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From Conventional to Microphotochemistry: Photodecarboxylation Reactions Involving Phthalimides

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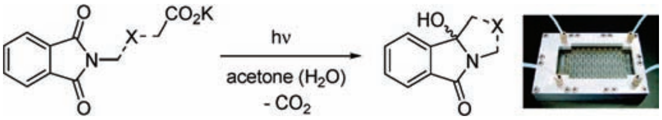
ABSTRACT



A series of acetone-sensitized photodecarboxylation reactions involving phthalimides have been investigated using conventional and microphotochemistry. Both, *intra-* and *intermolecular* transformations were compared. In all cases examined, the reactions performed in microreactors were superior in terms of conversions or isolated yields. These findings unambiguously prove the advantage of microphotochemistry over conventional photochemical techniques.

Recently, microprocess engineering has revolutionized the chemical process industry, and a number of synthetic transformations have been realized on micro- to pilot production scales.[1] The small size of these devices, in combination with favorable heat and mass transport, makes them especially beneficial for modern R&D processes.[1h] Likewise, microphotochemistry, i.e., photochemistry in microstructured reactors, has emerged as a new photochemical synthesis tool.[2] Microphotoreactors have a number of advantages over conventional batch photoreactors. (a) The thin layers within the microchannel plates allow extensive penetration of the solution by light; (b) the short residence time within the reactors (*flow-through*) avoids undesired side reactions or decompositions; (c) the small scales reduce the amounts of waste and materials;[1d] (d) the miniaturized scale allows online UV-[3] or IR-monitoring;[4] and (e) microreactors can be operated in series or in parallel clusters for scale-up or optimization studies.[5]

To evaluate the efficiency of microphotochemistry in comparison to conventional laboratory photochemistry, we have chosen five acetone-sensitized photodecarboxylation (PDC) reactions of phthalimides as model systems. In conventional reactors, the selected PDC reactions show high quantum yields of up to 60%.[6] The photochemistry of phthalimides has been studied in detail over the last decades and is thus well understood.[7] Semitechnical scale reactions of selected transformations using a 308 nm excimer light source have also been reported.[8]

All microreactions were studied in a commercially available reactor (dwell device, mikroglas) which was placed under a UV panel (Luzchem) fitted with 5 UVB lamps (Figure 1). The dwell reactor is made out of Foturan glass[9] and has a total path length of 1.15 m (20 turns) on a 118

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Figure 1. Experimental setup: microreactor (dwell device, mikroglas) under a UV exposure panel (Luzchem).

mm × 73 mm aperture. The reactor consisted of a (bottom) serpentine reaction channel 0.5 × 2 mm (D × W) with an internal volume of 1.68 mL, with a second (top), heat-exchanging channel through which water is passed to control the reactor temperature. The reaction mixture was pumped through the reaction channel via a programmable syringe pump and collected in a flask outside the irradiated area.

The results obtained with the dwell device were compared to similar experiments in a conventional Rayonet chamber reactor (RPR-200) equipped with either 16 or 5 UVB lamps. The latter lamp arrangement allowed a direct comparison with the chosen microreactor setup in terms of light power. A standard Pyrex[9] Schlenk flask (32 mm inner ø) equipped with a coldfinger (24 mm ø) was used as the reaction vessel. Due to the circular arrangement of the lamps around the flask, the effective path length through the solution was thus 4 mm. A maximum irradiation time of 1 h was set for this comparison study.

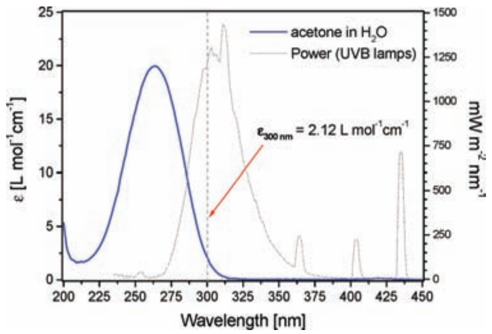

Figure 2. UV spectra of acetone (in water) vs lamp power. The broken vertical line represents the cutoff wavelength of Pyrex and Foturan glass at 300 nm.[9]

Figure 2 shows the adsorption spectrum of an acetone/water mixture (1:1 vol %) in comparison with the emission spectrum of the UVB lamps. Despite the relatively poor overlap of the spectra, it should be noted that acetone functions as a sensitizer as well as a cosolvent.[10] Hence, it is available in large excess amounts ($c_{\mathrm{acetone}} = 6.8$ M).

The light penetration profile was calculated from the adsorption spectra and the experimental conditions (Figure 3).[11] As indicated by vertical lines, the narrow microchannel (0.5 mm) allows complete penetration of light at 300 nm. In contrast, total adsorption is achieved within the Schlenk vessel after ca. 1.5 mm, way below its effective path length of 4 mm.

