

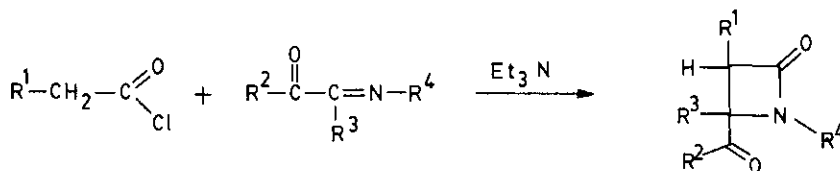
HIGHLY STEREOSELECTIVE SYNTHESIS OF CIS- AND TRANS-4-BENZOYL-2-OXOAZETIDINES

Benito Alcaide, Gema Domínguez, Gerardo Escobar, Ursula Parreño,  
and Joaquín Plumet\*

Universidad Complutense, Facultad de Químicas, Dpto. de Química  
Orgánica, Ciudad Universitaria, 28040-Madrid, Spain

**Abstract** — The reaction of the system acid chloride-triethylamine with 1,2-iminoketones yields exclusively cis- $\beta$ -lactams, which may be isomerized to the corresponding trans isomers in a straightforward manner.

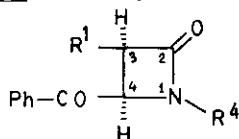
Monocyclic  $\beta$ -lactam antibiotics constitute an important group of compounds of clinical use<sup>1</sup>. Among these systems, monobactams<sup>2</sup> are  $\beta$ -lactams substituted on the C-3 and C-4 positions. The stereochemistry of the substituents on these positions cis or trans is important for their biological activity. Thus, aztreonam<sup>3</sup> presents trans stereochemistry, while other systems such as carumonam<sup>4</sup> present cis substitution. The introduction of an acyl group on the C-4 of the  $\beta$ -lactam ring has allowed for the preparation of a new type of precursors of potentially interesting systems. In a previous paper<sup>5</sup> we have reported a simple route for the preparation of 4-acyl- $\beta$ -lactams by the cycloaddition of ketenes or ketene precursors to 1,2-iminoketones derived from benzyl ( $R^2 = R^3 = C_6H_5$ ) or biacetyl ( $R^2 = R^3 = CH_3$ )(Scheme).



Scheme

In the case of 1,2-iminoketones derived from phenylglyoxal<sup>6</sup> ( $R^2 = C_6H_5$ ,  $R^3 = H$ ) the corresponding cycloaddition process yields acyl- $\beta$ -lactams with cis stereochemistry on carbons C-3 and C-4 (Scheme). The assignment of a cis stereochemistry to these compounds is evident by just examining the values of the coupling constant  $J_{3,4}$ , larger than 5.0 Hz in all cases<sup>7</sup>. Table 1 shows the yields and spectral and physical data for the compounds described in this report.

Table 1

cis-4-Benzoyl- $\beta$ -lactams

Comp.	R <sup>1</sup>	R <sup>4</sup>	Mp (°C) <sup>a</sup>	Yield (%) <sup>b</sup>	IR (cm <sup>-1</sup> ) <sup>c</sup>		<sup>1</sup> H-NMR ( $\delta$ , ppm) <sup>d</sup>		
					$\nu_{C=O}$	$\nu_{N-C=O}$	H-3	H-4	J <sub>3,4</sub> (Hz)
<u>1</u>	C <sub>6</sub> H <sub>5</sub>	p-MeOC <sub>6</sub> H <sub>4</sub>	185-7	75	1670	1740	4.9	5.7	6.9
<u>2</u>	CH <sub>3</sub>	p-MeOC <sub>6</sub> H <sub>4</sub>	152-4	75	1690	1745	3.8	5.5	6.0
<u>3</u>	C <sub>2</sub> H <sub>5</sub>	p-MeOC <sub>6</sub> H <sub>4</sub>	106-8	60	1670	1730	3.5	5.4	6.0
<u>4</u>	<sup>i</sup> C <sub>3</sub> H <sub>7</sub>	p-MeOC <sub>6</sub> H <sub>4</sub>	148-9	65	1680	1730	3.4	5.4	7.2
<u>5</u>	Cl	p-MeOC <sub>6</sub> H <sub>4</sub>	170-2	25	1680	1750	5.3	5.7	6.0
<u>6</u>		p-MeOC <sub>6</sub> H <sub>4</sub>	220-2	75	1690	1760	6.5	6.4	6.6
<u>7</u>		p-MeC <sub>6</sub> H <sub>4</sub>	230-1	55	1690	1760	6.0	5.9	6.6
<u>8</u>		C <sub>6</sub> H <sub>5</sub>	238-9	30	1690	1760	6.3	6.1	5.4
<u>9</u>		p-MeOC <sub>6</sub> H <sub>4</sub>	214-6	60	1685	1755	6.1	5.9	6.4
<u>10</u>		p-MeC <sub>6</sub> H <sub>4</sub>	200-2	40	1680	1755	6.1	5.9	6.3
<u>11</u>		C <sub>6</sub> H <sub>5</sub>	240-1	40	1680	1755	6.2	5.9	6.4
<u>12</u> <sup>e</sup>	C <sub>6</sub> H <sub>5</sub>	H	184-6	68	1670	1750	4.9	5.4	6.0
<u>13</u> <sup>e</sup>	CH <sub>3</sub>	H	oil	60	1690	1760	3.8	5.2	6.0

