



## Photodecarboxylative benzylations of phthalimide in pH 7 buffer: a simple access to 3-arylmethyleneisindolin-1-ones

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### ABSTRACT

Photoadditions of phenylacetates to phthalimide in pH 7 buffer solution give the corresponding benzylation-hydroxyphthalimidines in moderate to high yields of up to 94%. In a micro-structured reactor, higher conversions and purities are achieved. With branched phenylacetates, photoaddition affords diastereoisomeric mixtures with low to moderate *d<sub>e</sub>* values. Subsequent acid-catalyzed dehydration furnishes the corresponding 3-arylmethyleneisindolin-1-ones in good to excellent yields and with high *E*-selectivities. Irradiation of the parent 3-phenylmethyleneisindolin-1-one under oxidative conditions only leads to *cis/trans*-isomerization.

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Arylmethyleneisindolin-1-ones (**I**; Fig. 1) and the structurally related aristolactams (**II**) incorporating the free NH-group represent important classes of pharmaceutically active compounds.<sup>1,2</sup> Consequently, a large number of synthetic pathways to these target compounds have been reported.<sup>3–9</sup> An alternative approach incorporating a photochemical key-step to N-alkylated derivatives of **I** has been developed by Griesbeck and co-workers.<sup>10</sup>

The key-step in the latter approach is the photodecarboxylative (PDC) addition of carboxylates to phthalimides, which represents a versatile alkylation method.<sup>11,12</sup> Multi-gram scale photoreactions have also been realized using a 308 nm excimer light source.<sup>13</sup> A major drawback of the original PDC procedure is the necessity of N-substituents due to an increase in pH during irradiation (final pH ca. 9–10). With ‘free’ phthalimide the initially formed benzylation-hydroxyphthalimidines are therefore obtained as their potassium salts and cannot be isolated easily. Early attempts to convert directly these salts to arylmethyleneisindolin-1-ones (**I**) by an acidic work-up and subsequent extraction furnished complex mixtures with unreacted starting materials. Since the acidity of phthalimide ( $pK_a = 8.3$ ) differs significantly from that of common carboxylic acids ( $pK_a = 5–6$ ), we therefore applied a mixture of acetone and pH 7 buffer solution for the irradiations instead

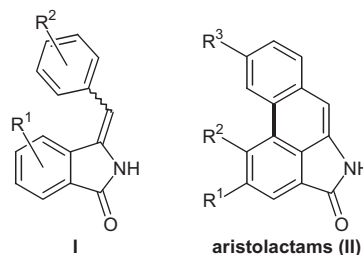
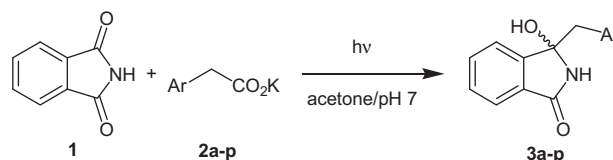


Figure 1. General structure of arylmethyleneisindolin-1-ones and aristolactams.



Scheme 1. Additions of phenylacetates **2a–p** to phthalimide (**1**).

(Scheme 1).<sup>14</sup> When phthalimide (**1**) was irradiated for 2–5 h ( $\lambda = 300 \pm 25$  nm) using this mixture in the presence of three equivalents of phenylacetates **2a–p**, the desired addition products **3a–p** were isolated in yields of up to 94% (Table 1).<sup>15</sup>

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**Table 1**  
Product yields for photodecarboxylative benzylations of **1**

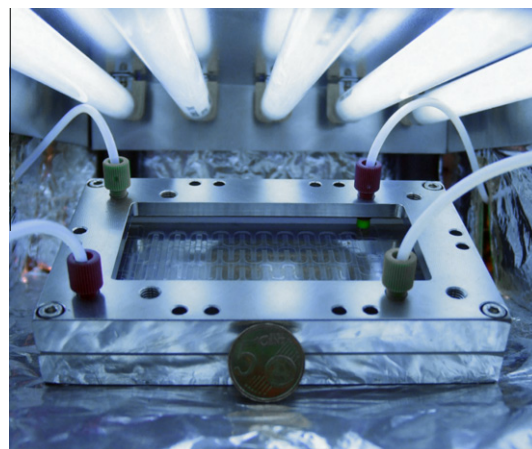
Product	Ar	Conversion <sup>a</sup> (%)	Time (h)	Yield (%)
<b>3a</b>	Ph	100	3	92
<b>3b</b>		100	3	92
<b>3c</b>		100	3	85
<b>3d</b>		100	2	92
<b>3e</b>		100	3	80
<b>3f</b>		100	3	86
<b>3g</b>		100	3	76
<b>3h</b>		100	3	92
<b>3i</b>		100	3	93
<b>3j</b>		100	3	91
<b>3k</b>		15 <sup>b</sup>	3	10 (67) <sup>c</sup>
<b>3l</b>		79 <sup>b</sup>	5	36 (46) <sup>c</sup>
<b>3m</b>		100	3	90
<b>3n</b>		100 <sup>b</sup>	3	93
<b>3o</b>		100	3	54
<b>3p</b>		100 <sup>b</sup>	2	94

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture.<sup>b</sup> Larger amounts of 'simple' PDC product detected.<sup>c</sup> Yield based on conversion.

