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Communication

Microflow Photochemistry—Photodecarboxylations in Microformats

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Abstract: This article summarizes selected examples of intra- and intermolecular photodecarboxylations involving phthalimides in a commercially available dwell device. Compared to batch conditions in a larger chamber reactor, the investigated transformations in the microreactor furnished higher conversions and yields after significantly shorter reaction times. The product qualities were commonly higher under flow conditions thus avoiding the need for further purifications.

Keywords: photodecarboxylation; photochemistry; microreactor; flow chemistry

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1. Introduction

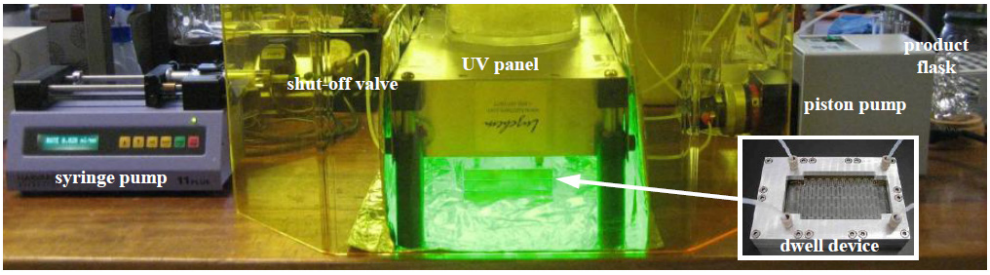
Microflow photochemistry combines the advantageous features of microreactors, flow operation and organic photochemistry [1–3]. The microscopic dimensions within micro-structured devices allow for an efficient penetration of light and subsequently yield high energy and quantum efficiencies [4,5]. In addition, continuous flow operation reduces photodecompositions of light-sensitive products [6] and avoids the accumulation of potentially hazardous materials in larger amounts, the latter especially problematic for heterogeneous gas-liquid reactions [7]. Likewise, irradiation enables the synthesis of

complex molecules with ease and numerous examples of highly effective photochemical transformations have been reported [8–10]. Of these, the photodecarboxylation of phthalimides has been developed as an efficient access to macrocycles or Grignard-type addition products [11,12]. As a result, the reaction has been used for the synthesis of known and potentially bioactive target compounds [13,14]. Examples of these reactions in meso- and micro-formats have also been reported [15–17].

2. Experimental Section

A UV panel (Luzchem, Ottawa, Canada) was selected as light source. The panel was fitted with 5 × 8 W UVB fluorescent tubes (λ = 300 ± 25 nm). The microreactor, a dwell device manufactured by mikroglass chemtech (Mainz, Germany), was placed underneath the panel. Its body is fabricated from Foturan™ glass and possesses two separate channels; the bottom reaction channel is 500 μm in depth, 2000 μm in width and 1.15 m in length with a volume of 1.68 mL, while the top channel was used for cooling during operations. The photoreactor module was enclosed on the sides with reflective tinfoil sheets and at the front with a UV shield to contain the UV light during irradiation. A small fan was placed in the back for cooling. The reaction channel inlet was connected to a programmable syringe pump (Harvard apparatus 11 plus, Holliston, MA, USA) via a shut-off valve and the outlet to a round bottom flask outside the irradiated area. The cooling channel was attached to a rotary piston pump (ISMATEC REGLO-CPF Digital, Wertheim, Germany), which drew cooling water in a loop from a reservoir. The complete reaction set-up incorporating the dwell device is shown in Figure 1.

Figure 1. Dwell device set-up.



2.1. General Procedure for Photodecarboxylative Cyclizations

A solution of **1** or **3a**,**b** (0.15 mmol) in an acetone/water mixture (1:1 vol%, 10 mL) was purged with nitrogen and loaded into a gas-tight syringe. The dwell device was prepared by pumping approximately 10 mL of the solvent mixture through its reaction channel. The shut-off valve was closed and the syringe containing the reaction mixture was loaded. The UV panel was ignited and ran for 2 min to achieve optimal light output. The cooling water flow and fan were subsequently started. After about 1 min, the shut-off valve was opened and the syringe pump started. The reaction mixture was pumped through a microreactor while irradiated with UVB light. Once the entire 10 mL of reaction mixture was pumped through the reactor system, the UV panel and syringe pump were both turned off simultaneously. The shut-off valve was closed and a syringe containing 10 mL of the plain solvent mixture was attached. The valve was once again opened and the syringe pump and the light

source were turned on in unison to flush the residual reaction mixture out of the channel. The washings and product mixture were collected together and subjected to work-up. Most of the acetone was evaporated and the crude product mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ (2 × 10 mL), brine (2 × 10 mL) and dried over $MgSO_4$. Filtration and evaporation gave pure **2** or **4a**,**b** as colorless solids.

