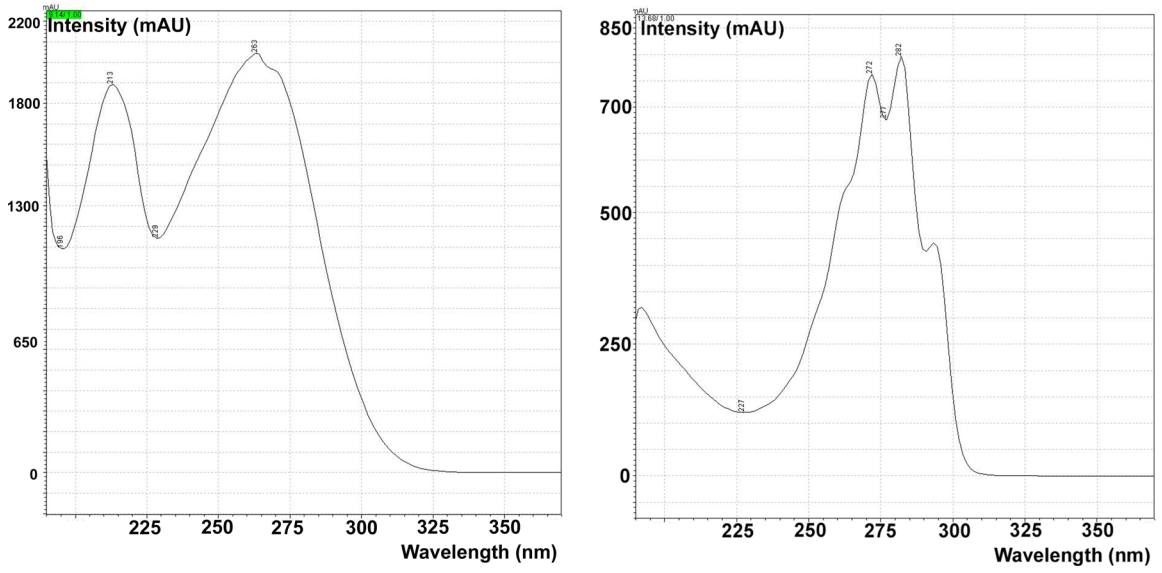

Figure 3. Absorption spectra of VD3 (a) and 7DHC (b).

(Zemax simulation) to ensure that all sections of the quartz coil received the same light energy. In order to achieve such intensification, the system was pressurized at 34 bar (33.5 atm) using a back pressure regulator IDEX BPR (PEEK). Once irradiated at high temperature and high pressure at the same time, the temperature was rapidly lowered, taking advantage of the high heat transfer provided by the capillary reactors. The sampling was carried out on ice using Supelco 7 mL clear vials, with screw caps and PTFE liners. All samples were stored at −20 °C in a nitrogen atmosphere for 1 h before HPLC analysis. The latter was carried out using HPLC (Shimadzu UFLC-XR) with a GraceSmart RP 18 5u column (150 mm × 4.6 mm), using cholesterol (95% Alfa Aesar) as the internal standard (IS), 100% acetonitrile (99% Merck) as the mobile phase, and a UV−visible Shimadzu diode array detector (RID-10A). The whole absorption spectra are shown in Figure 2. In these conditions all peaks were clearly separated. The retention time as well as UV−vis spectra were used for identification (Figure 3): for VD3, characteristic peaks at 213 and 264 nm were found (Figure 3a). For 7DHC, the peaks were at 272 and 282 nm (Figure 3b). Standards of 7DHC and VD3 (Alfa Aesar 95%) were used for quantification at 190 nm, quantifying the side products together as the difference according to sampling.

