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

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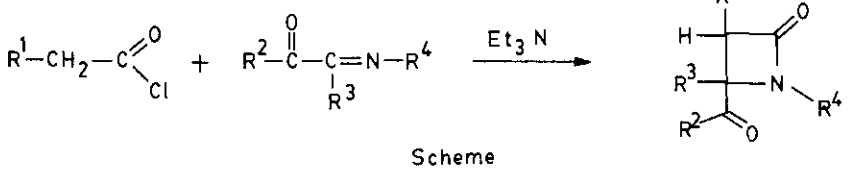
Abstract — The reaction of the system acid chloride-triethylamine with 1,2-iminoketones yields exclusively cis-β-lactams, which may be isomerized to the corresponding trans isomers in a straightforward manner.

Monocyclic β-lactam antibiotics constitute an important group of compounds of clinical use[1]. Among these systems, monobactams[2] are β-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[3] presents trans stereochemistry, while other systems such as carumonan[4] present cis substitution. The introduction of an acyl group on the C-4 of the β-lactam ring has allowed for the preparation of a new type of precursors of potentially interesting systems. In a previous paper[5] we have reported a simple route for the preparation of 4-acyl-β-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).

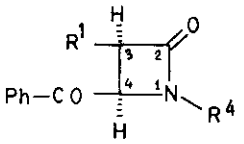


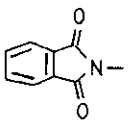
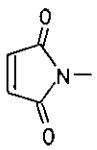
Scheme

In the case of 1,2-iminoketones derived from phenylglyoxal[6] (R^2= C_6H_5, R^3= H) the corresponding cycloaddition process yields acyl-β-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[7]. Table 1 shows the yields and spectral and physical data for the compounds described in this report.

Table 1

cis-4-Benzoyl-β-lactams



Comp.	R^1	R^4	Mp(°C)[a]	Yield(%)[b]	IR(cm^{-1})[c] νC=0	IR(cm^{-1})[c] νNC=0	^{1}H-NMR(δ,ppm)[d] H-3	^{1}H-NMR(δ,ppm)[d] H-4	^{1}H-NMR(δ,ppm)[d] $J_{3,4}$(Hz)
1	C_6H_5	p-$MeOC_6H_4$	185-7	75	1670	1740	4.9	5.7	6.9
2	CH_3	p-$MeOC_6H_4$	152-4	75	1690	1745	3.8	5.5	6.0
3	C_2H_5	p-$MeOC_6H_4$	106-8	60	1670	1730	3.5	5.4	6.0
4	$^iC_3H_7$	p-$MeOC_6H_4$	148-9	65	1680	1730	3.4	5.4	7.2
5	Cl	p-$MeOC_6H_4$	170-2	25	1680	1750	5.3	5.7	6.0
6		p-$MeOC_6H_4$	220-2	75	1690	1760	6.5	6.4	6.6
7		p-MeC_6H_4	230-1	55	1690	1760	6.0	5.9	6.6
8		C_6H_5	238-9	30	1690	1760	6.3	6.1	5.4
9		p-$MeOC_6H_4$	214-6	60	1685	1755	6.1	5.9	6.4
10		p-MeC_6H_4	200-2	40	1680	1755	6.1	5.9	6.3
11		C_6H_5	240-1	40	1680	1755	6.2	5.9	6.4
12[e]	C_6H_5	H	184-6	68	1670	1750	4.9	5.4	6.0
13[e]	CH_3	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.

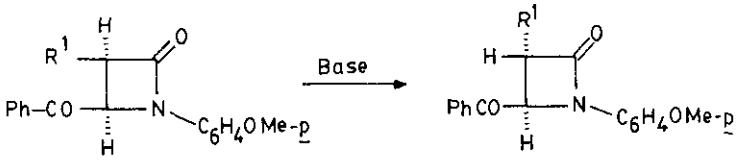
d Spectra registered in $CDCl_3$ or DMSO-d_6 solutions at 60 MHz. The coupling constants $J_{3,4}$ were determined on appropriately expanded spectra. Only the most indicative signals are reported.

e These compounds were prepared from 1 and 2 by reaction with cerium ammonium nitrate, according to the method of Kronenthal, Han and Taylor[8]. ν_{NH} 3270-3300 cm^{-1}.

In the formation of β-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[9] or the order of addition of the reagents[10]. In our cases and under the experimental conditions utilized[11], cis isomers were formed exclusively. However, in the presence of bases, it is possible to effect their isomerization to the corresponding trans isomers[12], 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-β-lactams.

Table 2

Isomerization of cis-β-lactams



Entry	R^1	Base	Solvent[b]	t(min)	T(°C)	Equilibrium distribution[a] cis	trans
1	C_6H_5	^nBuLi	THF	120	-5	14	86
2	C_6H_5	^nBuLi	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[c]	CH_3	^nBuLi	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[c]	CH_3	NaOH	CH_3CN/H_2O	4320	25	28	72
9	CH_3	NaOH	CH_3CN/H_2O	60	Reflux	40	60
10[c]	C_2H_5	^nBuLi	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	$^iC_3H_7$	^nBuLi	THF	30	25	100	0
15[c]	$^iC_3H_7$	NaOH	CH_3CN/H_2O	15	25	42	58
16	$^iC_3H_7$	NaOH	CH_3CN/H_2O	1320	25	0	100

Table 2 (cont.)

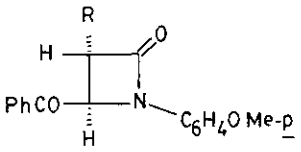
a Determined by ^{1}H-NMR from the signals corresponding to protons attached to carbons C-3 and C-4(see Tables 1 and 3) on sufficiently expanded spectra of the mixtures. The yield of the isomerization was quantitative except in those cases expressly indicated.

b Conditions ^{n}BuLi/THF: 0.64 mmol of ^{n}BuLi and 0.32 mmol of cis-β-lactam in 20 ml of anhydrous THF.
Conditions NaOH/CH_3CN-H_2O: Molar ratio, NaOH:β-lactam= 2:1; the β-lactam is dissolved in the minimun amount of acetonitrile and then NaOH, dissolved in the minimun 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-β-lactams[a]



			IR(cm^{-1})[b]		^{1}H-NMR(δ,ppm)[c]		
Entry	R	Mp(°C)	νC=O	νNC=O	H-3	H-4	$J_{3,4}$(Hz)
1	C_6H_5	166-8	1680	1750	4.25	5.33	3.0
2	CH_3				3.30	5.15	3.0
3	C_2H_5				3.50	5.00	2.4
4	$^iC_3H_7$	118-9	1685	1725	3.00	5.10	2.0

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

b In KBr pellet.

c In $CDCl_3$ solution.

In conclusion, the method developed in this report allows for the straighforward preparation of cis- or trans-4-benzoyl-β-lactams. The functionalization of the carbonyl group for the synthesis of β-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. β-Lactams 1-5 and 12-13 were prepared at room temperature, β-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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