a All products were crystallized from EtOH.

b Yields of pure isolated products with correct elemental analyses.

c In KBr pellet.

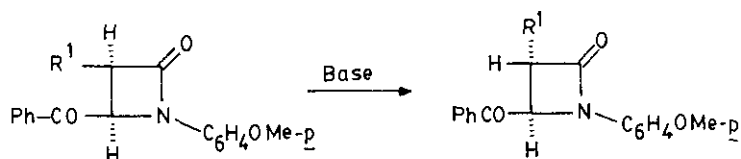
d Spectra registered in CDCl<sub>3</sub> or DMSO-d<sub>6</sub> solutions at 60 MHz. The coupling constants J<sub>3,4</sub> were determined on appropriately expanded spectra. Only the most indicative signals are reported.

e These compounds were prepared from 1 and 2 by reaction with cerium ammonium nitrate, according to the method of Kronenthal, Han and Taylor<sup>8</sup>.

$\nu_{NH}$  3270-3300 cm<sup>-1</sup>.

In the formation of  $\beta$ -lactams by reaction of the system acid chloride- triethylamine with Schiff bases, cis or trans isomers are obtained depending upon the structural characteristics of the starting imine<sup>9</sup> or the order of addition of the reagents<sup>10</sup>. In our cases and under the experimental conditions utilized<sup>11</sup>, cis isomers were formed exclusively. However, in the presence of bases, it is possible to effect their isomerization to the corresponding trans isomers<sup>12</sup>, except for 3-alkyl derivatives, when *n*-BuLi was used as basic reagent. The differences with 3-phenyl substituted compounds might be due to the increase of acidity of the latter. Work is now in progress in order to determine the relative acidity of the 3- and 4-hydrogens. Table 2 shows the experimental conditions for the isomerization and Table 3 shows the physical and spectroscopic data for the corresponding trans- $\beta$ -lactams.

Table 2

 Isomerization of cis- $\beta$ -lactams


Entry	$R^1$	Base	Solvent <sup>b</sup>	t(min)	T(°C)	Equilibrium distribution <sup>a</sup>	
						<u>cis</u>	<u>trans</u>
1	$C_6H_5$	<i>n</i> BuLi	THF	120	-5	14	86
2	$C_6H_5$	<i>n</i> BuLi	THF	30	25	0	100
3	$C_6H_5$	NaOH	$CH_3CN/H_2O$	15	25	63	37
4	$C_6H_5$	NaOH	$CH_3CN/H_2O$	1320	25	0	100
5 <sup>c</sup>	$CH_3$	<i>n</i> BuLi	THF	30	25	100	0
6	$CH_3$	NaOH	$CH_3CN/H_2O$	15	25	68	32
7	$CH_3$	NaOH	$CH_3CN/H_2O$	1320	25	42	58
8 <sup>c</sup>	$CH_3$	NaOH	$CH_3CN/H_2O$	4320	25	28	72
9	$CH_3$	NaOH	$CH_3CN/H_2O$	60	Reflux	40	60
10 <sup>c</sup>	$C_2H_5$	<i>n</i> BuLi	THF	30	25	100	0
11	$C_2H_5$	NaOH	$CH_3CN/H_2O$	15	25	55	45
12	$C_2H_5$	NaOH	$CH_3CN/H_2O$	1320	25	27	73
13	$C_2H_5$	NaOH	$CH_3CN/H_2O$	4320	25	17	83
14	<sup>i</sup> $C_3H_7$	<i>n</i> BuLi	THF	30	25	100	0
15 <sup>c</sup>	<sup>i</sup> $C_3H_7$	NaOH	$CH_3CN/H_2O$	15	25	42	58
16	<sup>i</sup> $C_3H_7$	NaOH	$CH_3CN/H_2O$	1320	25	0	100

