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Synthesis of β-Lactams from Diazoketones and Imines: The Use of Microwave Irradiation

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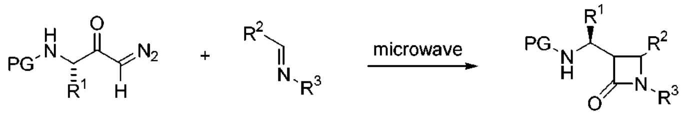
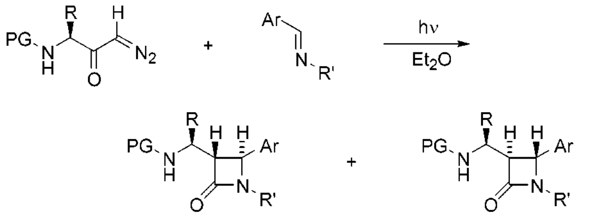
ABSTRACT



The transformation of diazoketones derived from α-amino acids to ketenes that, in turn, react further with imines to afford *β*-lactams, can be realized not only by utilizing photochemical reaction conditions but also under the action of microwave irradiation. Under the latter reaction conditions 4-alkenyl-substituted *β*-lactams derived from amino acids, substrates that were not previously accessible, have been prepared. *β*-Lactams possessing a *trans*-substitution pattern at the ring were obtained exclusively.

The use of α-amino acids for the preparation of β-lactams has been explored to some extent in our group.[1] The photochemical decomposition of diazoketones derived from α-amino acids[2] in the presence of imines leads to the formation of β-lactams; almost any suitably protected amino acid can be employed in this reaction. Only two of the four possible diastereoisomers were found, namely, those in which the substituents at positions C-3 and C-4 were in the *trans*-configuration (Scheme 1). The resulting aminoalkyl-substituted β-lactams are useful precursors for the preparation of compounds with potential biological activities such as the similarly substituted carbapenem[3] or trinem[4] antibiotics.

Scheme 1



PG: protecting group (Cbz, Boc, Fmoc)

The *trans*-substitution—otherwise hard to achieve[5]—was found to be responsible for the special activity of these antibiotics against resistant bacterial strains. Nevertheless, a major drawback of this method was its limitation to the use of aromatic aldimines.

Microwave (MW) irradiation has proved to be very efficient in various reactions, especially in organic synthesis.[6] Bose et al. observed a dramatic change in the diastereoselectivities during β-lactam formation from acid chlorides when the reaction was performed with MW irradiation.[6e,7]

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(1) (a) Podlech, J. *Synlett* **1996**, 582. (b) Podlech, J.; Linder, M. R. *J. Org. Chem.* **1997**, *62*, 5873. (c) Podlech, J.; Steurer, S. *Synthesis* **1999**, 650. (d) Podlech, J.; Linder, M. R. In *Bioorganic Chemistry—Highlights and New Aspects*; Diederichsen, U., Lindhorst, T. K., Westermann, B., Wessjohann, L., Eds.; Wiley-VCH: Weinheim, 1999; p 43. (e) Linder, M. R.; Podlech, J. *Org. Lett.* **1999**, *1*, 869.

(2) (a) Matthews, J. L.; Braun, C.; Guibourdenche, C.; Overhand, M.; Seebach, D. In *Enantioselective Synthesis of α-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; p 105. (b) Podlech, J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 471. (c) Podlech, J.; Seebach, D. *Liebigs Ann.* **1995**, 1217.

(3) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: London, 1992.

(4) (a) Di Modugno, E.; Erbetti, I.; Ferrari, L.; Galassi, G.; Hammond, S. M.; Xerri, L. *Antimicrob. Agents Chemother.* **1994**, *38*, 2362. (b) Wise, R.; Andrews, J. M.; Brenwald, N. *Antimicrob. Agents Chemother.* **1996**, *40*, 1248. (c) Ghiron, C.; Rossi, T. *Targets Heterocycl. Chem.* **1997**, *1*, 161.

(5) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; p 295.

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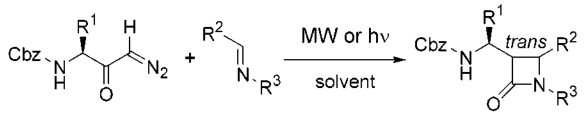
Especially noteworthy is the preferred *trans*-substitution pattern of the products in this reaction.

We have examined whether microwave irradiation can be used for the generation of ketenes starting with diazoketones[9] derived from Cbz-protected alanine and *tert*-leucine, respectively (Table 1).[10] Surprisingly, we found that these reaction conditions are not only an alternative for the preparation of the β-lactams mentioned above but are, in fact, applicable even when nonaromatic imines are used in this reaction.