Selected physical and spectral data for 9b-hydroxy-1, 2, 3, 9b-tetrahydro-pyrrolo[2,1-a]isoindol-5-one (**2**) [18]: Melting point = 125–127 °C. R_f (SiO_2, ethyl acetate:*n*-hexane = 1:1) = 0.35. ^{1}H-NMR: (400 MHz, acetone-d_6): δ (ppm) = 1.54 (m; 1H; CH_2), 2.30 (m; 2H; CH_2), 2.57 (m; 1H; CH_2), 3.35 (m; 1H; CH_2), 3.61 (m; 1H; CH_2), 5.26 (br.s; 1H; OH), 7.50 (m; 1H; CH_{arom}), 7.60 (m; 3H; CH_{arom}). ^{13}C-NMR: (100 MHz, acetone-d_6): δ (ppm) = 28.2 (1C; CH_2), 36.0 (1C; CH_2), 42.0 (1C; CH_2), 96.7 (1C; C–OH), 123.5 (1C; CH_{arom}), 123.5 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 132.9 (1C; Cq_{arom}), 133.0 (1C; CH_{arom}), 149.3 (1C; Cq_{arom}), 170.0 (1C; C=O).

2.2. General Procedure for Photodecarboxylative Additions to N-*methylphthalimide*

N-Methylphthalimide (**5**; 0.38 mmol) was dissolved in 5 mL of acetone. The addition partner **6a**–**f** or **8a**–**e** (1.13 mmol) was added to K_2CO_3 (0.57 mmol) and dissolved in 5 mL of distilled water. These solutions were then added together in a conical flask and made up to 25 mL using a mixture of acetone/water (50:50). The solution was sonicated for 5 min and then degassed with a slow stream of nitrogen. The microreactor was operated and the reaction mixture treated as described above in Section 2.1. Conversion rates of **5** and, for compounds **9a**–**e**, diastereoselectivities were determined by comparison of baseline-separated signals in the ^{1}H-NMR spectrum of the crude product. Whenever necessary, pure products were isolated by column chromatography using silica gel and ethyl acetate/*n*-hexane mixtures.

Selected physical and spectral data for 3-benzyl-3-hydroxy-2-methylisoindolin-1-one (**7a**) [19]: Melting point = 148–152 °C. R_f (SiO_2, ethyl acetate:*n*-hexane = 1:1) = 0.28. ^{1}H-NMR: (400 MHz, $CDCl_3$): δ (ppm) = (s; 3H; NCH_3), 3.09 (d; ^2J = 14.0 Hz; 1H; CH_2), 3.46 (d; ^2J = 14.0 Hz; 1H; CH_2), 3.67 (br.s; 1H; OH), 6.86 (m; 2H; CH_{arom}), 7.10 (br.m; 3H; CH_{arom}), 7.25 (d; ^3J = 7.6 Hz; 1H; CH_{arom}), 7.32 (ddd; ^3J = 7.6, ^4J = 1.0 Hz; 1H; CH_{arom}), 7.41 (d; ^3J = 7.6 Hz; 1H; CH_{arom}), 7.45 (ddd; ^3J = 7.6 Hz, ^4J = 1.0 Hz; 1H; CH_{arom}). ^{13}C-NMR: (100 MHz, $CDCl_3$): δ (ppm) = 24.2 (s, 1C, NCH_3), 42.7 (s, 1C, CH_2), 90.9 (s, 1C, COH), 123.0 (s, 1C, CH_{arom}), 123.2 (s, 1C, CH_{arom}), 127.3 (s, 1C, CH_{arom}), 128.3 (s, 2C, CH_{arom}), 129.8 (s, 1C, CH_{arom}), 130.3 (s, 2C, CH_{arom}), 131.4 (s, 1C, CH_{arom}), 132.0 (s, 1C, Cq_{arom}), 134.7 (s, 1C, Cq_{arom}), 146.5 (s, 1C, Cq_{arom}), 167.4 (s, 1C, C=O).

