





## Regio- and Stereoselective 1,6-Photocyclization of Aspartic Acid-Derived Chiral γ-Ketoamides[1]

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**ABSTRACT:** Chiral  $\alpha$ -acylamino  $\gamma$ -ketoamides 2 were irradiated and regio-isomeric 1,6-cyclization products 3 and 4 obtained in high yields. Symmetrically N,N-disubstituted substrates 2a,b reacted diastereoselectively to give the all-cis products 3a,b in high yields. High 1,3-asymmetric induction was also observed for the unsymmetrically N,N-disubstituted 2d and 2e. The stereoselectivity of these reactions is discussed in terms of SOC-controlled spin inversion geometries. © 1999 Elsevier Science Ltd. All rights reserved.

In a long-term research project, we are investigating the photochemical behaviour of N- and C-activated amino acids and peptide model substrates. The motivation for these studies is to achieve a better understanding of energy and electron transfer processes in oligopeptides. On the other hand, photochemical transformations of enantiomerically pure amino acids from the pool of chiral natural compounds serves also as a new and only inadequately used pathway to interesting target molecules. The N-terminal activation has been intensively studied by us in the last years.[2] Introduction of chromophors at the carbon terminus has been shown to be more problematic. We have recently used the pyruvate and the benzoyl group in order to generate substrates for highly stereoselective Yang cyclizations.[3,4]

In order to study also remote hydrogen activation reactions and their cyclization stereocontrol, we have synthesized chiral  $\gamma$ -ketoamides from aspartic acid. The Friedel-Crafts acylation of arenes by N-acylated aspartic acid anhydrides 1 can be performed with divergent regioselectivity to give  $\gamma$ -ketoacids[5] which subsequently were coupled by the DCC/DMAP method with sarcosine methyl ester or with other achiral amines to give the starting materials 2 (equation 1). As already reported by Wessig and coworkers[6] for achiral  $\gamma$ -ketoamides, unsymmetrically N,N-disubstituted compounds exist as two slow interconverting amide rotamers. The sterically less demanding methyl group (R³) in 2c-f is E-located in the major conformer as determined by NOE enhancements and the CC long-range coupling pattern.

In order to investigate the photochemical reactivity of 2a-f in the absence of external stabilizing interactions we performed the photolyses in benzene. Substrate 2c (PHT = N, N-phthaloyl) which combines phthalimide and benzoyl chromophor was photostable even after prolonged irradiation. This confirmed our earlier assignments in that the lowest phthalimide  $\pi\pi^*$ -triplet is not active in homolytic hydrogen activation and benzoyl triplets serve as effective sensitizers to generate the triplet excited imides. [7,8]

In contrast to 2c, the N-monoacylated substrates were reactive and gave 1,6-cyclization (and no fragmentation) products in high yields. The substrates with a symmetrically disubstituted amide group 2a,b resulted in only one diastereoisomer (in the detection limit of the <sup>1</sup>H NMR integration) 3a and 3b, respectively (equation 2).

Ph  
AcHN
$$R^3$$
 $hv$ 
 $PhH$ 
 $d.r. > 97:3$ 
 $AcHN$ 
 $R^4$ 
 $AcHN$ 
 $R^5$ 
 $R^5$ 
 $R^4$ 
 $R^5$ 
 $R^5$ 
 $R^6$ 
 $R^6$ 
 $R^6$ 
 $R^6$ 
 $R^6$ 
 $R^6$ 
 $R^6$ 
 $R^6$ 
 $R^6$ 