In this way we have synthesized 4-vinyl- and 4-crotyl-substituted β-lactams, which should be useful starting materials for further transformations. In those cases in which both reaction conditions were tested, similar results were obtained (entries 1 and 4). Again, the *trans*-substituted β-lactams were formed exclusively (Figure 1). In the cases of the crotyl-substituted derivatives **5** and **6**, a partial isomerization to the *Z*-substituted olefin was observed (28% and 26%, respectively).[11]

The unfavorable use of the high-boiling *o*-dichlorobenzene, which is hard to remove after the reaction, was avoided by performing the reaction in 1,2-dimethoxyethane. To realize the required temperature of 160−180 °C, the reaction was performed in a sealed Teflon tube, leading to a similar yield and selectivity (Table 1, entry 4). It has been repeatedly reported that MW-assisted reactions can be performed without a solvent with the starting materials adsorbed on supports such as silica gel, alumina, or clay.[6,7e,12] Under these reaction conditions, we obtained the homologated β-amino acids instead of the desired β-lactams. Obviously traces of water present on the support have trapped the intermediate ketene **A** (Scheme 4). Even with virtually water-free alumina (activity grade I) only the β-amino acids were isolated.

Table 1. Photochemical or Microwave-Assisted Formation of β-Lactams



1 – 6 a,b

	β-lactam				MW[a]		hν[b]	
	R1	R2	R3		yield (%)	dr	yield (%)	dr
1	Me	2-furyl	Bn	**1**	80	2:1	76	2:1
2	Me	2-furyl	allyl	**2**	75	2:1	c	
3	*t*Bu	2-furyl	Bn	**3**	85	9:1	c	
4	Me	2-furyl	Bn	**1**	67[d]	2:1	76	2:1
5	Me	vinyl	allyl	**4**	60[e]	2:1	f	
6	Me	crotyl	Bn	**5**	60[e]	2:1[g]	f	
7	Me	crotyl	allyl	**6**	40[e]	2:1[g]	f	

[a] Reaction performed in *o*-dichlorobenzene at 180 °C (regulated via a temperature sensor) in an MW oven.[10] For details see Supporting Information. [b] Reaction performed in a quartz photo reactor in Et_2O at −15 °C within 2 h as previously described in ref 1a,b. [c] Reaction not performed. [d] Reaction performed in a sealed Teflon tube in 1,2-dimethoxyethane at 180 °C. [e] Various amounts of the corresponding β-amino acid amide are formed as side products.[8] [f] No β-lactam formed. [g] A partial *E* → *Z* isomerization of the double bond was observed during MW irradiation (∼27%).

This synthesis of β-lactams is not restricted to the particular substitution pattern stemming from the parent amino acids and can also be applied, e.g., to a diazoketone derived from butyric acid[1b] (Scheme 2).

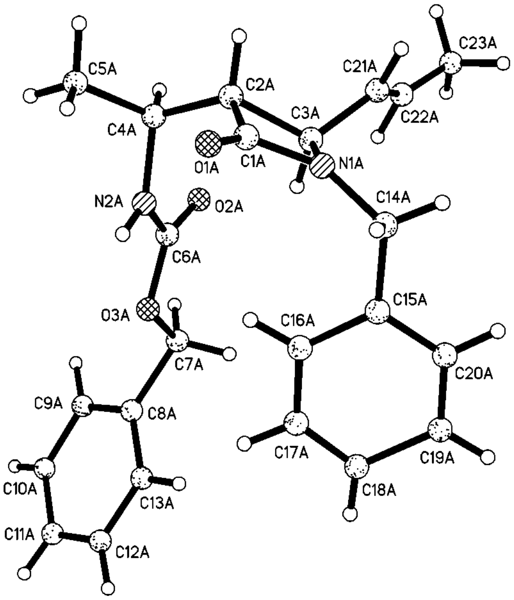


Figure 1. Crotyl-substituted β-lactam **5a** (major isomer, X-ray).

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(6) (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279. (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (c) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. (d) Abramovitch, R. A. *Org. Prep. Proc. Int.* **1991**, *23*, 683. (e) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1. (f) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. *J. Org. Chem.* **1991**, *56*, 6968. (g) Langa, F.; De la Cruz, P.; De la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* **1997**, *4*, 373. (h) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233. (i) Mingos, D. M. P.; Whittaker, A. G. In *Chemistry Under Extreme or Non-Classical Conditions*; von Eldik, R., Hubbard, C. D., Eds.; John Wiley & Sons/Spektrum Akademischer Verlag: New York, 1997; p 479. (j) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (k) Fini, A.; Breccia, A. *Pure Appl. Chem.* **1999**, *71*, 573. (l) Loupy, A. *Top. Curr. Chem.* **1999**, *206*, 153. (m) Varma, R. S. *Green Chem.* **1999**, *1*, 43. (n) Varma, R. S. *J. Heterocycl. Chem.* **1999**, *36*, 1565.

