



## Photochemical synthesis of cyclic peptide models from phthalimido acetamides and phthaloyl dipeptide esters

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### ABSTRACT

The photochemistry of several phthalimido acetamides and phthaloyl dipeptide esters has been investigated. Their photocyclization ability strongly depended on the substitution pattern of the amide linker group. While secondary amide-derived starting materials were largely unreactive, the corresponding tertiary amide-linked derivatives furnished the desired cyclic peptide model compounds in acceptable to good yields (41–80%). The structurally related ester-linked model derivatives also remained unreactive upon irradiation. Preferential hydrogen-abstraction from the *E*-*cis*-substituent is suggested to explain the observed differences in cyclization ability.

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Due to their biological importance, the photochemistry of amino acids and peptides has been intensively studied over the past decades.<sup>1</sup> Photoinduced electron transfer cyclization reactions of their related *N*-protected phthaloyl derivatives have likewise been widely explored.<sup>2</sup> In contrast, the photocyclization of phthalimido acetamides by hydrogen-abstraction are rather rare.<sup>3</sup> The photochemistry of a series of phthalimido acetamides and phthaloyl dipeptide esters, both readily accessible by standard peptide coupling,<sup>4</sup> was thus explored.

To find the most suitable solvent system, the photocyclization of phthaloyl dipeptide ester **1a** was selected as a model reaction (Scheme 1; Table 1). Photoirradiation for 3 h with 300 nm light furnished regioisomer **2a** as the sole product. The presence of water had a significant impact on the conversion rates, which increased with increasing amounts of water. Previous studies have shown that the presence of water alters the photophysical properties through hydrogen-bonding and subsequently enhances photochemical reactivity.<sup>5</sup> No significant differences between acetone and acetonitrile mixtures were found in terms of conversion rates, although acetone is known to function as a triplet-sensitizer, while irradiation in acetonitrile operates *via* direct excitation.<sup>6</sup> Due to the

increased solubility of the starting material and product in acetone and the reduced toxicity of this co-solvent,<sup>7</sup> all subsequent irradiations were performed in a 1:1 acetone/water mixture.

The secondary amide linked phthalimido acetamides **4a** and **4b** underwent partial photodecomposition and remaining starting materials were recovered in 88% and 85% yield, respectively, after exhaustive irradiation for 48 h (Scheme 2). The rigid *Z*-*trans*-conformation and the likely formation of a solvent shell around the secondary amide linker in the starting materials **4a** and **4b**, in combination with the required *E*-*cis*-conformation in the prospective products **5a** and **5b** prevent successful cyclization.<sup>8–10</sup> Compound **5a** is also known to be unstable and decomposes by polymerization.<sup>5a,11</sup>

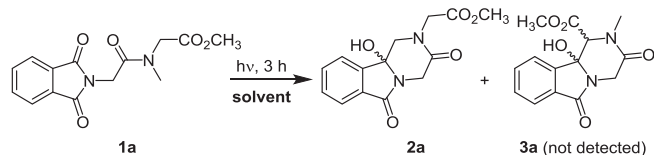
In contrast, tertiary phthalimido acetamides underwent successful cyclization reactions. A similar conformationally controlled photocyclization of secondary vs. tertiary aryl enamides has been reported by Rigby and co-workers.<sup>12</sup> Irradiation times varied significantly depending on the *N*, *N*-disubstitution pattern and amino acid linker (Scheme 3; Table 2).

The symmetrical glycine-derived tertiary phthalimido acetamides **6a–e** furnished the desired cyclic peptide models **7a–e** in moderate to good yields (51–75%).<sup>13</sup> The phthalimides **6b**, **6d**, **6e** and **6i** furthermore resulted in the formation of diastereoisomeric mixtures. Likewise, the branched  $\alpha$ -amino acid containing starting materials **6f** and **6g** yielded the corresponding cyclization products

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**Scheme 1.** Solvent study using phthaloyl dipeptide ester **1a**.

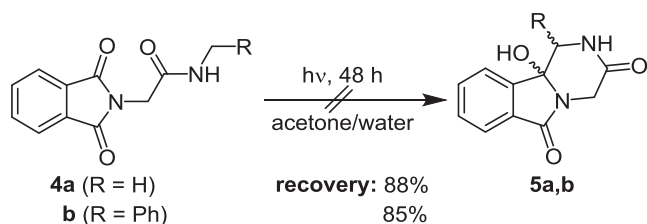
**Table 1**  
Crude product compositions for the photocyclization of **1a** in different solvent systems ([**1a**] = 12.5 mM).

Entry	Solvent system (vol%)	Composition (%) <sup>a</sup>		
		<b>1a</b>	<b>2a</b>	<b>3a</b>
<b>a</b>	acetone (100)	95	5	n.d. <sup>b</sup>
<b>b</b>	acetone/water (83:17)	69	31	n.d. <sup>b</sup>
<b>c</b>	acetone/water (50:50)	20	80	n.d. <sup>b</sup>
<b>d</b>	acetonitrile (100)	94	6	n.d. <sup>b</sup>
<b>e</b>	acetonitrile/water (83:17)	74	26	n.d. <sup>b</sup>
<b>f</b>	acetonitrile/water (50:50) <sup>c</sup>	17	83	n.d. <sup>b</sup>

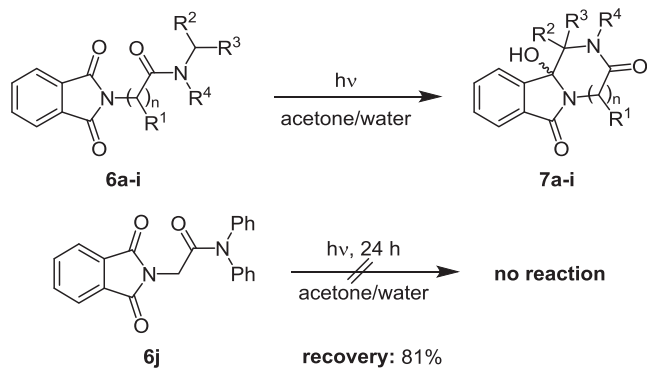
<sup>a</sup> After 3 h irradiation in a test tube (18 mL) as determined by <sup>1</sup>H NMR spectroscopic analysis of the crude mixture (±3%).

