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Synthesis of Peptidomimetics Containing a β-Lactam Moiety Using Peptidic Diazoketones and Imines in a Staudinger Reaction

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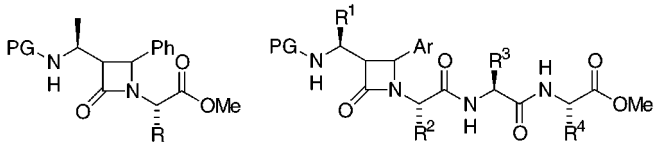
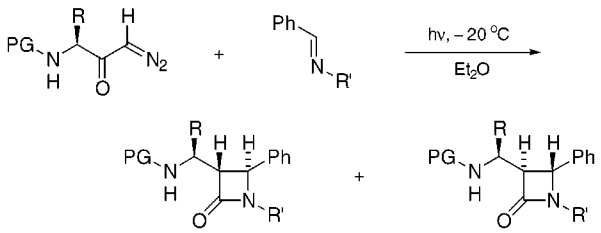
ABSTRACT



Rearrangement of α-amino acid or oligopeptide derived diazoketones in the presence of *N*-benzylbenzaldimine, α-amino acid, or tripeptide derived imines, respectively, led to peptidyl-substituted β-lactams. The *trans*-substituted diastereoisomers are formed exclusively.

The utilization of α-amino acids for the preparation of β-lactams has been explored in our group.[1] The photochemical decomposition of α-amino acid derived diazoketones[2] in the presence of imines leads to the formation of β-lactams; nearly all suitably protected amino acids can be employed in this reaction. Only two of the four possible diastereoisomers were found in which the substituents in positions C-3 and C-4 were *trans*-arranged (Scheme 1).

Scheme 1



The resulting aminoalkyl-substituted β-lactams are useful precursors for the preparation of possibly biologically active compounds such as the similarly substituted carbapenem,[3] trinem,[4] or meropenem[5] antibiotics. The *trans*-substitution —which is usually hard to achieve[6]—was found to be responsible for the special activity of these antibiotics against resistant bacterial strains. The incorporation of β-lactam moieties in oligopeptide strands is of additional interest. The small ring should lead to a conformational restraint,[7] the

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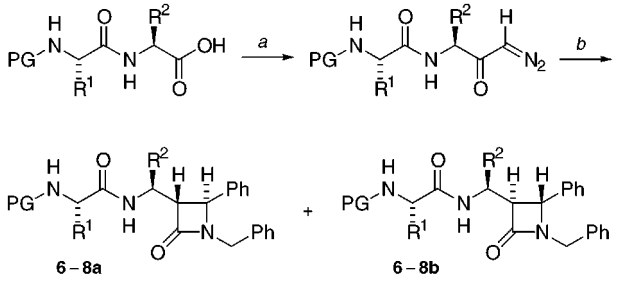
Table 1. Preparation of β-Lactams from Peptidic Starting Materials[9]

entry	diazoketone	imine	lactam	ratio **a**/**b**	yield (%)
1	Cbz-Ala-Ala-CHN_2	PhCH=NBn (**1**)	**6a**,**b**	4:1	76
2	Cbz -Ala-Val-CHN_2	PhCH=NBn (**1**)	**7a**,**b**	4:1	47
3	Boc-Ala-Leu-CHN_2	PhCH=NBn (**1**)	**8a**,**b**	4:1	76
4	Cbz -Ala-CHN_2	PhCH<Leu-OMe (**2**)	**9a**,**b**	2:1	78
5	Cbz -Ala-CHN_2	PhCH<Ala-Ala-Ala-OMe (**3**)	**10a**,**b**	11:1	45
6	Cbz -Ile-CHN_2	PhCH<Ala-Ala-Ala-OMe (**3**)	**11a**,**b**	2:1	42
7	Cbz -Ala-CHN_2	PhCH<Val-Ala-Val-OMe (**4**)	**12a**,**b**	>19:1	66
8	Cbz -Tle-CHN_2	PhCH<Val-Ala-Val-OMe (**4**)	**13a**,**b**	>19:1	74
9	Fmoc-Ala-CHN_2	2-thienyl-CH<Ile-Gly-Val-OMe (**5**)	**14a**,**b**	>19:1	73

conformation being dependent on the relative configuration of the stereogenic centers in the β-lactam ring. Therefore, we wish to present a useful modification of our β-lactam synthesis in which we utilize peptidic starting materials.

First, we used diazoketones derived from oligopeptides in our β-lactam synthesis. Following a published procedure,[2a,8] we synthesized diazoketones starting from Cbz-Ala-Ala-OH, Cbz-Ala-Val-OH, and Boc-Ala-Leu-OH, respectively.[9] Photochemical decomposition of these diazoketones in the presence of *N*-benzylbenzaldimine **1**[10] led to mixtures of two diastereoisomers **6**−**8a**,**b**, respectively, with yields ranging from 45 to 75% (Scheme 2, Table 1, entries 1−3).

