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A Photochemical Route for Efficient Cyclopeptide Formation with a Minimum of Protection and Activation Chemistry

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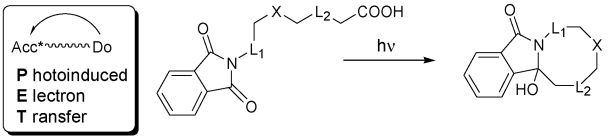
Synthetic cyclic oligopeptides can depict reactive conformational motifs of bioactive oligopeptides[1] and are thus intensively investigated as peptidomimetica,[2] as pharmaceutically active low-molecular weight analogues[3] or as artificial arrays with defined nanostructures.[4] Synthetic routes to these target structures are numerous, taking advantage of the highly developed techniques in peptide synthesis.[5] Due to the fact that these compounds are macrocyclic polylactams, the fundamental restrictions in (thermal) macrocyclization chemistry have to be considered.[6] Photochemical macrocyclizations constitute an alternative class of reactions which often are controlled by the excited-state rather than ground-state properties.[7] Following our studies on the intramolecular photodecarboxylation of ω-phthalimido alkyl carboxylates[8] and its intermolecular version[9] in aqueous media, this concept was also investigated as a general route to macrocyclic products (Scheme 1).[10] In fact, the synthesis of medium- and macrocyclic amines,[11] lactones,[12] polyethers,[11] thioethers,[13] as well as cycloalkynes[14] was realized.[15]

Scheme 1. Photoinduced Electron Transfer Decarboxylation/ Cyclization Reaction of ω-Phthalimido Alkylcarboxylates with Divergent Linker Chains (L_1, L_2) And Spacer Functional Groups X

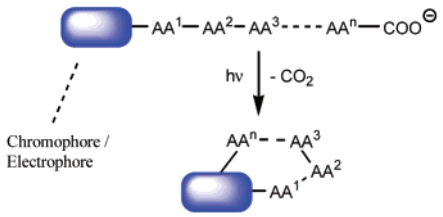


To further explore the scope of this reaction and to develop a flexible route to cyclopeptides using the photodecarboxylation/ cyclization protocol, we investigated a series of C-unprotected di- and tripeptides activated by the N-terminal phthalimide functionality. The basic concept is shown schematically for a cyclic peptide incorporating a tripeptide motif in Scheme 2: a chromo-/electrophore which is N-terminal AA^1-linked to an oligopeptide chain serves as excited-state electron acceptor and oxidizes the C-terminal carboxylate group with subsequent extrusion of CO_2 and cyclization.

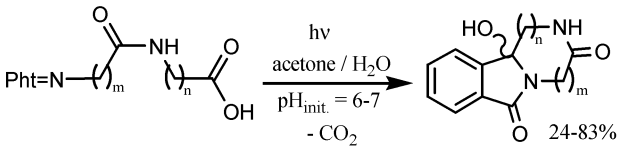
In preliminary studies we, however, did not succeed in cyclizing the phthalimide substrate of the Gly-Gly dipeptide,[11] indicating that hydrogen bonding between the imido carbonyl groups and a *proximate* amide NH might deactivate the electron-transfer reactivity and interfere with the cyclization step. When this hydrogen bond was inhibited, as for example in *N*-phthaloyl Ala-Pro, photocyclization occurred in moderate yields.[16]

As primary spacers AA^1, unbranched ω-amino acids were applied with increasing $(CH_2)_n$ spacer lengths of $n = 1, 2, 3, 5, 10$, and 11. As the C-terminal amino acid we used glycine, sarcosine (Sar), β-alanine (βAla), ϵ-aminocaproic (ϵAca), and 11-aminoundecanoic

Scheme 2



Scheme 3



acid (Auda). The photolyses ($\lambda = 300$ nm) were performed in water/acetone mixtures at initial pH_{init} values of 6−7. Analogous to that in the Ala-Pro derivative,[16] protection of the primary amide group restored the cyclization activity, and already the sarcosine substrate Gly-Sar gave the six-membered lactam in 53% yield. From these first trials we suspected that a secondary amide is *not applicable* as primary functional group in the peptide tether due to the hydrogen-bonding hypothesis.[11,17] Photochemical reactivity was, however, recovered by using longer secondary spacer chains (Scheme 3); the Gly-βAla couple gave solely the decarboxylation/ hydrogen transfer product, but longer amino acids as second components also restored the cyclization activity. For example, the Gly-ϵAca substrate gave the 10-membered product in 69% yield. Thus, hydrogen-bonding deactivation can be overwritten by using the appropriate substitution pattern.

