Photochemical Synthesis of N-Substituted 3-Hydroxy-2-pyrrolidinones

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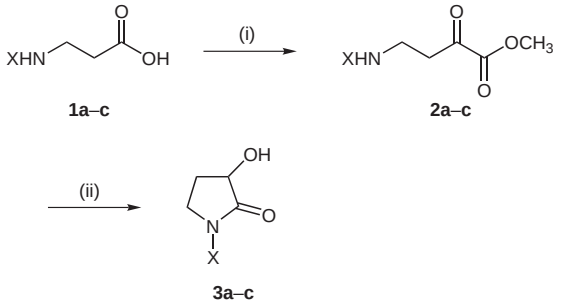
Abstract: A new three-step synthesis to 3-hydroxy-2-pyrrolidinones starting from β-amino acids has been developed. The key step is a novel reductive photocyclization.

Key words: 3-hydroxy-2-pyrrolidinone, 4-hydroxypyroglutamic acid, α-keto ester, β-amino acid, reductive photocyclization

Hydroxy-substituted pyrrolidinones are components of many natural products, which exhibit valuable pharmacological properties.[1] For instance, the N-substituted derivatives are of interest for the treatment of brain disorders or as cognition activators.[2] Due to their low toxicity they have attracted much attention in current pharmaceutical research.[3] Syntheses of the racemic core as well as enzymatic and stereoconservative preparations have been described.[4] Herein we present a novel three-step synthesis of N-substituted 3-hydroxy-2-pyrrolidinones and 4-hydroxypyroglutamic acids starting from β-amino acids with a novel reductive photocyclization as the key reaction step.

Following the Wasserman methodology,[5] β-alanine derivatives **1a**–**c** were coupled with (cyanomethylene)triphenylphosphorane yielding cyano keto phosphoranes. Oxidative cleavage with ozone led to α,β-diketo nitriles, which were converted into the α-keto methyl esters **2a**–**c** (Scheme 1). Photolysis of the keto esters gave the 3-hydroxy-2-pyrrolidinones **3a**–**c** in 46% to 62% yields (Table 1).[6]

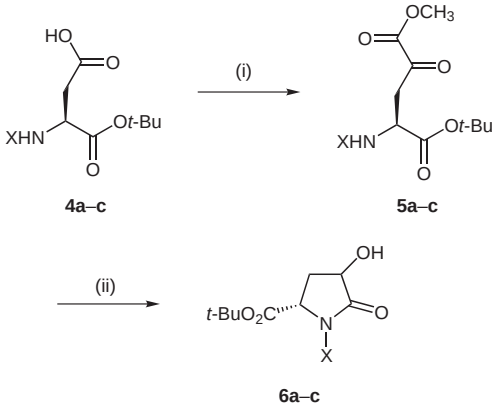


Scheme 1 *Reagents and conditions*: (i) a) Ph_3P=CHCN, EDC, DMAP, CH_2Cl_2, 0 °C, 18 h; b) O_3, CH_2Cl_2, MeOH, –78 °C, 1 h; (ii) hν, CH_2Cl_2, 20 °C, 14 h.

Table 1 Irradiation of α-Keto Methyl Esters **2a**–**c**

Educt	X	Product	Yield (%)
2a	Boc	**3a**	62
2b	*Z*-Gly	**3b**	46
2c	*Z*-Ala	**3c**	62

The carboxylic acid side chains of N-terminal substituted aspartic acids **4a**–**c** were modified in the same way leading to α-keto methyl ester derivatives **5a**–**c** (Scheme 2). After irradiation of **5a**–**c** the N-substituted 4-hydroxy-pyroglutamic acids **6a**–**c** were obtained in good to excellent yields as 1:1 mixtures of diastereomers (Table 2). Only a few other synthetic pathways to 4-hydroxy-pyroglutamic acids have been described, and these start either from nitrones[7] or from 4-hydroxy prolines.[8]



Scheme 2 *Reagents and conditions*: (i) a) Ph_3P=CHCN, EDC, DMAP, CH_2Cl_2, 0 °C, 18 h; b) O_3, CH_2Cl_2, MeOH, –78 °C, 1 h; (ii) hν, CH_2Cl_2, 20 °C, 14 h.

Table 2 Irradiation of α-Keto Methyl Esters **5a**–**c**

Educt	X	Product	Yield (%)
5a	Boc	**6a**	91
5b	Boc-Gly	**6b**	63
5c	Boc-Pro	**6c**	61

This novel photocyclization reaction (**2** → **3** and **5** → **6**) provides an easy access to the 3-hydroxy-2-pyrrolidinone and 4-hydroxypyroglutamic acid building blocks, especially to the pharmaceutically interesting N-substituted

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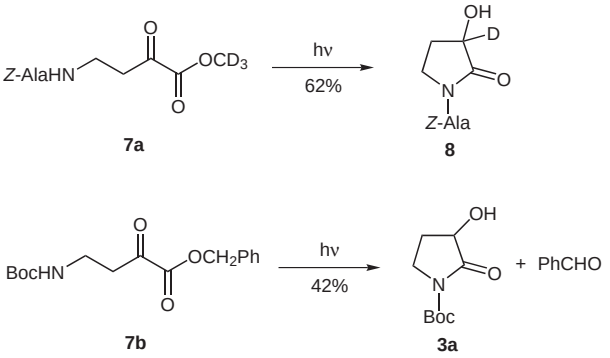
derivatives.[2,3] Enantiopure pyrrolidinone derivatives could be prepared through esterification with a chiral acid, and separation of the diastereomers.[9]