Scheme 2



[a] NEt_3, $ClCO_2Et$, CH_2N_2, THF.[8] [b] PhCH=NBn, *hν*, Et_2O, −20 °C. See Table 1 for specification of substituents.

The ratios of the isomers were determined by HPLC and ^{1}H NMR spectroscopy, and separation of the products by MPLC yielded the pure isomers.[11] The *trans*-configuration was established by ^{1}H NMR spectroscopy, and the relative configuration of the β-lactams was determined by comparison with previously prepared, similar compounds.[1]

For the preparation of α-amino acid and peptide derived imines **2**−**5**, we used a very mild method developed by Texier-Boullet in which equimolar amounts of amine and aldehyde were condensed in the presence of activated alumina.[12] Addition of small amounts of benzene or methylene chloride—to allow for a better stirring—gave faster reactions.[13] This protocol led to the quantitative formation of the corresponding imines without any racemization (epimerization) or tautomerization (as checked by ^{1}H NMR spectroscopy).

Irradiation of the amino acid derived diazoketones in the presence of imines **2**−**5** yielded the corresponding β-lactams **9**−**14a**,**b** with yields ranging from 42 to 78% (Figure 1). As

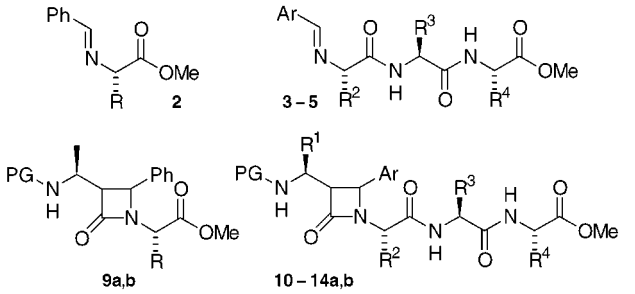


Figure 1. Imines derived from amino acids and peptides as used for the preparation of β-lactams.

in previous investigations,[1] we observed an influence of the additional stereogenic centers introduced with the imine moieties. Selectivities up to >95:5 could be obtained with peptidic imines **4** and **5** (entries 7−9). No second isomer could be detected in these cases, neither in the NMR spectra of the crude products nor during MPLC separation and purification.

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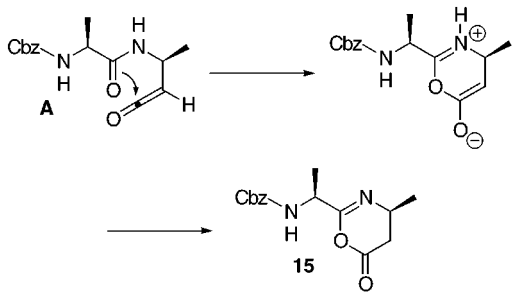
(15) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. The calculations have been performed with PCModel for Windows, version 6.00; Serena Software: Bloomington, IN, 1996.

Fortunately, a previously observed intramolecular stabilization[2a] of peptidic ketenes **A** seems to play no role with our reaction conditions or, what is much more likely, is not fast enough to compete with the attack of the imine. Obviously, dihydrooxazinones such as **15**[14] would not lead to the formation of β-lactams (Scheme 3).

Scheme 3



We performed MM2 calculations[15] with peptide analogues accessible with our protocol and found that β-lactams should be able to stabilize β-turns. Depending on the configuration of the *trans*-substituted β-lactam, the conformation is either a type I or a type II β-turn (Figure 2). These β-turn mimics bear up to three residues in the turn area. This is advantageous in comparison with previously presented β-turn mimics,[16] since this might allow for a better tuning of possible biological activities.[17] Work in this direction is ongoing in our laboratories.

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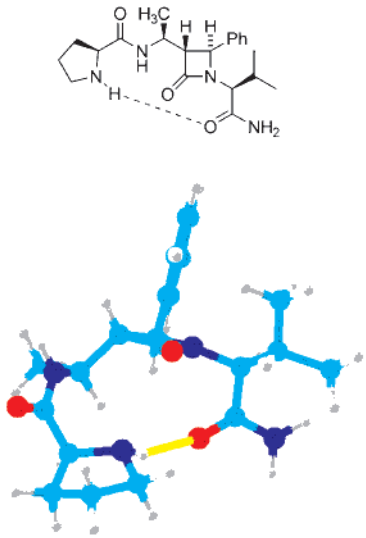

Figure 2. Tripeptide analogon stabilized by a hydrogen bond (MM2 calculation).

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