THE BEHAVIOUR OF 4-BENZOYL-2-AZETIDINONES WITH BASES. REGIOSELECTIVITY IN THEIR ALKYLATION REACTIONS

Benito Alcaide, Gema Domínguez, Angel Martín-Domenech, and Inmaculada Martín

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

Carlos Cativiela and José A. Mayoral

Departamento de Química Orgánica, Instituto de Ciencias de los Materiales de Aragón, Universidad de Zaragoza, 50009-Zaragoza, Spain

Joaquín Plumet*

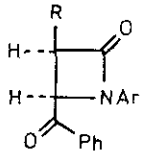
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, 06071-Badajoz, Spain

Abstract — 4-Benzoyl-2-azetidinones react with alkyl halides in the presence of bases in a regioselective fashion depending on the substitution pattern in the β-lactam ring and on the alkylating agent. In this way, different kinds of products derived from C- and O-alkylation of 4-benzoyl-β-lactams, **10**, **11**, **14**, and **16**, as well as produts derived from ring expansion of the β-lactam moiety and subsequent O-alkylation, **15**, have been obtained. In addition, the reaction course for the isomerization of cis-4-benzoyl-2-azetidinones **1** has been elucidated on the basis of experimental data and MNDO calculations.

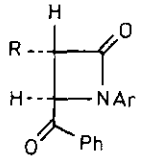
In a previous paper we have reported a simple route for the totally stereoselective synthesis of cis-4-benzoyl-2-azetidinones **1** by the reaction of the system acid chloride-triethylamine with phenylglyoxal anyls as well as their total or partial isomerization to the trans isomer **2** by treatment with bases in various experimental conditions.[1] Two alternative mechanisms could account for this isomerization process involving either enolate **3** or **4** formed by removal of a proton on the C-3 and C-4 positions, respectively. Investigation of the reaction course of this process and the study of some alkylation reactions in these and other related 4-benzoyl-2-azetidinones constitute the main aims of the present report.[2]

Calculations in order to determine the relative acidity of hydrogens attached to C-3 and C-4 in

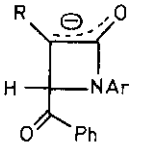
cis-β-lactam **1a** have been performed in the following way: Catalán et al.[3] showed that there is a linear relationship between the experimental acidity of meta- and para-substituted phenols with the theoretical acidity estimated on the basis of the energy difference between the neutral molecule and the corresponding anion. We have used this approach to estimate the relative acidities of the hydrogens on C-3 and C-4 in compounds **5** as models for **1**. Semiempirical MO calculations[4] using the MNDO approach[5] have been used to calculate the heats of formation of



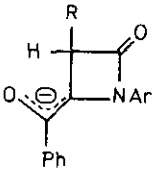
1



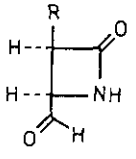
2



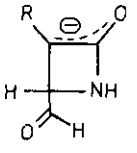
3



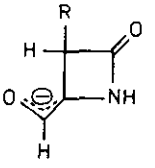
4



5



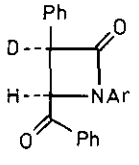
6



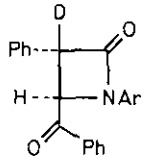
7

(a: R = Ph; b: R = Me) (Ar = p-$MeOC_6H_4$)

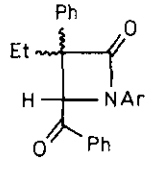
enolates **6** and **7**. When R = Ph calculations indicate that anion **6a** is about 47 KJ/mol more stable than **7a**.[6,7] Chemical evidence supports the above observation. Thus treatment of **1a** with NaH in DMSO and trapping of the intermediate carbanion with D_2O induces the formation of a mixture of epimeric deuterated β-lactams **8** and **9**. The doublet at 6.3 ppm (H-3) disappears whilst H-4 in **8** and **9** appears as a singlet at 6.3 and 6.9 ppm, respectively.[8]