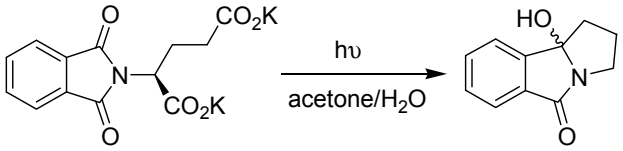
3. Results and Discussion

A set of intra- and intermolecular photodecarboxylations involving phthalimides was chosen as model reactions to investigate the effectiveness of the microreactor setup. For comparison, batch reactions were performed using a conventional Rayonet (Branford, CT, USA) chamber photoreactor (RPR-200) equipped with 16 × 8 W UVB fluorescent tubes (λ = 300 ± 25 nm) [18,19]. A Pyrex Schlenk flask (inner diameter: 32 mm) with an inserted cooling-finger (outer diameter: 24 mm) and an approximate volume of 150 mL was used as reaction vessel. Irradiations were performed on 100 mL scales.

3.1. Intramolecular Photodecarboxylative Cyclization Reactions

The photodecarboxylative cyclization of the L-glutamic acid derived compound **1** furnished the tricyclic product **2** (Scheme 1) via a cascade of α- and ω-decarboxylations [20,21]. Under batch conditions, prolonged irradiation for several hours is typically required to reach high conversion. Consequently, irradiation of **1** for 2 h furnished compound **2** in an isolated yield of 42%. To evaluate the efficiency of the microreactor platform, the irradiation time was shortened to 21 min instead. When using the traditional chamber reactor, the isolated yield of **2** was low with 17%. The comparison reaction carried out in the microreactor with a residence time of 21 min resulted in a significantly improved yield of **2** of 33%. ^{1}H-NMR-analysis of the crude product obtained under flow conditions furthermore showed no signs of impurities, thus avoiding the need for further purification.

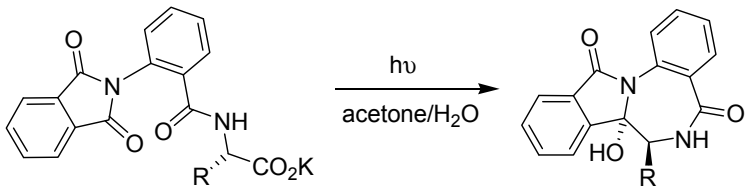
Scheme 1. Photodecarboxylative cyclizations of phthaloly-L-glutamic acid **1**.



1 **2**

The photocyclization of the anthranilic acid-linked dipeptide models **3a** and **3b** is known to proceed with memory of chirality and exclusively yields the *trans*-diastereoisomers of the polycyclic (1,4)-benzodiazepines **4a** and **4b** (Scheme 2; Table 1) [22]. Upon extended irradiation under conventional conditions for a period of 4 h and 2.5 h, the corresponding cyclization products **4a** and **4b** were isolated in yields of 40% and 58%, respectively. When the reactions were transferred to the microreactor, residence times were shortened to allow for more reasonable operation times and to avoid clogging of the reaction channel due to product precipitation. The L-alanine-derived product **4a** was formed in a yield of 35% with a residence time of less than 3 h. The result obtained for the L-leucine-derived compound **3b** showed a marked improvement with an enhanced yield of **4b** of 87% being achieved after an irradiation period of just under 1 h. The differences in performances for both compounds may be due to alterations in conformational folding, with the leucine-containing compound **3b** preferentially populating a reactive conformation responsible for successful photocyclization [23,24]. Noteworthy, no further purifications were again required for the crude products obtained under microflow conditions. Flow operation thus increases product qualities and avoids time- and resource-demanding purification steps.

Scheme 2. Photodecarboxylative cyclizations of the dipeptide models **3a** and **3b**.



3a (R = Me)
b (R = *i*-Bu)

4a,b

Table 1. Comparison of microreactor *versus* batch reactor performances.

