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RING EXPANSION OF 4-BENZOYL-β-LACTAMS

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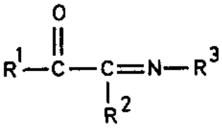
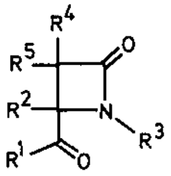
Abstract —— Diastereomerically pure 4-benzoyl-β-lactams react with NaH/DMF in the presence of an alkyl halide to give 5-alkoxy-γ-lactams.

The introduction of new functional groups in the β-lactam ring continues to attract the interest of several research groups[1]. Just a few cases of monocyclic 4-acyl-β-lactams syntheses have been reported[2] in spite of their potential utility for the development of synthetic routes to other 4-substituted monocyclic or bicyclic β-lactams[2d,2g]. Previously[3] we have reported the cycloaddition reaction of 1,2-iminoketones 1 with acyl chlorides in the presence of Et_3N to give 4-acyl-β-lactams 2. When R^4=H, only one of the two possible diastereoisomers was observed and isolated from the reaction mixture[3a].



$$R^1-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle R^2}{|}}{C}=N-R^3$$

1

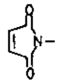
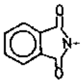
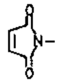


2

Thus a first question is the configurational assignment of the isolated product. The chemical shifts intervals for structurally related compounds appear to indicate that the same stereoisomers were formed in all cases (Table 1).

Table 1

^{1}H-nmr chemical shifts intervals for the proton attached to C-3 in 4-acyl-β-lactams 2^a (R^4=H)

R^1= R^2	R^5	Resonance interval (ppm)	Number of compounds analyzed
C_6H_5	C_6H_5	5.0-5.2	4
C_6H_5		5.8-5.9	10
C_6H_5		6.0-6.3	3
C_6H_5	CH_3	3.9-4.1[b]	2
CH_3	C_6H_5	4.3-4.5[c]	4
CH_3		5.0-5.1[d]	3

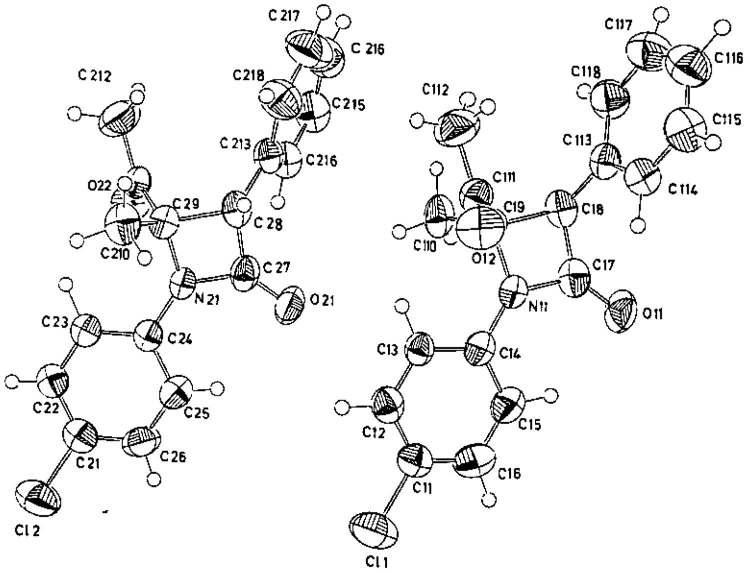
a) Spectra was recorded in $CDCl_3$ except for the phthalimidoyl derivatives which were recorded in DMSO-d_6.

b) $\delta_{C\underline{H}_3}$ = 1.2 ppm in both cases

c) $\delta_{C\underline{H}_3}$ = 1.7 ppm in all cases; $\delta_{C\underline{H}_3CO}$ = 1.9-2.0 ppm