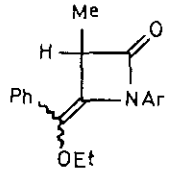
8



9



10

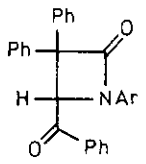


11

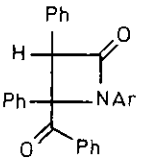
(Ar = p-$MeOC_6H_4$)

Interception of the enolate **3a** by alkylation was also possible. Thus, reaction of **1a** with LDA in THF[9] and subsequent addition of ethyl iodide afforded a mixture of cis- and trans-β-lactams **1a** and **2a** in a 1:1 ratio together with β-lactam **10** which was isolated in 43% yield as a pure

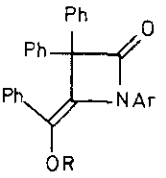
product. No trace of other by-products from C(4)- or O-alkylation was observed in any case. With NaH in DMF as base, 20% of pure **10** was isolated. In this case the crude reaction mixture was formed by a complex mixture of products from which only **10** could be isolated and identified.[10] In both cases, only one diastereoisomer of **10** was detected. The β-lactam **1b** also isomerizes to the *trans isomer* **2b**.[1] MNDO calculations indicate that in this case enolates **6b** and **7b** have the same stability ($\Delta\Delta H_f$ < 1 KJ/mol). Alkylation of **1b** with NaH in DMF followed by addition of ethyl iodide gave a mixture of β-lactams **1b** and **2b** in a 1:1 ratio together with β-lactam **11** which was isolated in 35% yield as only one diastereoisomer of unknown configuration. No trace of products from C4-alkylation was observed.



12



13



14

(Ar = p-$MeOC_6H_4$)

a: R = Me
b: R = Et
c: R = CH_2Ph
d: R = $CH_2CH{=}CH_2$

The above results prompted us to investigate alkylation reactions of 4-benzoyl-β-lactams **12** and **13**, both with only one possibility of enolization. Thus, treatment of β-lactam **12** with NaH in DMF followed by reaction with different primary alkyl halides only afforded the O-alkylated compounds **14**.[11] Analysis of the crude reaction mixture by ^{1}H-nmr shows aparently the presence of only one stereoisomer. Comparison of spectroscopic data for compounds **14** appears to indicate that the same isomer was formed in all cases. X-Ray structure determination of **14a** establishes the stereochemistry of the double bond as *Z*[12] (Figure).

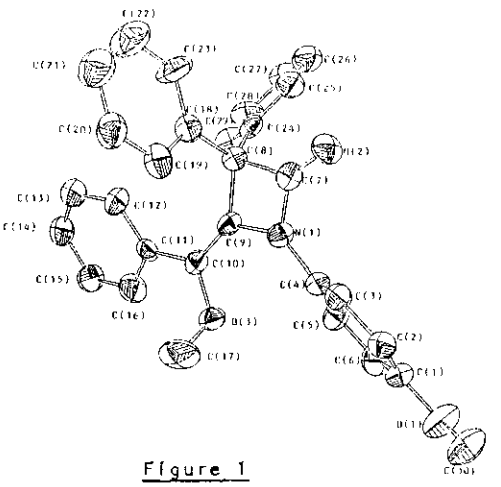
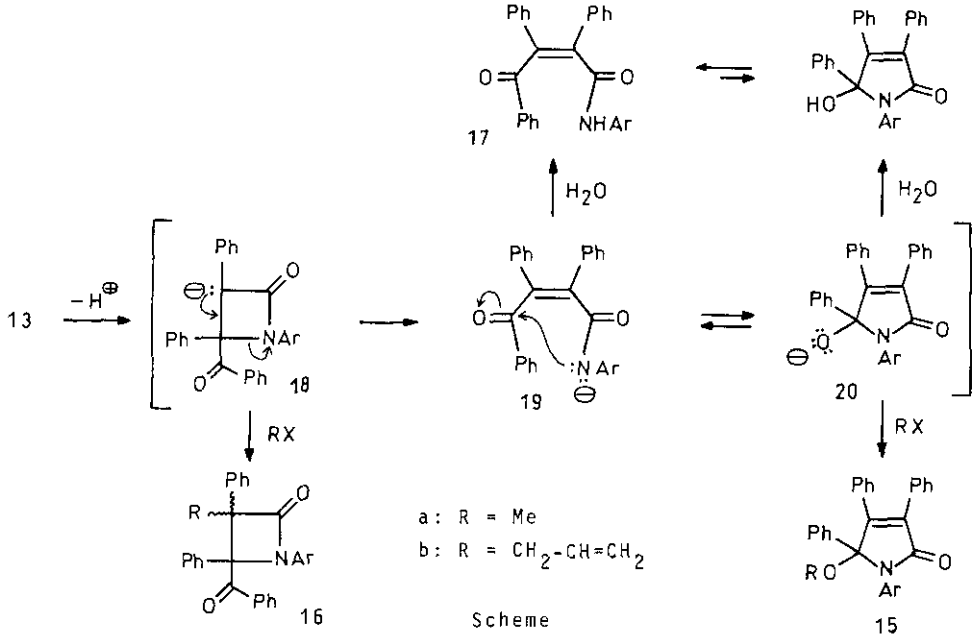