3. RESULTS AND DISCUSSION

3.1. Effect of Temperature. A set of temperatures above the boiling point of the solvent were checked between 80 and 260 °C. Despite the fact that temperatures can easily affect vitamins, cholecalcipherol (VD3) is known for its thermal resistance.[39] In addition, flow chemistry allows work to be undertaken under anoxic conditions, which enhances the resistance of these compounds even more since the oxidation

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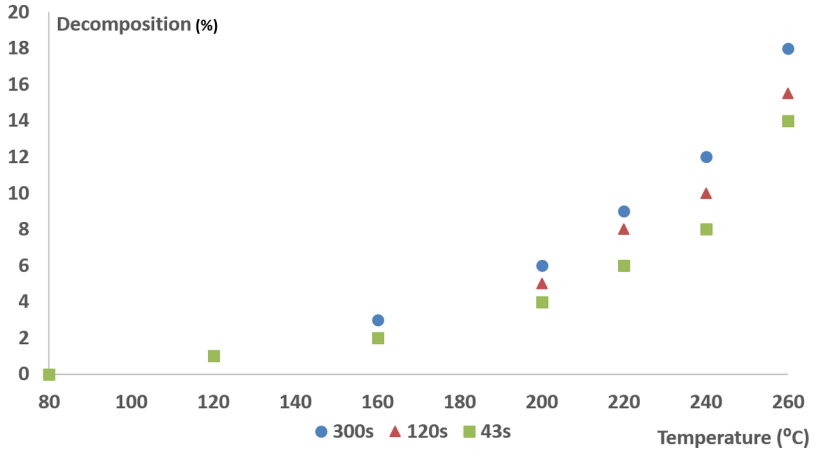

Figure 4. Decomposition of 7DHC at different temperatures and different residence times.

risk is avoided. Hence, in order to ensure 7DHC stability under the harsh conditions in continuous flow, a high-p,T test was previously done without using light energy. In this case, the decrease of 7DHC and the existence of other peaks was evaluated. As shown in Figure 4, losses of 7DHC are relevant only above 200 °C. Also some important changes in the range between 240 and 260 °C were found. This could suggest a critical stability point for 7DHC in this range. These differences are also more important with longer thermal residence times (TRT). In order to ensure the operating temperature in the irradiation chamber, when needed, a dark preheating step was also introduced in the setup before the irradiation chamber (Scheme 3). The irradiation time (IT) then only refers to one

Scheme 3. Correlation between Irradiation Times and Thermal Residence Time (BPR = Back Pressure Regulator)

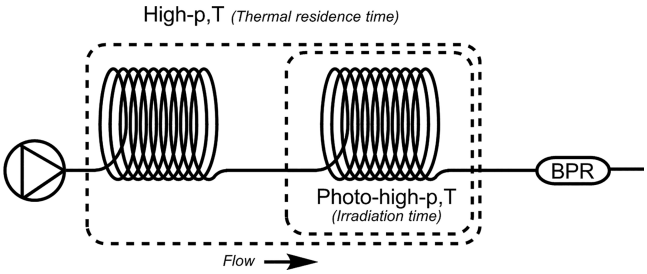

Table 1. Correlation between Irradiation Times and Thermal Residence Time

Irradiation time (s)	Thermal residence time (s)
43	100
120	280
300	728

part of the TRT, which is longer. In this connection, Table 1 shows the equivalence between TRT and IT in the range from 43 to 300 s. It is important to note at this point that VD3 was not detected in any of these experiments. Thus, and as expected, photoactivation is strictly needed.

After the stability test, the reaction was carried out using a UV-lamp with 400 W power. As this mainly refers to heating power and unavoidably heats up anything within close distance, this was used also to maintain the temperature in the irradiation chamber. The additional heating by the oven then guaranteed achieving the desired temperature. The temperature was controlled with three thermocouples located in the irradiation chamber. The energy supplied by the UV-lamp accordingly reduces the energy demand of the oven, which results in lower energy in the preheating (dark) part of the setup. Here, the desired temperature was reached only in the last sections of the preheating, reducing the thermal stress of 7DHC.