<sup>b</sup> n.d. = not detected (<3%).

<sup>c</sup> Solution turbid during irradiation.



**Scheme 2.** Attempted photocyclization of secondary phthalimido acetamides **4a** and **4b**.



**Scheme 3.** Photocyclization of symmetrical tertiary phthalimido acetamides **6a-j**.

**Table 2**  
Experimental details for the photocyclization of symmetrically substituted tertiary phthalimido acetamides **6a-j** (c = 10 mM).

Entry	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Time (h)	Diastereoisomeric ratio (%) <sup>a</sup>	Yield <b>7</b> (%)
<b>a</b>	1	H	H	H	CH <sub>3</sub>	15	—	51
<b>b</b>	1	H	CH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	24	84:16	58
<b>c</b>	1	H	CH <sub>3</sub>	CH <sub>3</sub>	<i>i</i> -Pr	36	—	57
<b>d</b>	1	H	Ph	H	CH <sub>2</sub> Ph	15	65:35	66
<b>e</b>	1	H	H	(CH <sub>2</sub> ) <sub>3</sub>	—	7	50:50	75
<b>f</b>	1	( <i>S</i> )-CH <sub>3</sub>	H	H	CH <sub>3</sub>	18	54:46	45
<b>g</b>	1	( <i>rac</i> )-Ph	H	H	CH <sub>3</sub>	18	57:43	41
<b>h</b>	2	H	H	H	CH <sub>3</sub>	7	—	53
<b>i</b>	2	H	CH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	7	80:20	49
<b>j</b>	1	H	Ph	Ph	—	24	—	n.r. <sup>b</sup> (81% <sup>c</sup> )

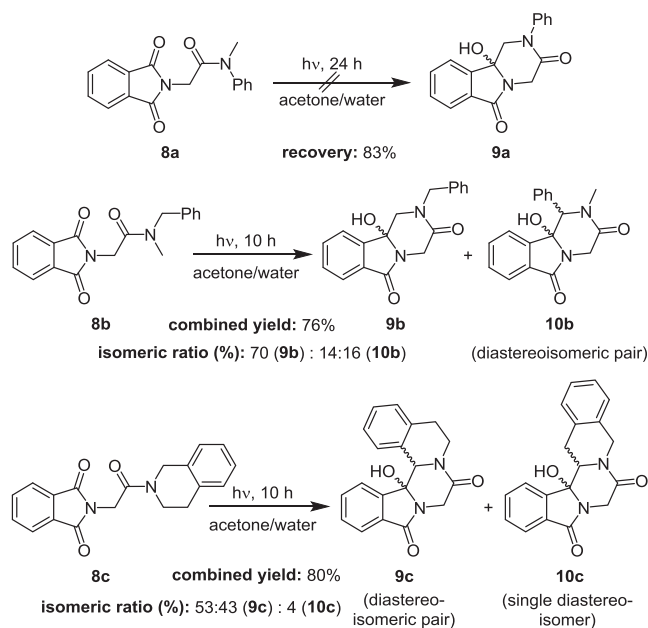
<sup>a</sup> Diastereoisomeric ratio determined by <sup>1</sup>H NMR spectroscopic analysis of the crude mixture (±3%).

<sup>b</sup> n.r. = no reaction.

<sup>c</sup> Recovered starting material.

**7f** and **7g** as diastereoisomeric mixtures in 45% and 41% yield, respectively. No competing hydrogen-abstraction from the amino acid side-chain was observed for the alanine-derived **6f** (within the detection limit of NMR spectroscopy).<sup>14</sup> The β-alanine-based phthalimido acetamides **6h** and **6i** likewise cyclized successfully and gave the tricyclic compounds **7h** and **7i** in acceptable yields of 53% and 49%, respectively. In contrast, longer phthalimido acetamides (n>2) are known to undergo hydrogen-abstraction from the internal γ-position.<sup>3a</sup> For all cyclization products, the newly formed C—OH group was observed as a characteristic singlet between 80 and 90 ppm in the <sup>13</sup>C NMR spectra. Due to the absence of a suitable abstractable hydrogen atom, the *N,N*-diphenyl derivative **7j** remained largely photostable and was recovered in 81% yield.

Three asymmetrically substituted tertiary phthalimido acetamides **8a–c** were furthermore investigated (**Scheme 4**) and a correlation between photocyclization efficiency and amide conformations was again noted.<sup>8,15</sup> Amide **8a** presumably exists exclusively in the *E*-*cis*-conformation due to favourable CH-π-interactions.<sup>16</sup> As a result, compound **8a** remained largely unreactive even after prolonged irradiation for 24 h and was recovered in 83% yield. In contrast, the tertiary amides **8b** and **8c** populate both amide conformers and irradiation gave the regioisomeric cyclization products **9/10b** and **9/10c**, respectively.



**Scheme 4.** Photocyclization of asymmetrical tertiary phthalimido acetamides **8a–c**.

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