Figure 1

As we have recently reported,[13] reaction of β-lactam **13** with NaH/DMF followed by addition of an primary alkyl halide yielded 5-alkyloxy-2-pyrrolones **15** together with C-alkylated β-lactams **16**. When the reaction was performed without alkylating agent, conjugated γ-keto-α,β-unsaturated amide **17** was obtained after quenching.

Formation of products **15** and **16** from β-lactam **13** may be accounted for by alkylation of the corresponding anions **18** and **20**.[14] Compound **17** could arise either directly from the open chain species **19** or from the cyclic alkoxide **20** followed by tautomerization of the resulting hydroxylactam isomer[15] (Scheme).



Scheme

In summary, 4-benzoyl-2-azetidinones react with alkyl halides in presence of bases in a regioselective fashion depending on the substitution pattern in the β-lactam ring and on the nature of the alkylating agent.

EXPERIMENTAL

Melting points were determined in a Büchi 510 apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer, ν values in cm^{-1}. ^1H-Nmr spectra were obtained on a Varian T60-A or on a Bruker WH-360FT spectrometers for $CDCl_3$ solutions and the chemical shifts are reported in δ (ppm from internal TMS). ^{13}C-Nmr spectra were determined on a Varian FT-80A spectrometer. Silica gel Merck 60 (70-230 mesh), 60 (230-400 mesh) and DC-Alufolien 60 F_{254} were used for conventional, flash column chromatography and analytical tlc, respectively. MNDO calculations were performed on a VAX-11/780 computer.

Alkylation reactions of 4-benzoyl-2-azetidinone 1a

a) **With LDA/THF as base.**- To a solution of diisopropylamine (0.196 ml) in 1.4 ml of anhydrous THF was added 0.89 ml of n-BuLi (Aldrich, 1.6M in hexane) and the mixture was kept at -78°C for 15

min under a nitrogen atmosphere. Then, the mixture was warmed up to -15ºC and a suspension of 200 mg (0.56 mmol) of **1a** in 5 ml of THF was added. The reaction mixture was stirred for 15 min after which time 0.114 ml (1.42 mmol) of ethyl iodide dissolved in 5ml of THF was added. After 15 min at -15ºC the reaction mixture was hydrolyzed with a saturated solution of NaCl, extracted with ethyl acetate (3x15 ml) and the aqueous layer was further extracted with methylene chloride. The combined organic extracts were dried over magnesium sulfate. The drying agent was removed by filtration and the resulting solution was concentrated in vacuo to afford 210 mg of crude product which was purified by column chromatography (hexane:diethyl ether, 2:1) followed by recrystallization from ethanol to give 100 mg of **10** (48%), mp 108-110ºC. Ir (KBr): 1745, 1695 cm^{-1}. ^{1}H-Nmr δ 1.1 (t, 3H, CH_3), 2.4 (q, 2H, CH_2), 3.7 (s, 3H, OCH_3), 5.5 (s, 1H, H-4), 6.7-7.8 (m, 14H, arom.). ^{13}C-Nmr δ 9.2 (CH_3), 28.7 (CH_2), 55.4 (OCH_3), 65.6 (C-3), 68.3 (C-4), 114.2, 118.4, 127.5, 127.7, 128.3, 128.4, 128.6, 129.0, 129.2, 131.0, 133.6, 134.0, 136.0, 156.3, 166.4 (C-2), 193.5 (COPh). Anal. Calc. for $C_{25}H_{23}NO_3$: C, 77.92; H, 5.97; N, 3.64. Found: C, 77.85; H, 5.95; N, 3.70.