Entry	Batch reactor		μ-Reactor	
	Time (h)	Yield of 4 (%)	Time (min)	Yield of 4 (%)
3a	4	40	168 [a]	35
3b	2.5	58	56 [a]	87

[a] Shortened residence time to avoid clogging by precipitation.

3.2. Intermolecular Photodecarboxylative Addition Reactions

The merits of using the microreactor were further investigated by attempting various benzylation reactions of *N*-methylphthalimide (**5**) with phenylacetates (**6a**–**f**) (Scheme 3; Table 2) [19]. For direct comparison reasons, the irradiation times were kept the same or similar in almost all cases. Simple decarboxylations (–CO_2H/–H exchange) are commonly observed for these benzylations, resulting in incomplete conversions and yielding the corresponding toluene derivatives of **6a**–**f** as by-products. For the parent phenylacetate **6a**, irradiation under batch conditions for 1 h furnished the desired product **7a** in a good yield of 80% after column chromatography. When conducted in the dwell device with a residence time of just 42 min, ^{1}H-NMR analysis of the crude product obtained showed only the presence of **7a**. No further purification of the product was needed, thus resulting in an improved yield of **7a** of 98%. The reactions involving phenylacetates **6b** and **6f** proceeded similarly but required prolonged reaction times of 4 h and 3 h, respectively. In the larger chamber reactor, the benzylated products **7b** and **7f** were both obtained after purification in yields of 53%. Under microflow conditions, the same transformations furnished pure products **7b** and **7f** directly in yields of 93% each. All other reactions involving the mono-halogenated phenylacetates **6c**–**e** showed incomplete conversions of **5** due to competing simple decarboxylations. Differences in return electron transfer rates [25] or radical stabilities [26–28] of the corresponding benzyl radicals may have caused this drop in chemoselectivity. Purification was thus required for both, batch and microflow operation modes. In the conventional Rayonet reactor, isolated yields of 39% (**7c**), 35% (**7d**) and 51% (**7e**) were achieved despite prolonged irradiation periods after 4–5 h. In case of the para-fluoro compound **6c**, the reaction in the microreactor with a residence time of 4 hours gave the desired product **7c** in 53% yield. Due to the limitations of the syringe pump employed, the residence time of the transformation involving carboxylate **6d** was kept below 5 h. Nevertheless, the benzylation product **7d** was isolated in a compared to the batch reaction increased yield of 60%. The photoreaction employing the ortho-iodo derivative **6e** was conducted with a residence time of less than 3 h due to precipitation of the product at lower flow rates and thus the danger of clogging. As a result, the corresponding addition product **7e** was obtained in a somewhat lower yield of 23%.

Scheme 3. Photodecarboxylative benzylations of *N*-methylphthalimide (**5**).

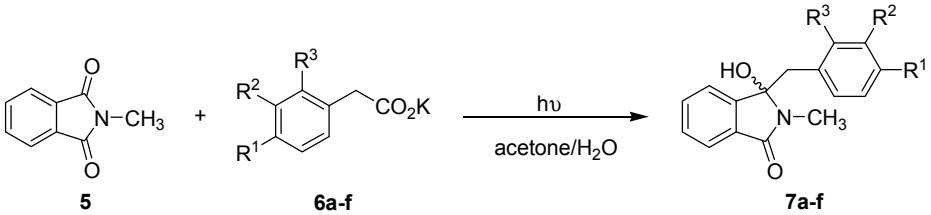
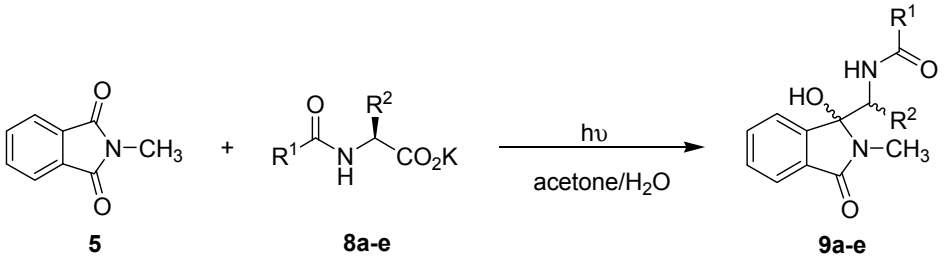


Table 2. Comparison of microreactor *versus* batch reactor performances.