The characteristic high-field shifted <sup>1</sup>H NMR signals[9] of the methoxycarbonyl group at C-2 indicated anisotropic effects due to the (cis) phenyl group in the pipecolic acid derivative 3a (75% yield). With the respect to the relative configurations at C-2 and C-3, however, these results contradicted the assignments

published recently by Wessig and coworkers.[6] Thus, we performed NOE measurements for 3a at different temperatures. The proton signal for the hydroxy group overlapped with the 5-H signal at room temperature and was not available for NOE experiments. At -42°C the 3-OH group was low-field shifted to 6.4 ppm and could be used for saturation experiments. Strong NOE enhancements were detected from the hydroxy group to H-2 and H-5, likewise from H-5 to both H-4 and H-2. Thus, the relative configuration is all-cis with respect to ester-,

phenyl-, and amide substituent at C-2, C-3 and C-5. Thus, simple diastereoselectivity is pronounced which originates from the radical-radical coupling step in addition to a high degree of induced diastereoselectivity which might result from conformational control of the spatial orientation of either the radical center at C-2 or C-3 during the approach of the two radical centers. A plausible answer could be drawn from the investigation of the N-methylated substrates 2d and 2e.

The unsymmetrically N,N-disubstituted substrates 2d and 2e efficiently gave 1:3 mixtures of the two regioisomeric  $\delta$ -lactams 3d,4d and 3e,4e, respectively (equation 3). The major regioisomers derived from  $\epsilon$ -hydrogen abstraction from the N-methyl group, thus approximately depicting the ground state conformational situation (vide supra). Both regioisomers were isolated diastereoisomerically pure (in the detection limit of the <sup>1</sup>H NMR integration). Thus, analogous to the Yang cyclization of aromatic  $\alpha$ -acetylamino ketones,[3] the amide substituent controls the stereochemical situation of the 1,n-biradical combination step.

Ph HO Ph HO Ph HO Ph HO Ph HO CH<sub>2</sub>COOMe 
$$\frac{hv}{PhH}$$
 R<sup>1</sup>HN CH<sub>3</sub> + R<sup>1</sup>HN CH<sub>2</sub>E (3)

2d-f 25:75 4d-f

E = COOMe d.r. > 97:3 (for 4d,e) d.r. = 76:24 (for 4f)

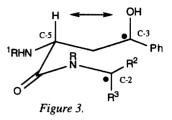
The relative configurations of products 4d,e were determined by NOE spectroscopy and CH-coupling analyses. The relative configuration of products 3d,e were assigned from the characteristic proton shifts of the ester methyl group which showed strong anisotropic effects due to the cis-phenyl group ( $\alpha$ -hydrogens were not significantly influenced) similar to those of 3a.[9] The N-trifluoroacetyl substituted substrate 2f gave a 3:1 mixture of diastereoisomeric products 4f. The regioisomer 3f was again detected only as minor component.

Conclusion. The regioselectivity of the photocyclization of substrates 2d-f is determined by the ground state conformer equilibrium situation. The concept of hydrogen bonding interactions in determining photocyclization stereoselectivities was described by the Wessig and the Giese group recently.[10-12] In contrast to these reports and to Yang cyclizations,[4] intramolecular hydrogen bonding seems not to determine the stereochemistry of the reactions reported herein, neither the configuration of the stereogenic center C-5 nor the relative configurations of the newly formed stereogenic centers C-3 and C-2.

In comparison with 1,4-biradicals, the less strained triplet 1,6-biradical can adopt a chair-like conformation which is preset for spin inversion and ring closure. In order to favor efficient intersystem-crossing of the triplet biradical, orthogonal p-porientation has been postulated to be an important contribution.[13,14] The asymmetric induction which was observed for the  $\delta$ -lactams 3a-f is probably due to this effect because the

strong steric phenyl (C-3) - ester (C-2) interaction is circumvented in the orthogonal biradical conformation. The assumption of a mechanistic scenario where intersystem crossing is directly coupled with the formation of a new carbon-carbon bond is in agreement with recent theoretical work on triplet biradical spin

inversion.[15,16] Yet, this effect has not been described for 1,n (n>4) biradical intermediates. The photocyclization of the unsymmetrically N,N-disubstituted substrates 2d and 2e revealed that additionally to the simple diastereoselectivity the configuration of the hydroxysubstituted benzyl-radical is controlled by the acylamino substituent at position C-5. This effect leads to the pronounced differentiation between the two diastereotopic faces of the benzylradical. Assuming a chair-like structure for the



approach of the two radical centers, 1,3-diaxial interactions disfavor a pseudo-axial phenyl substituent and thus determine the stereochemistry at C-3.

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