Figure 5 shows the evolution of the reaction at different temperatures with different irradiation times using a 0.05 M solution of 7DHC in *t*-BME as starting material. In light of these results, apparently no relevant reaction is detected below 100 °C. Yet, Figure 5 shows that, with the same irradiation time, a temperature effect is given, which is seen to be synergistic together with the irradiation. Furthermore, the behavior of the reaction is different above and below 200 °C. Above this temperature and at almost stable 7DHC conversion, the amount of VD3 decreases at the expense of increasingly formed side compounds, which include P3, L3, T3, and also otherwise decomposed 7DHC. This phenomenon may be caused by VD3 decomposition or a shift in the equilibrium of the VD3 synthesis, enhancing the amount of P3 and probably the amount of T3 and L3 as well. This is not observed below 200 °C where, despite lower conversions and lower yield, more control over side products is given. Yet, note that side product formation is inherent to the reaction because of the intermediate P3.

The maximum conversions achieved are in the range 40−80%, depending on the irradiation time, with a maximum yield of VD3 around 20−25%. It should be stressed that such conversions and yields are reached with really short times by using the photo-high-p,T microflow setup. Below 160 °C, the difference in the amount of side compounds between 2 and 5 min irradiation times can be explained because of the amount of P3. Yet, since P3 is the reaction intermediate, a high increase of P3 is expected derived from photoactivation in the first steps. Simultaneously with the P3 synthesis, isomerization also occurs, and therefore P3 is balanced between synthesis and isomerization. According to Figure 5, the maximum of P3 is around 2 min IT. Yet, after a 5 min IT, the higher yield of VD3 under the same conditions confirms that thermal isomerization is also carried out. The results of Figure 5 also suggest that, at temperatures above 200 °C, both the kinetics of side compounds and the decomposition of 7DHC and VD3 give

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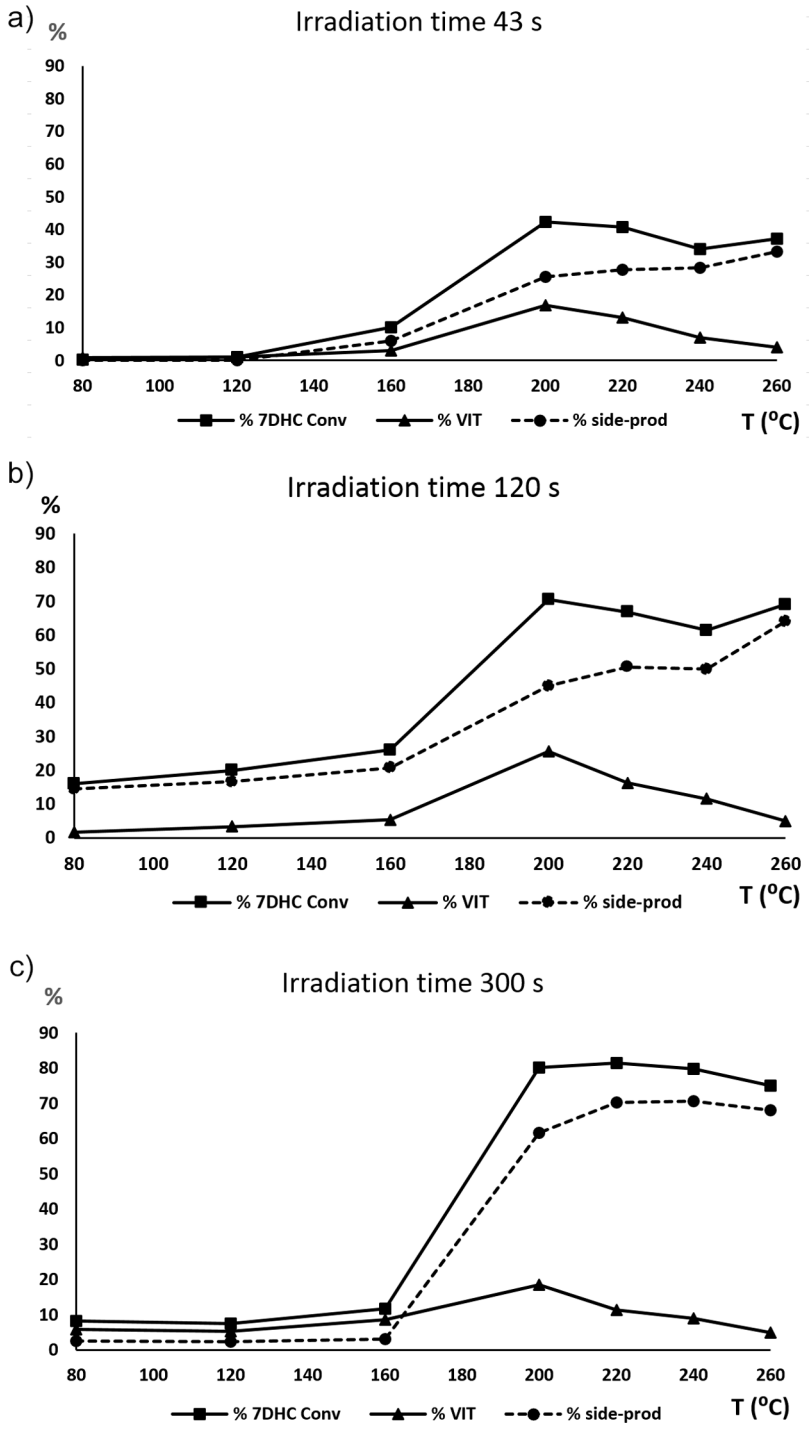