Another way to improve the photocyclization efficiency is to increase of the chain lengths of the primary amino acid tether; whereas the βAla-Gly substrate gave only 24% of the corresponding seven-membered lactam, the βAla-βAla couple gave the eight-membered lactam already in 32% yield, and the ϵAca-βAla substrate resulted in the 11-membered lactam in 55% yield.[18]

The lactams **1a**,**b** were characterized by X-ray structure analyses (Figure 1). The product **1a** from the βAla/γ-aminobutyric acid pair (ring size: 9) has the *E*-amide configuration; in the larger ring **1b** (ring size: 10) from the Gly-ϵAca pair the amide configuration switched to *Z*.[19]

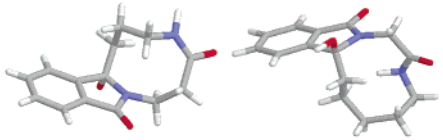


Figure 1. Structures of the products **1a**,**b** in the crystal.

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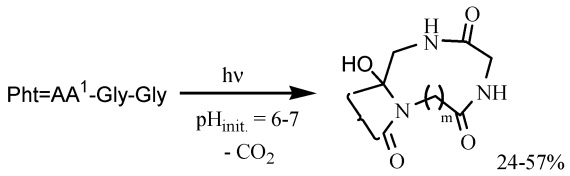
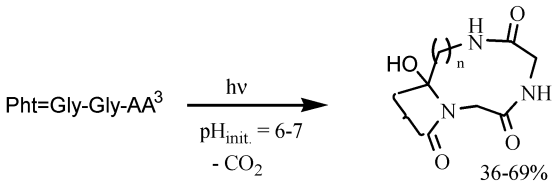
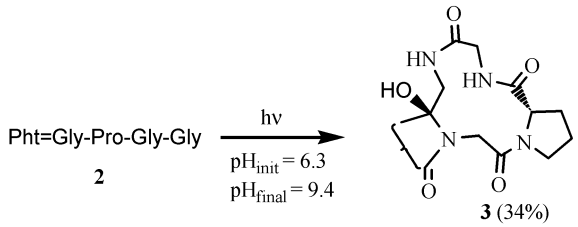
Scheme 4



Scheme 5



Scheme 6



The chain elongation concept proved to be also successful for tripeptide substrates; the photocyclization path was still active when longer amino acid spacers were used as the first (i.e., AA^1-Gly-Gly, Scheme 4) or third (i.e., Gly-Gly-AA^3, Scheme 5) component. The triglycine derivative[20] resulted in decarboxylation and unselective photodecomposition. Elongating the primary linker chain stepwise increased the cyclization efficiacy: from βAla ($m = 2$, 24%), to ϵAca ($m = 5$, 42%) and Auda ($m = 10$, 57%). All experiments were conducted under the same substrate concentration conditions (10 mM), and thus dilution effects cannot be responsible for the high yields of photocyclization products. Likewise, the diglycine-linked tripeptides Pht═GlyGlyAA^3 became reactive for chain-elongated amino acids as the internal tethers. In this series, the βAla substrate resulted solely in photosolvolysis. Photocyclization was observed with $AA^3 = \gamma$-aminobutyric acid ($n = 3$, 36%), ϵAca ($n = 5$, 51%), and Auda ($m = 10$, 69%). Diglycine-containing cyclopeptides are thus available in flexible chain modifications which appear important for the design of new β-turn mimetica.[21]

One step further in this protocol, the *N*-phthaloyl derivative of the tetrapeptide Gly-Pro-Gly-Gly (**2**) was synthesized by standard coupling and deprotection procedures from *N*-phthaloyl glycine, proline, and diglycine in 68% yield. The irradiation of this substrate was performed in a 4:1 water/acetone mixture with 0.5 equivalents of potassium carbonate and resulted in the 12-membered cyclopeptide **3** in 34% yield (Scheme 6). A control (dark) experiment showed that the pH is constant over the reaction time, whereas photolysis led to a substantial increase in pH. Consequently, continuous pH control served as a useful analytic tool to follow the progress and to identify the chemoselectivity of the reaction.[22] Whereas photosolvolysis or solvolysis in general resulted in a slight decrease in pH (due to the formation of a phthalamide acid), photocyclization went parallel with a strong increase in pH. The latter effect is due to the charge shift from the carboxylate anion to give an alkoxide which leads to an increase in OH^- concentration.[23]

In summary, this protocol represents a new route for cyclopeptide formation with a minimum of protection and activation chemistry and is applied for more complex structures in ongoing work. These preliminary results suffer from medium chemical yields due to substantial hydrolysis at high pH, a competing process which can be suppressed using buffered aqueous conditions.[18]

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Supporting Information Available: Details of the photocyclization reactions, NMR-spectroscopic data of selected photocyclization products, pH reaction profiles, and X-ray crystallographic data of **1a** and **1b** (PDF). An X-ray crystallographic file of **1a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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