The progress of the reaction was easily monitored by TLC analysis or by passing the departing nitrogen stream through a saturated barium hydroxide solution until the precipitation of barium carbonate stopped. In most cases, the photoproduct **3** simply precipitated upon concentration of acetone, and could be isolated by filtration. All compounds **3** showed characteristic singlets for the C–OH group at around 90 ppm in their <sup>13</sup>C NMR spectra. In isolated cases the corresponding 'simple' decarboxylation products (–CO<sub>2</sub>H ↔ –H exchange), that is, toluene derivatives, or dibenzyls (Ar–CH<sub>2</sub>CH<sub>2</sub>–Ar) were detected by NMR in the crude products, but no attempt was made to isolate these compounds. Total consumption of phenylacetate due to these competing side reactions may, however, explain the incomplete conversion rates for products **3k** and **3l**.

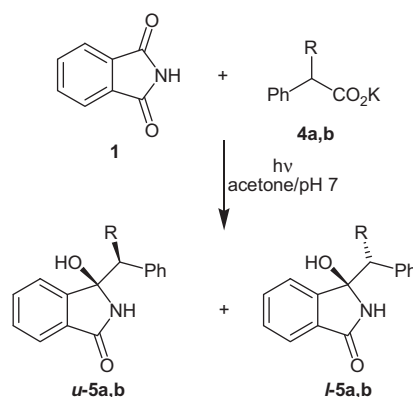
The easy reaction protocol was also applied to 'micro-photochemistry', that is, photochemical reactions in micro-reactors.<sup>16</sup> The syntheses of **3b** and **3e** were used as the model reactions. A commercially available micro-reactor (dwell device, mikrogas), which was placed under a UV panel (Luzchem) fitted with five UVB lamps, was chosen (Fig. 2).<sup>17</sup> Using a residence time of 2 h, improved yields of 97% (**3b**) and 98% (**3e**) were achieved. The thin layer within the micro-channel plate (0.5 mm) obviously favors a better penetration of the solution by light.

The PDC reactions involving branched carboxylates **4a** and **4b** resulted in *like*- and *unlike*-mixtures of **5a** and **5b** in high yields

**Figure 2.** Micro-reactor (dwell device, mikrogas) under a UV exposure panel (Luzchem). A 5 Euro-cent coin is used to illustrate the size of the reactor.

(Scheme 2). Complete conversions were achieved after 2 h and 4 h of irradiation. In both cases, two complete sets of signals were observed in the NMR spectra which were assigned to the individual diastereoisomers. The diastereoisomeric ratios (*de*) were determined by integration of baseline separated signals in the <sup>1</sup>H NMR spectra. Stereoselectivities were low with 13% for **5a** and moderate with 33% for **5b** (Table 2), respectively. An assignment of the diastereoisomers was not possible.

The arylmethyleisindolin-1-ones **6a–p** were easily available in moderate to high yields of 41–97% via acid-catalyzed dehydration in dichloromethane (Scheme 3; Table 3).<sup>18</sup> In almost all cases, high *E*-selectivities were obtained as confirmed by <sup>1</sup>H NMR spectroscopy. The olefinic proton of the *Z*-isomer is strongly influenced by the shielding effect of the aromatic ring, whereas no such effect was observed in the case of the *E*-isomer.<sup>3a</sup> Under the standard hydrolysis conditions, the acetoxy-substituted derivatives **6d**, **i**, and **k** underwent partial hydrolysis of the ester group (ca. 30%). Thus, complete hydrolysis to the corresponding phenolic compounds was enforced by heating the irradiation products **3d**, **i**,

**Scheme 2.** Additions of branched phenylacetates **4** to phthalimide (**1**).**Table 2**  
Product yields and *de* ratios for photodecarboxylative additions of **4** to **1**

Product	R	Time (h)	<i>de</i> <sup>a</sup> (%)	Yield (%)
<b>5a</b>	Me	2	13	97
<b>5b</b>	Et	4	33	94

<sup>a</sup> *de* ratios were determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture.

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