Figure 5. Effect of the temperature on the 7DHC conversion and the VD3 yield operating at 34 bar with (a) 43 s, (b) 2 min, and (c) 5 min irradiation time.

lower VD3 yields, making the reaction inefficient. The latter can only be controlled by reducing the IT (43 s), but assuming at the same time a reduction in both conversion and yield. However, the unreacted and unaltered 7DHC and P3 can be recycled after a 43 s IT.

3.2. Effect of Concentration. The solubility limit of 7DHC in *t*-BME was experimentally determined and found to be 0.22 M (84.5 mg/mL) at room temperature. Thus, the concentration used in the experiments was set equal to or lower than this value. The solubility of all other isomers involved in the reaction is much higher than the one obtained for 7DHC. Hence, for this variable, three levels were fixed: low (0.05 M), medium (0.11 M), and high (0.22 M). The goal of this study is to unveil the influence of the concentration of the initial 7DHC on the reaction yield. This could be correlated with the effect of the concentration in the light transfer according to the Lambert−Beer law (L−B). Following L−B, the higher the concentration, the lower should be the transmittance of 7DHC solution. Nevertheless, a negligible effect of the concentration was found and the effect using different concentrations was very similar. For these experiments, a 3.2 mm external diameter and 0.5 mm internal diameter capillary was used. Therefore, as

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Table 2. Estimation of Annual Average VD3 Productivity of a Single Capillary Using Photo-high-p,T Setup

			Productivity				
7DHC [M]	7DHC [mg/h]	IT [s]	[mg/h]	[g/day]	[g/month]	[kg/year]	Tablets/year [millions]
0.05	384	43	69	1.7	50	0.6	40
	137	120	32	0.8	23	0.3	18
	51	300	9	0.2	7	0.1	5
0.11	845	43	152	3.6	109	1.3	88
	301	120	70	1.7	51	0.6	41
	113	300	20	0.5	15	0.2	12
0.22	1690	43	304	7.3	219	2.6	175
	601	120	141	3.4	101	1.2	81
	226	300	41	1.0	29	0.4	23