b) **With NaH/DMF as base.**- To a cold (0ºC) mixture of **1a** (500 mg, 1.40 mmol) and 0.14 ml (1.70 mmol) of ethyl iodide in 15 ml of anhydrous DMF, was added, under a nitrogen atmosphere, 48 mg (1.60 mmol) of sodium hydride (80% dispersion in mineral oil). After addition was complete, the temperature was raised to room temperature and was stirred for 5 h, after which time, it was hydrolyzed with a saturated solution of NaCl, extracted with ethyl acetate (3x15 ml) and the combined organic extracts were dried over magnesium sulfate. The drying agent was removed by filtration and the solvent was distilled in vacuo to afford 425 mg of reaction crude. Fractional recrystallization of the crude product from ethanol gave 110 mg (20%) of pure **10**.

Reaction of 4-benzoyl-2-azetidinone 1b with NaH and ethyl iodide in DMF. The same procedure as for **1a** was followed (reaction time, 20 h). From 300 mg (1.02 mmol) of **1b**, 120 mg of **11** (35%) was isolated after chromatography of the crude reaction mixture (hexane: ethyl acetate, 2:1). The product was isolated as a transparent yellowish oil which could not be crystallized. Ir (KBr): 1740 cm^{-1}, ^{1}H-Nmr δ 1.0 (t, 3H, CH_3), 1.2 (d, 3H, CH_3), 3.2-4.1 (m, 6H, OCH_2, H-3, OCH_2), 6.6-7.6 (m, 9H, arom.). Anal. Calc. for $C_{20}H_{21}NO_3$: C, 74.30; H, 6.50; N, 4.35. Found C, 75.10; H, 6.45; N, 4.20.

Synthesis of 4-(α-alkyloxybenzylidene)-2-azetidinones 14. General procedure.- To a cold (0ºC) solution of 2-azetidinones **12** (1 mmol) in anhydrous DMF, an excess of NaH (80% suspension in mineral oil) was added under nitrogen. After 10 min the alkylating agent (2.5-6.5 mmol) was added at room temperature and the mixture was stirred for 2 h. Hydrolysis and work-up (extraction with ethyl acetate, drying with sodium sulfate and evaporation of the solvent in vacuo) afforded the

crude 2-azetidinone **14** which was purified as indicated in each case.

4Z-(α-Methoxybenzylidene)-1-(p-methoxyphenyl)-3,3-diphenyl-2-azetidinone (14a).- This compound was prepared from **12** (1g, 2.30 mmol), DMF (30 ml), NaH (200 mg, 6.65 mmol), and methyl iodide (0.41 ml, 6.65 mmol). The crude reaction mixture was crystallized from ethanol and chromatographed on silica gel using benzene as eluent. Yield, 460 mg (45%), mp 150-152°C (ethanol). Ir (KBr): 1780 cm^{-1}. ^{1}H-Nmr δ 3.2 (s, 3H, OCH_3), 3.8 (s, 3H, CH_3OAr), 6.7-7.5 (m, 19H, arom.). ^{13}C-Nmr δ 54.8 (CH_3OAr), 57.4 (=C-OCH_3), 70.8 (C-3), 113.1 (C-4), 169.4 (C-2). Anal. Calc. for $C_{30}H_{25}NO_3$: C, 80.54; H, 5.59; N, 3.13. Found C, 80.15; H 5.70; N, 2.90.