(7) (a) Banik, B. K.; Manhas, M. S.; Kaluza, Z.; Barakat, K. J.; Bose, A. K. *Tetrahedron Lett.* **1992**, *33*, 3603. (b) Bose, A. K.; Jayaraman, M.; Okawa, A.; Bari, S. S.; Robb, E. W.; Manas, M. S. *Tetrahedron Lett.* **1996**, *37*, 6989. (c) Khajavi, M. S.; Sefidkon, F.; Hosseini, S. S. S. *J. Chem. Res., Synop.* **1998**, 724. (d) Bose, A. K.; Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S. *Tetrahedron* **2000**, *56*, 5603. (e) Kidwai, M.; Venkataramanan, R.; Kohli, S. *Synth. Commun.* **2000**, *30*, 989.

(8) We assume that this side product is formed by hydrolysis of the iminium enolate depicted in Scheme 3, although it is not clear at what stage in the reaction this hydrolysis occurs.

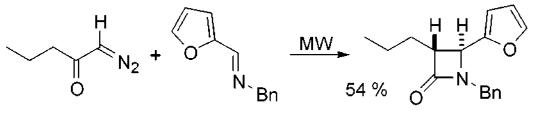
(9) Diazoketones were prepared as described in refs 1b and 2c. Imines derived from aromatic aldehydes were prepared according to Texier-Boullet, F. *Synthesis* **1985**, 679. Imines derived from acrolein or crotonaldehyde were prepared analogously, but were distilled prior to use.

(10) The MW experiments were performed in an MLS-ETHOS 1600 apparatus (MLS GmbH) using a flask equipped with a reflux condenser (mounted outside the apparatus) or in a Teflon autoclave (100 mL). A control and monitoring software (ETHOS PC98) was used, and the temperature was monitored via a temperature sensor.

(11) Commercially available crotonaldehyde as used for imine formation contained ∼4% *Z*-isomer, which was not separated before use. An *E* → *Z* isomerization at elevated temperatures has been reported: Slayden, S. W. In *The Chemistry of Double-Bonded Functional Groups. Supplement A3. Part 1*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1997; p 537.

(12) (a) Dittmer, D. C. *Chem. Ind.* **1997**, 779. (b) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 2039.

Scheme 2

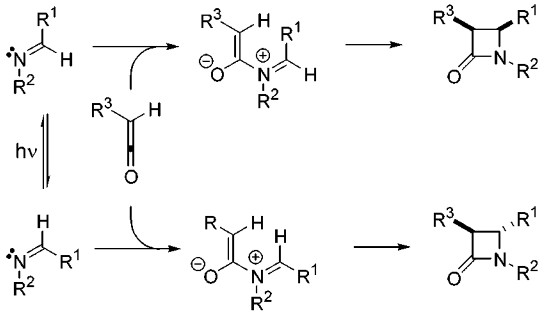


rac-**7**

Conditions as described in Table 1.

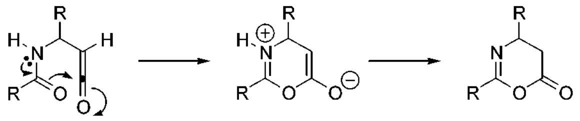
We assume that the observed reactivity was effected by microwave-induced heating rather than a dielectric polarization of the substrates. When the synthesis of β-lactam **3** was performed without MW irradiation at 160 °C in *o*-dichlorobenzene, the *trans*-substituted products were again formed, although the reaction was significantly less selective (64:36).[13] We assume that the unusual *trans*-selectivity is due to either a photochemically[14] or (here) thermally[15] induced *syn*/*anti*-isomerization of the imines (Scheme 3).

Scheme 3



Surprisingly, although a plethora of Staudinger-type reactions has been described, to the best of our knowledge not one single example of the use of aminoalkyl-substituted ketenes **A** has been reported previously. It is known that these ketenes undergo stabilization by intramolecular nucleophilic attack leading to the oxazinones **B**[2b] that cannot react further to afford β-lactams (Scheme 4).

Scheme 4



A **B**

Nevertheless, when the attack of the imine is fast (i.e., the imine is sufficiently reactive), this oxazinone formation is suppressed and the corresponding β-lactam is formed exclusively. *cis*-Substituted imines should be more reactive than the corresponding *trans*-isomers because they are less sterically hindered.

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Supporting Information Available: Experimental procedures and full characterization for compounds **1**−**7** and X-ray data for β-lactams **1a**, **2a**, and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The rates of the thermal and the MW-assisted formation of β-lactam **3** have been compared. After 5 min 80% conversion for the thermal reaction and 85% for the MW reaction, respectively were detected, i.e., identical rates within the limits of experimental error. The photochemical reaction is not comparable in this context, since it is, as a result of increasing extinction, dependent on the concentration of the starting materials.

(14) (a) Wettermark, G. In *The Chemistry of the Carbon*−*Nitrogen Double Bond*; Patai, S., Ed.; Interscience: London, 1970; p 565. (b) Wettermark, G.; Wallström, E. *Acta Chem. Scand.* **1968**, *22*, 675.

(15) McCarty, C. G. In *The Chemistry of the Carbon*−*Nitrogen Double Bond*; Patai, S., Ed.; Interscience Publishers: London, 1970; p 363.