Entry	R^1	R^2	R^3	Batch reactor		μ-Reactor	
				Time (h)	Yield of 7 (%)	Time (min)	Yield of 7 (%)
6a	H	H	H	1	80	42	98 [a]
6b	CH_3	H	H	4	53	240	93 [a]
6c	F	H	H	4	39	240	53
6d	H	H	Br	5	35	280	60
6e	H	H	I	4	51	168 [b]	23
6f	Cl	Cl	H	3	53	180	93 [a]

[a] Pure product, no purification required. [b] Shortened residence time to avoid clogging by precipitation.

Scheme 4. Photodecarboxylative addition of *N*-protected amino acids (**8a**–**e**) to *N*-methylphthalimide (**5**).



5 **8a-e** **9a-e**

Table 3. Comparison of microreactor *versus* batch reactor performances.

Entry	R^1	R^2	Batch reactor		μ-Reactor	
			Time (h)	Yield of 9 (%)	Time (min)	Yield of 9 (%)
8a	CH_3	*i*-Pr	3.5	52	210	58
8b	CH_3	*i*-Bu	3	26	42 [a]	18
8c	CH_3	*sec*-Bu	3	78	21 [a]	27
8d	*t*-BuO	CH_3	3	65	168 [a]	93
8e	*t*-BuO	Bn	3	34	168 [a]	53

[a] Shortened residence times to avoid clogging by precipitation.

N-Acyl protected amino acids successfully undergo photodecarboxylative additions with **5** (Scheme 4) [29]. A selection of these reactions was thus performed with the amino acid derivatives **8a**–**e** in the microreactor and compared to analogue reactions conducted in the conventional chamber reactor (Table 3). To avoid precipitation of photoproducts within the microchannel and thus clogging, high flow rates had to be maintained for some of the reactions, thus causing reduced residence times. Even after prolonged irradiations, conversions of **5** were incomplete, suggesting consumption of **8a**–**e** due to alternative photoreactions [30]. Yields and conversions varied depending on the amino acid utilized, thus supporting electronic [31] as well as steric effects [32]. The isoleucine derived product **9c** was formed as a mixture of four stereoisomers. For all other amino acids, diastereoselectivities (*d.e.*) were moderate and ranged from 22% to 38% [33]. Under batch conditions, the corresponding addition products **9a**–**e** were formed in acceptable to good yields of 26%–78% after 3–3.5 h of irradiation. When conducted in the dwell device, the amounts of **9a**–**e** naturally varied depending on residence times. For amino acids **8a**, **d** and **e**, yields were significantly higher than for the batch counterparts.

Despite the much shorter residence times of 42 min and 21 min, compounds **9b** and **9c** were generated in reasonable amounts of 18% and 27%, respectively. The results demonstrate once again that photodecarboxylative additions progress more efficiently in the microreactor and this observation is strengthened by the fact that the product quality was generally improved compared to operations in the chamber reactor.

4. Conclusions

A range of photodecarboxylation cyclization and addition reactions has been transferred successfully to microflow conditions. Despite the larger light power of the Rayonet chamber reactor with its sixteen UVB fluorescent tubes, the smaller dwell device utilized the light emitted from its five fluorescent tubes more efficiently. As a result, the chosen microreactor repeatedly enabled a decrease in reaction time compared to the conventional batch reactor. In addition, higher yields and better product qualities were typically observed, thus minimizing or completely avoiding the need of purification steps. These performance features make microflow photochemistry a green chemical synthesis tool [34]. A current drawback of microflow devices is the lengthy operation time and subsequently their low productivity. However, microreactors offer interesting applications in early research and development processes, where only small amounts of materials are needed [35]. Small-scale manufacturing plants have also been realized using automated and parallel microflow photochemical reactors, for example the innovative Heraeus Noblelight process for the synthesis of anti-cancer precursors [36]. In conclusion, microflow photochemistry represents a sustainable technology with a bright future.

Acknowledgments

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Oelgemöller, M. Highlights of photochemical reactions in microflow reactors. *Chem. Eng. Technol.* **2012**, *35*, 1144–1152.
2. Oelgemöller, M.; Shvydkiv, O. Recent advances in microflow photochemistry. *Molecules* **2011**, *16*, 7522–7550.
3. Coyle, E.E.; Oelgemöller, M. Micro-photochemistry: Photochemistry in microstructured reactors. The new photochemistry of the future? *Photochem. Photobiol. Sci.* **2008**, *7*, 1313–1322.