4Z-(α-Ethoxybenzylidene)-1-(p-methoxyphenyl)-3,3-diphenyl-2-azetidinone (14b).- This compound was prepared from **12** (780 mg, 1.82 mmol), DMF (30 ml), NaH (136 mg, 4.55 mmol), and ethyl iodide (0.36ml, 4.55 mmol). The crude reaction mixture was disgregated in ethyl ether, crystallized from ethanol, and the product was chromatographed on silica gel using benzene as eluent. Yield, 510 mg (61%), mp 154-156°C. Ir (KBr): 1780 cm^{-1}. ^{1}H-Nmr δ 0.8 (t, 3H, CH_3), 3.4 (q, 2H, CH_2), 3.8 (s, 3H, OCH_3), 6.5-7.5 (m, 19H, arom.). ^{13}C-Nmr 14.1 (CH_3), 54.8 (OCH_3), 65.5 (OCH_2), 70.8 (C-3), 113.2 (C-4), 169.2 (C-2). Anal. Calc. for $C_{31}H_{27}NO_3$: C, 80.69; H, 5.85; N, 3.03. Found C, 80.1; H, 5.90; N, 2.85

4Z-(α-Benzyloxybenzylidene)-1-(p-methoxyphenyl)-3,3-diphenyl-2-azetidinone (14c).- This compound was prepared from **12** (800 mg, 1.84 mmol), DMF (40 ml), NaH (442 mg, 14.72 mmol), and benzyl chloride (1.06 ml, 9.20 mmol). Reaction time, 5 h. The pure 2-azetidinone **14c** was obtained directly from the crude reaction mixture by crystallization in ethanol. Yield, 910 mg (95%), mp 122-124°C. Ir (KBr): 1785 cm^{-1}. ^{1}H-Nmr δ 3.7 (s, 3H, OCH_3), 4.3 (s, 2H, OCH_2), 6.4-7.3 (m, 24H, arom.). ^{13}C-Nmr δ 54.8 (OCH_3), 70.8 (C-3), 71.6 (CH_2Ph), 113.1 (C-4), 169.2 (C-2). Anal. Calc. for $C_{36}H_{29}NO_3$: C, 82.60; H, 5.54; N, 2.67. Found C, 82.40; H, 5.60; N, 2.55.

4Z-(α-Allyloxybenzylidene)-1-(p-methoxyphenyl)-3,3-diphenyl-2-azetidinone (14d).- This compound was prepared from **12** (770 mg, 1.77 mmol), DMF (30 ml), NaH (425 mg, 14.16 mmol), and allyl chloride (0.72 ml, 8.85 mmol). Reaction time, 5 h. The pure 2-azetidinone **14d** was obtained directly from the crude reaction mixture by crystallization in ethanol. Yield, 750 mg (90%), mp 136-138°C. Ir (KBr): 1775 cm^{-1}. ^{1}H-Nmr δ 3.7 (s, 3H, OCH_3), 3.7-3.8 (dd, 2H, CH_2), 4.7-5.0 (m, 2H, $CH=CH_2$), 5.2-5.7 (m, 1H, $CH=CH_2$), 6.7-7.5 (m, 19H, arom.). ^{13}C-Nmr δ 54.8 (OCH_3), 71 (C-3 and OCH_2), 133.3 (C-4), 117.7 ($CH=CH_2$), 169.2 (C-2). Anal. Calc. for $C_{33}H_{27}NO_3$: C, 81.18; H, 5.71; N, 2.95. Found C, 81.20; H, 5.90; N, 2.80.

Reaction of 4-benzoyl-2-azetidinone 13 with NaH and alkyl halides in DMF. General procedure.- A mixture of **13** (1 mmol) and NaH (80% suspension in mineral oil, 3 mmol) in anhydrous DMF (25 ml) was stirred at room temperature. After 10 min the alkyl iodide (2.5 mmol) was added. The reaction

mixture was stirred at room temperature during 3h. After hydrolysis, the organic layer was taken up 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 reaction mixture which was purified as indicated in each case.