Table 2 (cont.)

a Determined by  $^1\text{H-NMR}$  from the signals corresponding to protons attached to carbons C-3 and C-4 (see Tables 1 and 3) on sufficiently expanded spectra of the mixtures. The yield of the isomerization was quantitative except in those cases expressly indicated.

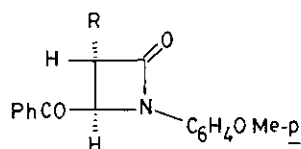
b Conditions  $^n\text{BuLi/THF}$ : 0.64 mmol of  $^n\text{BuLi}$  and 0.32 mmol of cis- $\beta$ -lactam in 20 ml of anhydrous THF.

Conditions  $\text{NaOH/CH}_3\text{CN-H}_2\text{O}$ : Molar ratio,  $\text{NaOH}:\beta\text{-lactam} = 2:1$ ; the  $\beta$ -lactam is dissolved in the minimum amount of acetonitrile and then  $\text{NaOH}$ , dissolved in the minimum amount of water, is added.

c The yield in these cases was 80-85%. No other product could be characterized.

Table 3

Physical and spectroscopic data for trans- $\beta$ -lactams<sup>a</sup>



Entry	R	Mp (°C)	IR (cm <sup>-1</sup> ) <sup>b</sup>		$^1\text{H-NMR}$ ( $\delta$ , ppm) <sup>c</sup>		
			$\nu\text{C=O}$	$\nu\text{NC=O}$	H-3	H-4	$J_{3,4}$ (Hz)
1	C <sub>6</sub> H <sub>5</sub>	166-8	1680	1750	4.25	5.33	3.0
2	CH <sub>3</sub>				3.30	5.15	3.0
3	C <sub>2</sub> H <sub>5</sub>				3.50	5.00	2.4
4	<sup>i</sup> C <sub>3</sub> H <sub>7</sub>	118-9	1685	1725	3.00	5.10	2.0

a  $\beta$ -Lactams corresponding to entries 1 and 4 were isolated as pure products. For entries 2 and 3 the  $^1\text{H-NMR}$  data were obtained from the spectra of mixtures enriched in the trans isomer (see Table 2).

b In KBr pellet.

c In  $\text{CDCl}_3$  solution.

In conclusion, the method developed in this report allows for the straightforward preparation of cis- or trans-4-benzoyl- $\beta$ -lactams. The functionalization of the carbonyl group for the synthesis of  $\beta$ -lactam systems of potential interest as well as synthetic applications of the isomerization process are currently under active investigation.

#### ACKNOWLEDGEMENTS

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11. The following experimental procedure was used: Two solutions of the iminoketone and the acid chloride in benzene were combined at the appropriate temperature. The molar ratio was acid chloride/iminoketone = 2/1. Then, a third solution of triethylamine in benzene, equimolar with the acid chloride, was added. The mixture was stirred at the same temperature of addition, until the starting imine was consumed (TLC). Generally, this took from 2 to 5 h. When the reaction was complete, the amine hydrochloride was removed by filtration and the resulting solution was concentrated in vacuo, and the crude product triturated with diethyl ether. A solid product was obtained which was then recrystallized from ethanol.  $\beta$ -Lactams 1-5 and 12-13 were prepared at room temperature,  $\beta$ -lactams 6-11 were prepared at 0°C.
12. The typical values of  $J_{3,4}$  for trans isomers are between 1.5 and 2.5 Hz.

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