4. Sugimoto, A.; Fukuyama, T.; Sumino, Y.; Takagi, M.; Ryu, I. Microflow photo-radical reaction using a compact light source: Application to the Barton reaction leading to a key intermediate for myriceric acid A. *Tetrahedron* **2009**, *65*, 1593–1598.
5. Aillet, T.; Loubiere, K.; Dechy-Cabaret, O.; Prat, L. Photochemical synthesis of a "cage" compound in a microreactor: Rigorous comparison with a batch photoreactor. *Chem. Eng. Proc.* **2013**, *64*, 38–47.
6. Maeda, H.; Nashihara, S.; Mukae, H.; Yoshimi, Y.; Mizuno, K. Improved efficiency and product selectivity in the photo-Claisen-type rearrangement of an aryl naphthylmethyl ether using a microreactor/flow system. *Res. Chem. Intermed.* **2013**, *39*, 301–310.
7. Terao, K.; Nishiyama, Y.; Tanimoto, H.; Morimoto, T.; Oelgemöller, M.; Kakiuchi, K. Diastereoselective [2 + 2] photocycloaddition of a chiral cyclohexenone with ethylene in a continuous flow microcapillary reactor. *J. Flow Chem.* **2012**, *2*, 73–76.
8. Bach, T.; Hehn, J.P. Photochemical reactions as key steps in natural product synthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000–1045.
9. Hoffmann, N. Photochemical reactions as key steps in organic synthesis. *Chem. Rev.* **2008**, *108*, 1052–1103.
10. Iriondo-Alberdi, J.; Greaney, M.F. Photocycloaddition in natural product synthesis. *Eur. J. Org. Chem.* **2007**, 4801–4815.
11. Griesbeck, A.G.; Kramer, W.; Oelgemöller, M. Synthetic applications of photoinduced electron transfer decarboxylation reactions. *Synlett* **1999**, *1999*, 1169–1178.
12. Kramer, W.; Griesbeck, A.G.; Nerowski, F.; Oelgemöller, M. Synthetic potential of the PET-decarboxylation of ω-phthalimido carboxylic acids. *J. Inf. Rec.* **1998**, *24*, 81–85.
13. Belluau, V.; Noeureuil, P.; Ratzke, E.; Skvortsov, A.; Gallagher, S.; Motti, C.A.; Oelgemöller, M. Photodecarboxylative benzylations of phthalimide in pH 7 buffer: A simple access to 3-arylmethyleneisoindolin-1-ones. *Tetrahedron Lett.* **2010**, *51*, 4738–4741.
14. Hatoum, F.; Engler, J.; Zelmer, C.; Wißen, J.; Motti, C.A.; Lex, J.; Oelgemöller, M. Photodecarboxylative addition of carboxylates to phthalimides: A concise access to biologically active 3-(aryl and alkyl)methylene-1*H*-isoindolin-1-ones. *Tetrahedron Lett.* **2012**, *53*, 5573–5577.
15. Griesbeck, A.G.; Kramer, W.; Oelgemöller, M. Photoinduced decarboxylation reactions. Radical chemistry in water. *Green Chem.* **1999**, *1*, 205–207.
16. Shvydkiv, O.; Gallagher, S.; Nolan, K.; Oelgemöller, M. From conventional to microphotochemistry: Photodecarboxylation reactions involving phthalimides. *Org. Lett.* **2010**, *12*, 5170–5173.
17. Shvydkiv, O.; Nolan, K.; Oelgemöller, M. Microphotochemistry—4,4'-dimethoxybenzophenone mediated photodecarboxylation reactions involving phthalimides. *Beilstein J. Org. Chem.* **2011**, *7*, 1055–1063.
18. Griesbeck, A.G.; Henz, A.; Kramer, W.; Lex, J.; Nerowski, F.; Oelgemöller, M.; Peters, K.; Peters, E.-M. Synthesis of medium- and large-ring compounds initiated by photochemical decarboxylation of ω-phthalimidoalkanoates. *Helv. Chim. Acta* **1997**, *80*, 912–933.
19. Hatoum, F.; Gallagher, S.; Baragwanath, L.; Lex, J.; Oelgemöller, M. Photodecarboxylative benzylations of phthalimides. *Tetrahedron Lett.* **2009**, *50*, 6335–6338.