expected by the excellent light penetration in the quartz made microcapillaries (transparency above 90% at 280 nm according to the supplier), there are even at high concentration enough photons for reaction at any place within the capillary. Also use of reflective aluminum in the internal part of the irradiation chamber favored internal reflections and therefore efficient irradiation on all sides. Thus, conversion is almost invariant with concentration. Yet, all reactions involved (including side ones) are intramolecular and thus hardly any dilution effect was to be expected. This conclusion is important in terms of productivity, since it allows operating with the highest concentration possible. Following this, and taking into account (i) the checked concentrations (0.05, 0.01, and 0.22 M), (ii) the mean of the VD3 yields for each case, (iii) the corresponding flow rate according to the length of the capillary tested for each IT (20, 7.12, and 2.67 mL/h respectively), and (iv) a 90% VD3 recovery in the purification step, the productivity results in Table 2. Besides the highest productivity of the 43 s IT capillary, Table 2 shows that operating with the described continuous photo-high-p,T setup, is possible to produce at least in the order of tens of millions of tablets (considering 15 μg VD3/tablet) per year using photo-high-p,T with just one coil as described in this paper. In addition, especially operating with the shortest IT, 7DHC and P3 can be recycled, and therefore converted to VD3 (recycling in not considered in Table 2). Comparing these results with previous literature (Fuse et al.,[28] 1.9 mg/h productivity with 15 min residence time), photo-high-p,T intensification of VD3 synthesis leads to 40 times better productivity with the lowest concentration (0.05 M), and 178 times better productivity with the highest concentration (0.22 M). Despite Fuse et al.[28] referred to calcitriol (a more unstable derivative) instead of VD3, the productivity of VD3 with the configuration described here is 1 and even 2 orders of magnitude better than the process reported before. Also the residence time is 20 times shorter than comparable continuous setups.

Taking Table 2 as a reference and considering our process design, an outlook for the scaling up of the vitamin synthesis is proposed in Figure 6. Quartz tubing is enlarged to mm-scale (by a factor of 10 possibly) and favorably uses gas−liquid segmented flow.[40] The thin liquid layers around the gas bubbles preserve the original characteristic dimensions of the microflow used in this study (own results to be published), while the characteristic dimensions of the whole segmented flow can be in the meso range giving already per capillary much enlarged throughput. Those tubing are still placed in parallel manner to further enlarge the throughput, surrounded and illuminated from a slightly separated, to avoid direct contact, reflecting a hot aluminum surface which has semicircular shape. This

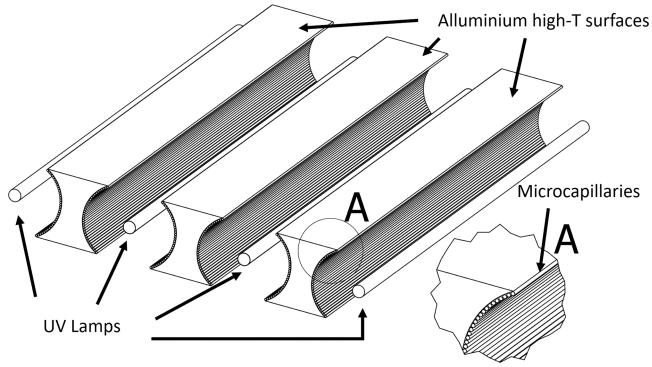

Figure 6. Outlook of the scaling up procedure for medium scale production.

multitube configuration is suitable for be numbering up as suggested in Figure 6, yet the degree of numbering up is probably exaggerated (for reasons of being generic). For pharma-scale applications it might be enough to have one lamp and possibly 10 parallel channels. In between, UV lamps are placed quartz-jacketed in order to isolate them from overheating.

3.3. Effect of Irradiation Time (IT). Flow chemistry and NPW[41] are known for its capability to reduce by orders of magnitude the residence times by intensifying the reaction kinetics.[36] Here, the residence time (irradiation time) is arranged simply by changing the flow rate of the solution through the reactor. Hence three levels of this factor are considered: 43 s, 2 min, and 5 min. Figure 7a shows a comparative view of the effect of irradiation time on VD3 yield at different temperatures using in all cases the same concentration (0.05 M). Apparently, the VD3 yield increases below 200 °C and decreases above this temperature. This is mainly because of (i) 7DHC and VD3 decomposition and (ii) because thermal equilibrium clearly allows side compounds above 200 °C. Moreover, below 200 °C the shorter the IT is, the lower the yield is. Nevertheless, the optimum conditions for P3 include a 2 min IT, and therefore its conversion to mainly VD3 can explain why the VD3 yield at the 2 min IT is higher than the yield at the longest residence time above 200 °C. In the light of these results, it can be concluded that the photo-high-p,T microflow setup operates close to the stability limits of 7DHC and VD3, and achieves the maximum intensification possible.