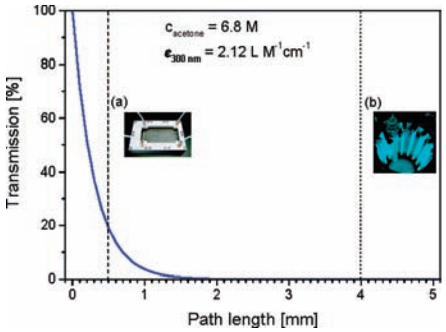

Figure 3. Light penetration profile for a 6.8 M acetone solution at 300 nm. The vertical broken line (a) represents the path length in the dwell device and the dotted line (b) the effective path length in the Schlenk flask.

The α-photodecarboxylation ($-CO_2H/-H$ exchange) of phthaloyl amino acids was initially chosen as the model reaction. This transformation has been developed as an efficient access to α-deuterated primary amines.[12] The reaction protocol was applied to microphotochemistry using the irradiation of phthaloyl glycine **1** in dry acetone as an example (Scheme 1). The effect of residence time on the conversion of the decarboxylation (after a single run) was examined by alteration of the flow rate (Table 1). As would be expected, conversion rates improved for both reactor types with increasing reaction times, but the microreactor gave better results overall. For example, *N*-methylphthalimide **2** was obtained in 92% yield next to 8% of unreacted starting material (**1**) after a residence time of 60 min.

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(9) The transmission of both Foturane and Pyrex is approximately 30% at 300 nm. The chosen Pyrex and Foturan glass prevents photodecomposition, which is commonly observed for reactions in Quartz vessels.[7]

(10) Direct excitation of phthalimide is also possible. Acetone sensitization is, however, known to give higher selectivities. See, for example: Griesbeck, A. G. *Chimia* **1998**, *52*, 272.

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Scheme 1. α-Photodecarboxylation of Phthaloyl Glycine **1**

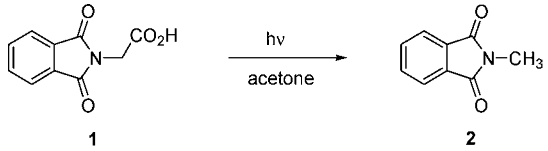


Table 1. Experimental Details of α-Decarboxylation of **1**

		conversion to **2** (%)[a]	
flow rate (mL/min)	residence time (min)	μ-reactor	Rayonet
0.5	3.4	5	2
0.15	11	23	7
0.08	21	44	19
0.042	40	74	39
0.028	60	92	59 (22[b])

[a] Determined by ^{1}H NMR spectroscopy. [b] With 5 UVB lamps.

In contrast, the larger Rayonet reactor gave lower conversions of just 59% (16 lamps) and 22% (5 lamps), respectively, after the same irradiation time.

Likewise, the photodecarboxylative cyclization of the potassium salt of phthaloyl-γ-aminobutyric acid **3** to the polycyclic product **5** was investigated (Scheme 2; Table 2).[13]

Scheme 2. Photodecarboxylative Cyclizations of **3** and **4**

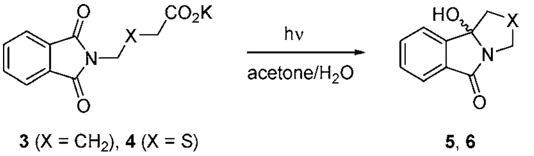


Table 2. Experimental Details of PDC-Cyclizations of **3** and **4**

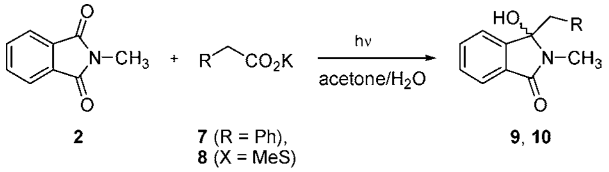
flow rate	residence time	yield of **5** (%)[a]		yield of **6** (%)[a]	
(mL/min)	(min)	μ-reactor	Rayonet	μ-reactor	Rayonet
0.08	21	33	46	39	36
0.042	40	69	53	70	59
0.028	60	77	69 (19[b])	80	72 (21[b])

[a] Isolated yields. [b] With 5 UVB lamps.

Using the microreactor, **5** was isolated in a yield of 77% after 60 min of irradiation. After an identical irradiation time, the yields were again lower with 69% (16 lamps) and 19% (5 lamps), respectively, in the Rayonet reactor. Sulfur atoms in α-position to a carboxylate group are known to accelerate photodecarboxylations, and the transformation of potassium phthalimidomethylsulfanyl acetate **4** to the thiazolidine derivative **6** was thus examined (Scheme 2).[14] Following the general trend, the dwell device gave higher yields than the Rayonet reactor (Table 2). After exposure for 60 min, the isolated yields of **6** were 80% under flow-through (microreactor) and 72% (16 lamps) or 21% (5 lamps), respectively, under batch conditions (Rayonet).