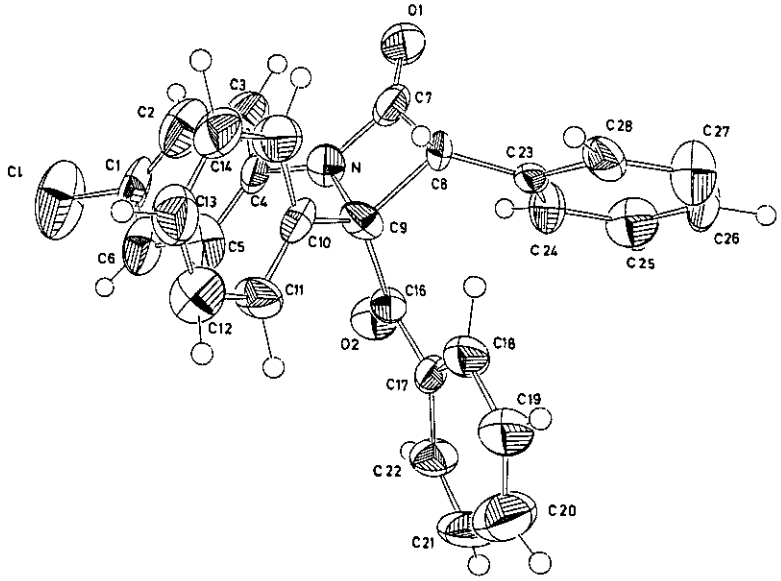
d) $\delta_{C\underline{H}_3}$ = 1.8-1.9 ppm; $\delta_{C\underline{H}_3CO}$ = 2.2-2.3 ppm

X-Ray analysis of two selected derivatives 2 (a $R^1=R^2=CH_3$; $R^5=C_6H_5$; R^3=p-Cl-C_6H_4-; b $R^1=R^2=R^5=C_6H_5$; R^3=p-Cl-C_6H_4-) allows for the determination of configuration of carbons 3 and 4[4]. The resulting ORTEP drawings are indicated in Figures 1 and 2.



Compound 2a

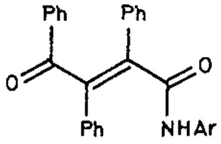
Figure 1

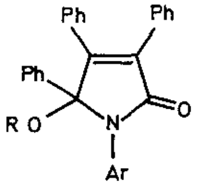


Compound 2b

Figure 2

Attempts of cis-trans isomerization of β-lactams 2 (c R^4=H; R^1=R^2=R^5=C_6H_5; R^3=p-MeO-C_6H_4-) in the conditions previously described[3b] failed. However reactions of 2c with NaH/DMF followed by hydrolysis gave the amide 3[5]. On the other hand reaction of 2 with NaH/DMF in the presence of an alkyl halide yielded γ-lactams 4[6] (Table 2).





(Ar= p-MeO-C_6H_4-)

3 4

Table 2

Analytical and spectroscopic data of compounds 4

$$\underline{2c} \xrightarrow[\text{b) R-X}]{\text{a) NaH/DMF}} \underline{4}$$

Entry	R	X	Mp[a]	Yield[b]	^{1}H-nmr[c]	Ir[d]	^{13}C-nmr[e]
a	CH_3	I	139-140(EtOH)	7%[f]	3.5(s,3H,-OCH_3) 3.7(s,3H,Ph-OCH_3)	1690(CO-N)	
b	C_2H_5	I	179-180(EtOH)	75%	1.3(t,3H,J=7 Hz, -CH_3) 3.7(c,2H,J=7 Hz, -CH_2-)	1690(CO-N)	168.7(C_2);96.4(C_5), 57 2(-OCH_2-);14.2(-CH_3)
c	CH_2-C_6H_5	Cl	155-156(Bu^nOH)	76%	4.7(c,2H,J=11.5 Hz,-CH_2-)	1690(CO-N)	168.76(C_2);97.01(C_5); 64.48(-OCH_2-)
d	CH_2-CH=CH_2	Br	175-176(EtOH)	66%[g]	4.22(tap.2H,-OCH_2) 5.06-5.53(m,2H,=CH_2-) 5.72-6.25(m,1H,-CH=)	1690(CO-N)	168.8(C_2),133.0(-CH=); 116.8(CH_2=);96.5(C_5) 62.8(-OCH_2-)

a) Parenthetically, solvent of crystallization.

b) In pure isolated product. The remaining material was starting β-lactam.

c) $CDCl_3$. 80 MHz.

d) In KBr pellet.

e) $CDCl_3$. 20 MHz.

f) Along with 4a, a mixture of both stereoisomers of 4-benzoyl-3-methyl-3,4-diphenyl-1-p-methoxyphenyl-2-oxoazetidine was obtained (58 %).

g) Along with 4d one stereoisomer of 3-allyl-4-benzoyl-3,4-diphenyl-1-p-methoxyphenyl-2-oxoazetidine was obtained (mp 128-129 °C,24 %). Configurational assignment is in progress.