The selectivity of the reaction has a decreasing tendency (Figure 7b). At low conversions (low temperatures) high selectivity is found, while at medium and especially high temperature the selectivity becomes very low because of the

DOI: 10.1021/acs.oprd.7b00318
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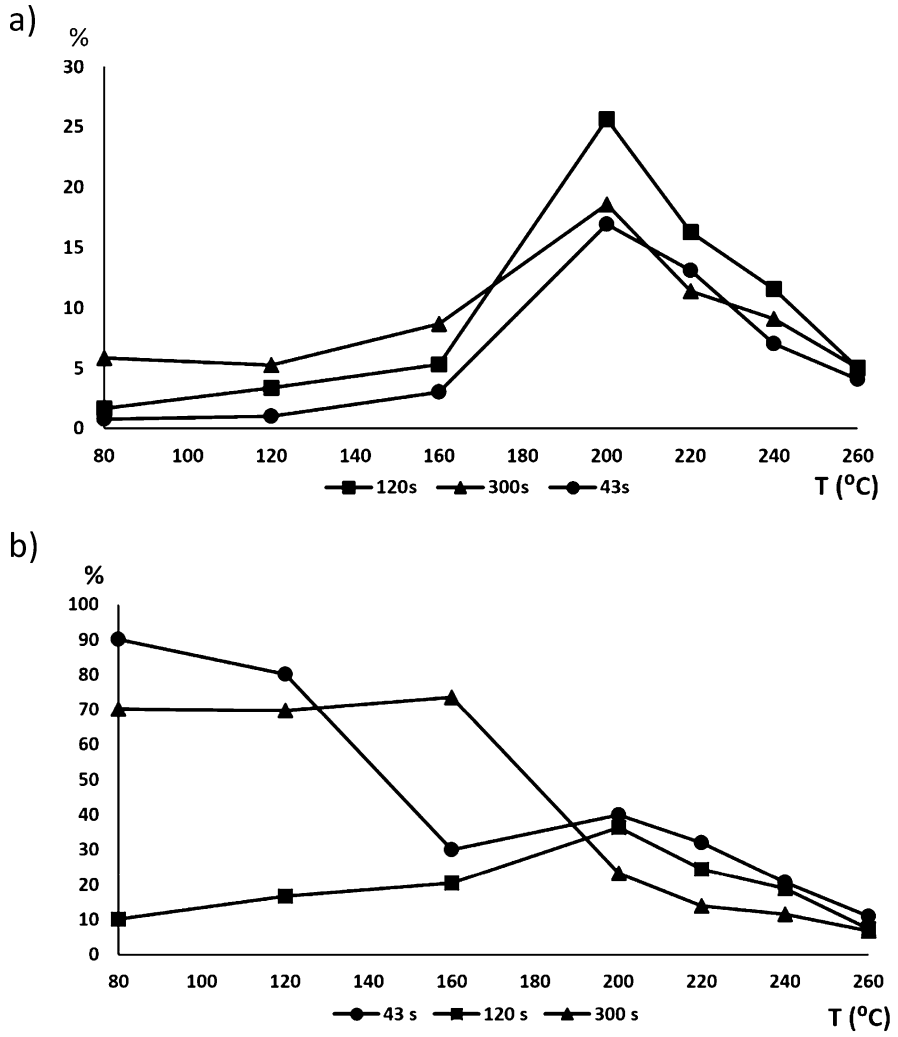

Figure 7. Effect of the irradiation time on the (a) VD3 yield and (b) in the reaction selectivity, operating at 34 bar and 0.05 M 7DHC concentration.

side compounds and decomposition. The latter is especially relevant above 200 °C. The low selectivity at 120 s of reaction time is because of the P3 peak, as discussed above.

