

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

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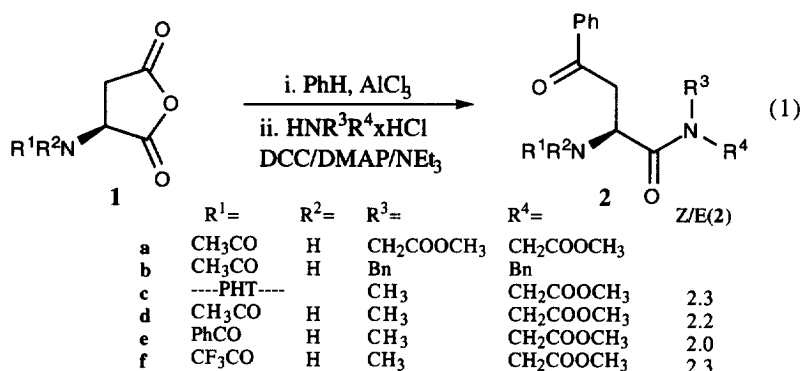
ABSTRACT : Chiral α -acylamino γ -ketoamides **2** were irradiated and regioisomeric 1,6-cyclization products **3** and **4** obtained in high yields. Symmetrically N,N -disubstituted substrates **2a,b** reacted diastereoselectively to give the all-cis products **3a,b** in high yields. High 1,3-asymmetric 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.

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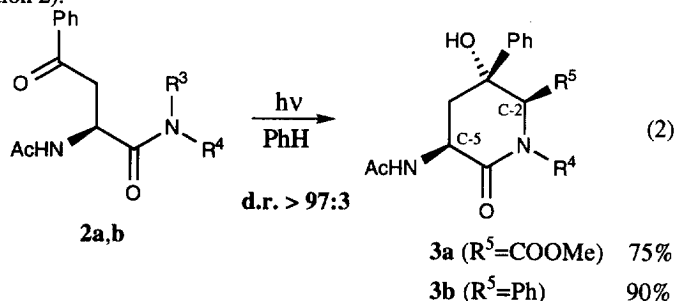
In a long-term research project, we are investigating the photochemical behaviour of N - and C -activated amino acids and peptide model substrates. The motivation for these studies is to achieve a better understanding of energy and electron transfer processes in oligopeptides. On the other hand, photochemical 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 γ -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 γ -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 γ -ketoamides, unsymmetrically N,N -disubstituted compounds exist as two slow interconverting amide rotamers. The sterically less demanding methyl group (R^3) 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]

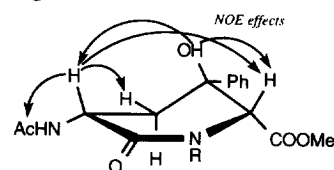


In contrast to **2c**, the N-monoacylated substrates were reactive and gave 1,6-cyclization (and no fragmentation) products in high yields. The substrates with a symmetrically disubstituted amide group **2a,b** resulted in only one diastereoisomer (in the detection limit of the ¹H NMR integration) **3a**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



The characteristic high-field shifted ¹H NMR signals[9] of the methoxycarbonyl group at C-2 indicated anisotropic effects due to the (cis) phenyl group in the pipercolic 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**.

Figure 1.



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 benzylic 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 benzylic radical. 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.

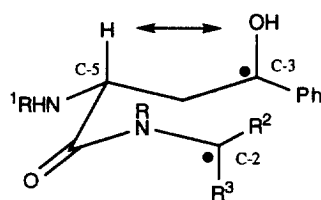


Figure 3.

Acknowledgements

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