The cyclization reactions (**2** → **3** and **5** → **6**) are surprising, because a reduction of the ketone group in the educts to the alcohol function in the photoproducts has occurred during the photolysis. To elucidate the mechanism of this, to our knowledge, new reductive photocyclization reaction, additional experiments were carried out. Photocyclization of ketoester **7a**, which is perdeuterated at the methoxy group, led to the pyrrolidinone **8** with a deuterium at C-3 (Scheme 3). This experiment was carried out in CH_2Cl_2; experiments with undeuterated α-ketoesters **2** in CD_2Cl_2 led to undeuterated cyclization products **3**. Thus, the ring deuterium in **8** has to come from the OCD_3-group of **7a**. As the ketone is reduced by hydrogen transfer from the alcohol group of the ester, we assumed that this alcohol becomes oxidized during the photocyclization. In order to check this, the benzyl ester **7b** was photolyzed, which led not only to the cyclization product **3a** but also to benzaldehyde, the oxidation product of benzyl alcohol (Scheme 3).

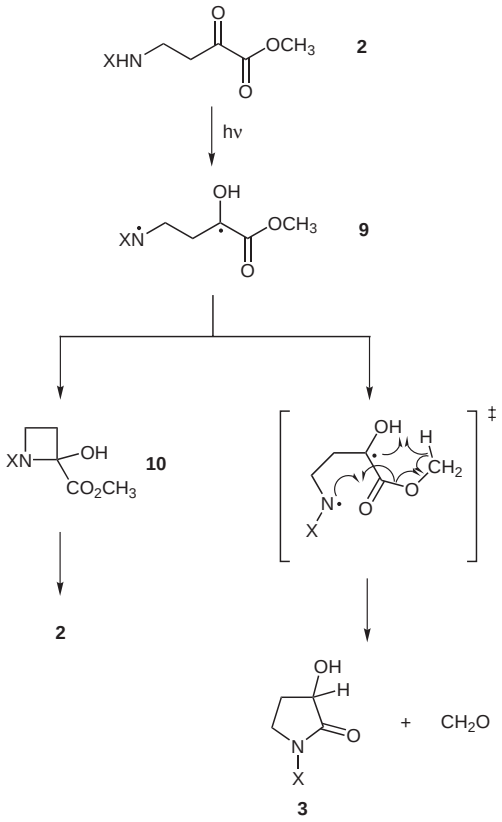


Scheme 3

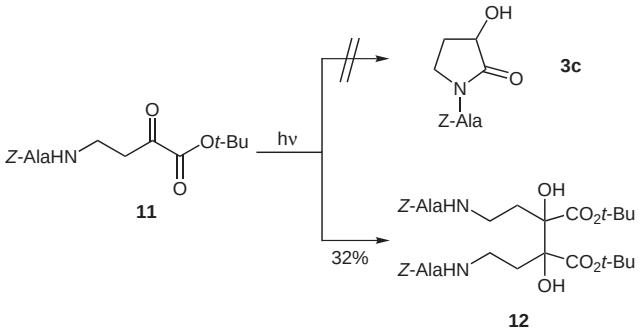
A possible mechanism that could explain these observations is the formation of diradical **9** as reactive intermediate, which could either react back to the starting material **2** via the strained hemiaminal **10**, or undergo a cyclization and intramolecular H-atom transfer yielding pyrrolidinone **3** (Scheme 4).

According to this reaction mechanism a *tert*-butyl ester should not lead to the hydroxypyrrolidinone. We demonstrated this by photolysis of the α-keto ester **11**, which did not form the cyclization product **3c** but yielded dimer **12** (Scheme 5). This dimerization is in accord with diradical **9** as intermediate, which dimerizes if the concerted cyclization/H-transfer is not possible.

In summary we present a new and short synthesis of N-substituted 3-hydroxy-2-pyrrolidinones and 4-hydroxypyroglutamic acids. The key step is a reductive photocyclization, which is to our knowledge a new reaction type.



Scheme 4 Possible mechanism for the reductive photocyclization.



Scheme 5 Irradiation of α-keto *tert*-butyl ester **11**.

Acknowledgment

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(6) **General Irradiation Procedure.**
The α-keto ester modified β-amino acids (**2** or **4**) were dissolved in 200 mL CH_2Cl_2 in a 250 mL pyrex flask. The solution was degassed with argon during 30 min and irradiated with a cooled 180 W mercury high-pressure lamp, which was immersed in the solution. After the photoreaction was finished the solvent was evaporated, and the residue purified by column chromatography yielding the pure 3-hydroxy-2-pyrrolidinones (**3**) or the 4-hydroxypyroglutamic acids (**6**).
Spectroscopic data for **3a** as an example: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (s, 9 H), 1.96 (dtd, *J* = 12.4, 10.5, 9.1 Hz, 1 H), 2.44 (dddd, *J* = 12.4, 8.2, 6.6, 1.5 Hz, 1 H), 3.31 (br s, 1 H), 3.52 (ddd, *J* = 10.9, 10.5, 6.6 Hz, 1 H), 3.83 (ddd, *J* = 10.9, 9.1, 1.5 Hz, 1 H), 4.37 (dd, *J* = 10.5, 8.2 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.1 (CH_2), 28.1 (CH_3), 42.2 (CH_2), 70.7 (CH), 83.6 (C), 149.9 (C), 174.8 (C). MS (ESI): *m/z* (%) = 425 (29) $[2 M + Na]^+$, 224 (100) $[M + Na]^+$, 168 (48) $[M - t\text{-Bu} + Na]^+$.

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