To the best of our knowledge this is the first case of ring expansion[7] of 4-acyl-β-lactams. Further work in order to extend the synthetic utility of these compounds 2 as well as the clarification of the mechanism of this process is now in progress.

ACKNOWLEDGMENTS

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2. To the best of our knowledge the following syntheses of monocyclic 4-acyl-β-lactams have been reported: (a) R.F. Abdulla and J.C. Williams Jr., Tetrahedron Letters, 21, 997 (1980); (b) H. Takata, Y. Ohnishi, H. Takehara, K. Tsuritani and T. Yamazaki, Chem. Pharm. Bull., 29, 1063 (1981); (c) S.B. Singh and K.N. Mehrotra, Can. J. Chem., 60, 1901 (1982); (d) S. Hanessian, A. Bedeschi, C. Battistini and M. Mongelli, J. Am. Chem. Soc., 107, 1438 (1985); (e) M. Ghosh, S. Ray and B. Chaterjee, Indian J. Chem., 248, 144 (1985); (f) D.K. Dutta, R.Ch. Boruah and J.S. Sandhu, Heterocycles, 24, 655 (1986); (g) Y. Ito, T. Kawabata and S. Terashima, Tetrahedron Letters, 27, 5751 (1986).

3. (a) B. Alcaide, M.A. León, R. Pérez Ossorio, J. Plumet, M.A. Sierra and C. Torre Synthesis, 989 (1982); (b) B. Alcaide, G. Domínguez, G. Escobar, U. Parreño and J. Plumet, Heterocycles, 24, 1579 (1986).

4. Crystallographic determinations

$C_{18}H_{16}NO_2Cl$ (2a) Triclinic $P_{\bar{I}}$, a= 9.921 (5), b= 13.908 (4), c= 11.113 (2), α=80.17 (2), β=101.27 (2), γ=89.59 (3); V= 1631 (1) A^3, Mr= 313.8, z= 4, Dc= 1.29 gr/cm^3, F(000)= 656, μ(MoKα)= 2.40 cm^{-1}, λ= 0.71069 A. Final R value: R= 0.048 and R_ω= 0.054 for 2a.

$C_{28}H_{20}NO_2Cl$ (2b) Hexagonal P_{65}, a=b= 10.922 (2), c= 32.67 (4) A, V= 3377 (4) A^3, Mr= 437.9, z= 6, Dc= 1.29 gr/cm^3, F(000)= 1368, μ(MoKα)= 1.91 cm^{-1}, λ= 0.71069 A. Final R value: R= 0.063 and R_ω= 0.051 for 2b.

5. Conditions. Molar ratio: β-lactam/NaH = 1/3. RT. Analytical data of 3. Mp 113-117°C ($CHCl_3$). Ir: 3300 (broad), 1690, 1675; ^{1}H-nmr (CD_3COCD_3): 3.7 (s, 3H; -OCH_3); 6.38 (s, 1H; -NH); 6.5-7.9 (m, 19H; aromatic).

6. Conditions. Molar ratio β-lactam/NaH/Alkyl halide= 1/3/2.5. In a typical experiment a mixture of β-lactam, and NaH in anhydrous DMF was stirred at room temperature. After 10 min the alkyl halide was added. The reaction mixture was stirred at room temperature during 3 h. After hydrolysis, the organic layer was taken in ethyl acetate, which was washed with water and then dried over anhydrous magnesium sulfate. Removal of the drying agent and concentration in vacuo afforded the crude product which was purified by column chromatography on silica gel (CH_2Cl_2) in the case of 4c. The other products was purified by crystallization in the appropriate solvent without prior chromatography.

7. For synthetic utility of β-lactam cleavage, see M.S. Manhas, S.G. Amin and A.K. Bose, Heterocycles, 5, 669 (1976). For recent examples of β-lactam ring expansion, see for example: (a) L. Crombie, R.C.F. Jones, S. Osborne and A.R. Mat-zin, J. Chem. Soc. Chem. Comm., 959 (1983); (b) L. Crombie, R.C.F. Jones and D. Haig, Tetrahedron Letters, 27, 5147 (1986); (c) J.M. Indelicato, J.W. Fisher and C.E. Pasini, J. Pharm. Sci., 75, 304 (1986); (d) L. Fodor, J. Szabo, E. Szucs G. Bernath, P. Sohar and J. Tamas, Magy. Kem. Foly, 91, 554 (1985); (e) A.K. Bose, L. Krishnam, D.R. Nagle and M.S. Manhas, Tetrahedron Letters, 27, 5955 (1986).

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