3.4. Statistical Analysis: Principal Component Analysis (PCA). In order to show the relevance of the reaction variables studied for VD3 yield quantification, a Principal Component Analysis (PCA) was performed using The Unscrambler software. With this method, the experimental variables with the most variability can be identified, and this information can be used for process optimization. In this connection, the loadings plot (Figure 8) shows the desired relation among studied variables and the subspace dimensions. According to this plot, the irradiation time (IT in the plot) accounts for 72% of the variability of the VD3 yield, while the temperature only accounts for 28%. This confirms that IT plays a more relevant role ahead of T, and therefore, this is the key variable for the VD3 synthesis. Statistically, this can be explained because the T profiles are rather similar. Additionally, temperature shows up as a synergistic effect, but in a secondary component. It is also important to note that concentration is in the center of the axis. This confirms that concentration slightly contributes to the variability of the VD3 yield in the reaction using the performed setup, thus in capillary based photo-high-p,T.

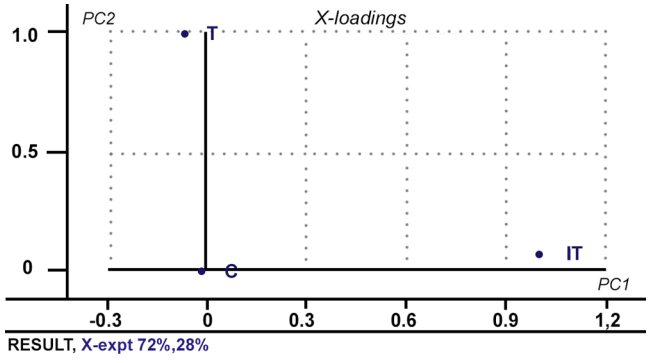

Figure 8. Effect of the reaction variables on the VD3 yield operating at 34 bar.

4. CONCLUSIONS

Process intensification by both photochemistry and thermal intensification may open additional options for photoreactions, yet is difficult to be combined in one step using conventional procedures and equipment because of safety risks. In this manuscript, this new kind of novel process is presented and investigated. The photo-high-p,T microflow setup used enables operation at high pressure and high temperature, while allowing also for irradiation in a safe manner.

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The synthesis of Vitamin D_3 was proven under photo-high-p,T conditions. The main result is a reduction of the reaction time to 43 s, which means orders of magnitude shorter times than in the case of the same process carried out in batch. Also previous comparable flow studies set the residence time at around 15 min. A 42% conversion of 7DHC is achieved, giving a 17% yield of vitamin D_3 and 25% of intermediates. This amounts to 40% selectivity. In addition, working under harsh conditions showed a thermal limitation of performing the reaction above 200 °C. Yet interestingly, working conditions close to 200 °C were found to be optimal. As a promising result, because of the small size of the capillary, no decrease in conversion within the range of concentration was found. The highest concentration used was close to the solubility limit the solvent used. This demands the use of new, tailored solvents which are specialized for the needs of flow processing (see www.one-flow.org). As given here, solvents would need to be identified which allow work in the molar range, which then probably will show the concentration dependence due to remarkable absorption losses. Nevertheless, the annual productivity achieved with the current photo-high-p,T microflow technique (just one microcapillary) suffices for several tens of millions of tablets and is between 1 and 2 orders of magnitude higher than comparable continuous processes described in the literature.

Moreover, a statistical analysis was performed in order to evaluate the influence of the variables (concentration, irradiation time, and temperature) on the yield of vitamin D_3. As a main and unsurprising result, irradiation time is the key variable in this reaction. As another truly new and insightful result, it was found that the temperature also has a synergistic influence on the irradiation step when both are combined at the same time. A common view is that the reaction is performed in two steps: photochemical and thermal. Nevertheless, these steps are performed in conventional equipment separating the steps spatially and timewise. Yet, this paper gives for the first time an approach of high T and irradiation at the same time, suggesting that temperature plays a synergistic effect with irradiation time in the reaction kinetics. As evident from the discussion of the single plots and as quoted above, the study also confirms that concentration does not have any role on the reaction performance.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This project was funded by the Horizon 2020: Marie Skolodowska-Curie Individual Fellowship awarded by Dr. Marc Escribà Gelonch under Grant Agreement Number 659233.

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