Reaction with methyl iodide.- After chromatography of the crude reaction mixture on silica gel using methylene chloride as eluent we obtained, in sequence, the β-lactam **16a** (58%), as an inseparable mixture of diastereoisomers (α/β = 5), and the γ-lactam **15a** (7%). Compound **16a**: yellow viscous oil. Ir ($CHCl_3$): 1740 (NC=O), 1685 (C=O) cm^{-1}. ^1H-Nmr ($CDCl_3$): δ 1.4 (s, 3H, CH_3, α isomer), 1.8 (s, 3H, CH_3, β isomer), 3.6 (s, 3H, OCH_3, β isomer), 3.7 (s, 3H, OCH_3, α isomer). Anal. Calc for $C_{30}H_{29}NO_3$: C, 80.54; H, 5.59; N, 3.13. Found C, 80.40; H, 5.70; N, 3.20. Compound **15a**: mp 139-140°C (ethanol). Ir (KBr): 1690 (C=O) cm^{-1}. ^1H-Nmr (DCCl$_3$): δ 3.5 (s, 3H, OCH_3), 3.7 (s, 3H, CH_3OAr), 6.5-7.7 (m, 19H, arom.). Anal. Calc. for $C_{30}H_{29}NO_3$: C, 80.54; H, 5.59; N, 3.13. Found C, 80.70; H, 5.45; N, 3.40.

Reaction with allyl chloride.- The crude reaction mixture (yellow solid) was crystallized from a mixture of n-hexane/ethyl acetate (4/1). The white solid was filtered, washed with the above mixture and crystallized from ethanol, yielding 66% of **15b**, mp 175-176°C. Ir (KBr): 1690 (C=O) cm^{-1}. ^1H-Nmr ($CDCl_3$): δ 3.63 (s, 3H, OCH_3), 4.22 (t, 2H, OCH_2), 5.06-5.53 (m, 2H, $=CH_2$), 5.72-6.25 (m, 1H, CH=), 6.50-7.70 (m, 19H, arom.). Anal. Calc. for $C_{28}H_{25}NO_3$: C, 81.18; H, 5.71; N, 2.95. Found C, 81.20; H, 5.70; N, 2.80.

From the mother liquors, by concentration in vacuo and crystallization from ethanol, compound **16b** was isolated in 24% yield, mp 128-129°C. Ir (KBr): 1760 (NC=O), 1680 (C=O) cm^{-1}. ^1H-Nmr ($CDCl_3$): δ 2.29 (d, 2H, CH_2), 3.70 (s, 3H, OCH_3), 4.43-4.93 (m, 2H, $=CH_2$), 5.36-5.86 (m, 1H, CH=), 6.60-7.70 (m, 19H, arom.). ^{13}C-Nmr ($CDCl_3$): δ 42 (CH_2), 55 (OCH_3), 71.8 (C-3), 78.7 (C-4), 118.3 (CH_2=), 167.3 (C-2), 199.4 (PhC=O). Anal. Calc. for $C_{28}H_{25}NO_3$: C, 81.18; H, 5.71; N, 2.95. Found C, 81.05; H, 5.85; N, 3.05.

N-(p-Anisyl)-4-oxo-2,3,4-triphenylbutenamide (17).- The above general procedure was follows, but without addition of the alkyl halide. The crude reaction mixture was crystallized from chloroform. Yield: 80%, mp 113-117°C (chloroform). Ir (KBr): 3300 (broad, NH), 1690 (PhC=O), 1675 (NHC=O) cm^{-1}. ^1H-Nmr (Acetone-d_6): δ 3.7 (s, 3H, OCH_3), 6.38 (s, 1H, NH), 6.5-7.9 (m, 19H, arom.). ^{13}C-Nmr ($CDCl_3$): 168.0 (PhC=O), 205.7 (NHC=O). Anal. Calc. for $C_{29}H_{25}NO_3$: C, 80.36; H, 5.31; N, 3.23. Found C, 80.40; H, 5.45; N, 3.05.