Photodecarboxylative additions of carboxylates to phthalimides have been recently established as efficient alternatives to Grignard additions.[15] These versatile reactions use stable and easily available carboxylates as alkylating agents. The photodecarboxylative benzylation of *N*-methylphthalimide **2** with phenylacetate **7** is known to proceed rapidly (Scheme 3).[15d]

Scheme 3. Photodecarboxylative Additions Involving **2**



When studied in the dwell device, the corresponding addition product **9** was obtained in 83% and 97% after just 14 and 21 min, respectively, whereas complete conversion was obtained after 40 min (Table 3). While the larger Rayonet chamber reactor achieved complete conversion after 40 min as well, it gave lower yields after shorter reaction times, in particular after

Table 3. Experimental Details of PDC Addition of **7** and **8**

flow rate	residence time	conversion to **9** (%)[a]		conversion to **10** (%)[a]	
(mL/min)	(min)	μ-reactor	Rayonet	μ-reactor	Rayonet
0.12	14	83	46	4	2
0.08	21	97	93	34	20
0.042	40	100	100	66	44
0.028	60	100	100 (29[b])	100	86 (17[b])

[a] Determined by ^{1}H NMR spectroscopy. [b] With 5 UVB lamps.

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14 min. Furthermore, the yield dropped significantly to 29% when irradiation was performed for 1 h with only 5 UVB lamps. Likewise, the addition of potassium 2-(methylthio)acetate **8** to **2** was investigated.[14b,15g] In the microreactor, quantitative conversion to **10** was accomplished after 60 min of irradiation. The Rayonet reactor again performed worth and gave conversions of 86% (16 lamps) and 17% (5 lamps) after the same reaction time.

The photobenzylation of **2** with **7** was selected to study the effect of the concentration on the efficiency of the addition (Table 4). To achieve this, the photoreaction was performed in acetonitrile, i.e., under conditions of direct excitation of **2**.[10]

Table 4. Concentration Study for PDC Addition of **7** in MeCN

concentrations (mmol/L)		conversion to **9** (%)[a]	
2	**7**	μ-reactor	Rayonet
15	45	100	100
30	90	100	93
60	180	64	53
90	270	45	38

[a] Determined by ^{1}H NMR spectroscopy.

The reaction time was furthermore set to 1 h, while the concentrations of **2** and **7** were increased systematically. The dwell device gave complete consumptions of **2** at concentrations of 15 and 30 mmol/L, respectively. In contrast, the batch reaction only showed total conversion at 15 mmol/L. At higher concentrations of **2**, the yields dropped gradually.

In all cases examined, the reactions performed in the microreactor gave higher conversions or yields. This superiority can be explained by the larger surface to volume ratio of the dwell device in combination with the better light penetration within the microreactor. These factors ultimately result in higher space−time yields (STYs) for all five acetone-sensitized photodecarboxylations (Figure 4). STYs depended on the reactor geometry and were calculated for reactions with incomplete conversions using the following equation[16]

$$\mathrm{STY} = n/(V_\mathrm{R} \times t)$$

n = amount of phthalimide converted
V_R = reactor volume
t = irradiation time

From direct comparison between the reactors, it is apparent that the STYs are considerably higher in the microreactor than in the Rayonet setup. Of all transformations studied, the photobenzylation to **9** furnished the highest STY.

In conclusion, we have demonstrated that the chosen photochemical transformations of phthalimides proceed more efficiently in a commercially available microreactor than in a conventional Rayonet chamber reactor. The small scales of the microreactions make them advantageous for pharmaceutical research, where only small amounts of materials are required, e.g., in biological screening.[17] Due to the limited amounts of chemicals and solvents consumed, microphotochemistry also falls within the emerging area of *Green Photochemistry*.[18,19] It is hoped that this technology will be rapidly adopted by the chemical and pharmaceutical community.[5b,20]

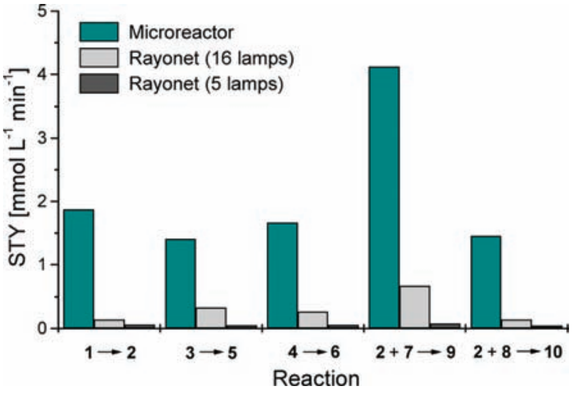

Figure 4. Space−time yields for all five acetone-sensitized photodecarboxylation reactions (microreactor and Rayonet with 16 lamps, 21 min; Rayonet with 5 lamps, 60 min).

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Supporting Information Available: Experimental procedures and NMR spectra of all photoproducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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