20. Sato, Y.; Nakai, H.; Mizoguchi, T.; Kawanishi, M.; Kanaoka, Y. Photochemistry of the phthalimide system. I. Photodecarboxylation of *N*-phthaloyl-α-amino acids. *Chem. Pharm. Bull.* **1973**, *21*, 1164–1166.
21. Griesbeck, A.G.; Henz, A.; Peters, K.; Peters, E.-M.; von Schnering, H.G. Photo electron transfer induced macrocyclization of *N*-phthaloyl-ω-amino-carboxylic acids. *Angew. Chem. Int. Ed.* **1995**, *34*, 474–476.
22. Griesbeck, A.G.; Kramer, W.; Lex, J. Stereoselective synthesis of 1,4-benzodiazepins via photoinduced decarboxylation of *N*-phthaloylanthranilic acid amides. *Synthesis* **2001**, 1159–1166.
23. Wagner, P.J. Conformational flexibility and photochemistry. *Acc. Chem. Res.* **1983**, *16*, 461–467.
24. Huang, F.; Nau, W.M. A conformational flexibility scale for amino acids in peptides. *Angew. Chem. Int. Ed.* **2003**, *42*, 2269–2272.
25. Yokoi, H.; Nakano, T.; Fujita, W.; Ishiguro, K.; Sawaki, Y. In-cage formation of carbanions in photoinduced electron-transfer reaction of carboxylate ions. *J. Am. Chem. Soc.* **1998**, *120*, 12453–12458.
26. Jackson, R.A.; Sharifi, M. Stabilization of benzylic radicals by substituents: An EPR study of para-substituted benzyl radicals. *J. Chem. Soc., Perkin Trans.* **1996**, *2*, 775–778.
27. Singh, N.K.; Popelier, P.L.A.; O'Malley, P.J. Substituent effects on the stability of para substituted benzyl radicals. *Chem. Phys. Lett.* **2006**, *426*, 219–221.
28. Suryan, M.M.; Stein, S.E. Stabilities of substituted benzyl radicals: Dissociation rates of amino-, hydroxy-, and cyanoethylbenzenes. *J. Phys. Chem.* **1989**, *93*, 7362–7365.
29. Gallagher, S.; Hatoum, F.; Zientek, N.; Oelgemöller, M. Photodecarboxylative additions of *N*-protected α-amino acids to *N*-methylphthalimide. *Tetrahedron Lett.* **2010**, *51*, 3639–3641.
30. Schaich, K.M. Free radical initiation in proteins and amino acids by ionizing and ultraviolet radiations and lipid oxidation—Part II: Ultraviolet radiation and photolysis. *CRC Critical Rev. Food Sci. Nutr.* **1980**, *13*, 131–159.
31. Ho, J.; Coote, M.L.; Easton, C.J. The distal effect of *N*-electron-withdrawing groups on the stability of peptide carbon radicals. *Aust. J. Chem.* **2011**, *64*, 403–408.
32. White, D.P.; Anthony, J.C.; Oyefeso, A.O. Computational measurement of steric effects: The size of organic substituents computed by Ligand Repulsive Energies. *J. Org. Chem.* **1999**, *64*, 7707–7716.
33. Gallagher, S. From conventional to microphotochemistry: A study of phthalimide and phthalonitrile derivatives. Ph.D. Thesis, Dublin City University, Dublin, Ireland, April 2011.
34. Newman, S.G.; Jensen, K.F. The role of flow in green chemistry and engineering. *Green Chem.* **2013**, *15*, 1456–1472.
35. Chin, P.; Barney, W.S.; Pindzola, B.A. Microstructured reactors as tools for the intensification of pharmaceutical reactions and processes. *Curr. Opin. Drug Dis. Dev.* **2009**, *12*, 848–861.
36. Werner, S.; Seliger, R.; Rauter, H.; Wissmann, F. Quarzglas-mikrophotoreaktor und synthese von 10-hydroxycamptothecin und 7-alkyl-10-hydroxycamptothecin. EP-2065387A2, 2009.