ACKNOWLEDGEMENTS

We thanks the CAICYT for financial support (Grant 320-84)

REFERENCES AND NOTES

1. B. Alcaide, G. Dominguez, G. Escobar, U. Parreño, and J. Plumet, Heterocycles, 1986, 24, 1579.
2. Examples of base-induced epimerization of monocyclic β-lactams are, to the best of our knowledge, very scarce. For one example, see: D. A. Nelson, J. Org. Chem., 1972, 37, 1447.
3. J. Catalán and A. Macías, J. Chem. Soc., Perkin Trans 2, 1979, 1632.
4. For other recent MO calculation on β-lactam ring, see: E. Sedano, J. M. Ugalde, F.P. Cossío, and C. Palomo, J. Mol. Struct. (Theochem.), 1986, 166, 481.
5. M. J. S. Dewar and W. Thiel, J. Am. Chem. Soc., 1977, 99, 4899.
6. Substitution of the formyl group at C-4 by a vinyl ketone residue did not modify significantly the results.
7. The structures were fully minimized with exception of geometrical parameters related with the phenyl ring which were fixed equal to standard values except for the dihedral angle C_6-C_5-C_3-C_2 (Figure 2)

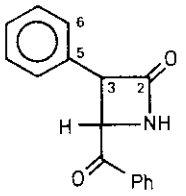


Figure 2

8. For other studies related with the deuteration of enolates derived from bicyclic β-lactams, see: H. Hirai, K. Sawada, M. Aratani, and M. Hashimoto, Tetrahedron Letters, 1985, 26, 1739.
9. LDA has been widely used in alkylations and aldolizations of position 3 in β-lactams. For selected examples, see: a) T. Durst, R. van der Elzen, and R. Legault, Can. J. Chem., 1974, 52, 3206; b) I. Shinkai, T. Liu, R. A. Reamer, and M. Sletzinger, Tetrahedron Letters, 1982, 23, 4899; c) A. Bevin-Hamlet and T. Dust, Can. J. Chem., 1983, 61, 411; d) J. d'Angelo and F. Pecquet-Dumas, Tetrahedron Letters, 1983, 24, 1403.
10. We have tested a great number of alkylation conditions employing different bases and solvents. The reported results are the only reproducible conditions.
11. The 4-(α-alkyloxybenzylidene)-β-lactams **14** appear to be unknown in the literature. However, several methods have been reported for the preparation of related 4-alkylidene-β-lactams. See, for example: a) I. Yamamoto, I. Abe, M. Nozawa, M. Kotani, J. Motoyoshiya, H. Gotoh, and K. Matcuzaki, J. Chem. Soc., Perkin Trans. 1, 1983, 2297; b) J. J. Tufariello, D. J. P. Pinto, A. S. Milowsky, and D. V. Reinhardt, Tetrahedron Letters, 1987, 28, 5481; c) A. Battaglia, G. Cainelli, D. Giacomini, G. Martelli, and M. Panunzio, Tetrahedron Letters, 1987, 28, 4347;

d)H. Alper and N. Hamel, Tetrahedron Letters, 1987, 28, 5237; e) S. Hirokami, T. Takahashi, M. Nagata, and T. Yamazaki, J. Org. Chem., 1987, 52, 2455; f) G. I. Georg and J. Kant, J. Org. Chem., 1988, 53, 692.

12. X-Ray analysis has been performed by Dr. A. Monge and Miss V. Pérez-García (Instituto de Química Inorgánica "Elhuyar"). Full data will be published by the authors in due course. We thank this private communication.

13. B. Alcaide, G. Dominguez, A. Martin-Domenech, J. Plumet, A. Monge, and V. Pérez-García, Heterocycles, 1987, 26, 1461.

14. While preparing for this paper a rather similar interpretation has been suggested by Manhas and coworkers to account for our results. See: M. S. Manhas, D. R. Wagle, J. Chiang, and A. K. Bose, Heterocycles, 1988, 27, 1755.

15. For related hydroxylactam-keto amide tautomerisms see: R. E. Valters and W. Flitsch, "Ring-Chain Tautomerism", ed. by A. R. Katritzky, Plenum Press, New York, 1985, pp. 49-87.

Received, 7th November, 1988