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NEW STEREOCHEMICAL OUTCOMES IN THE CYCLOADDITION OF ACID HALIDES OR EQUIVALENTS TO CINNAMYLIDENEAMINES: A CONCISE NEW APPROACH TO 4-ACETOXYAZETIDIN-2-ONES[1].

J.M. Aizpurua, F.P. Cossío , B. Lecea, C. Palomo*

Departamento de Química Orgánica . Facultad de Ciencias Químicas.
Universidad del País Vasco. Alza,San Sebastián . Spain.

Abstract: The reaction between 2-methylcinnamylideneamines and acid halides or equivalents leads to the stereospecific formation of cis- β-lactams. A new three steps approach to 4-acetoxyazetidin-2-ones as building blocks of β-lactam antibiotics is also described.

Although many methods are now available for the synthesis of β-lactams, the acid halide imine method or equivalent provided the most easy access to the β-lactam ring. However, from this method, it is often difficult to predict the stereochemistry of the product. For example, phthalimidoacetic acid generally gives trans- β-lactams[2] and alkoxyacetic acids often produce mixtures of cis and trans isomers, depending upon the experimental conditions employed[3] . Recently, we[4a] and others[4b] have found that the cis stereochemistry in the β-lactam formation increases when the bulk of the N-substituent is increased. Also, it has been described[5] that cinnamylidene Schiff bases react with acid halides or anhydrides to afford azetidinones, generally with a high degree of cis stereoselectivity. These results prompted us to report our own, related observations on the stereochemistry of β-lactam formation. Our finding is that increasing the bulk of the aldehyde in the starting Schiff base **2** the cis stereochemistry in the resulting β-lactam **3** predominates. Thus, we observed that methoxyacetyl chloride and phthalimidoacetyl bromide upon treatment with Schiff bases derived from cinnamaldehyde and 4-anisidine or 4-aminophenol yielded mixtures of cis and trans isomers, while 2-methylcinnamylideneamines, upon treatment with these acid halides yielded only the corresponding cis isomers. For example, whereas the Schiff base derived from cinnamaldehyde and 4-trimethylsiloxyaniline gave an equimolar mixture of the cis and trans 3-phthalimido- β-lactam (entry 3), the same acid bromide afforded only the cis isomer when the Schiff base derived from 2-methylcinnamaldehyde and 4-trimethylsiloxyaniline was involved in the cycloaddition process (entry 4). Results of some experiments are given in Table 1 to illustrate the stereospecificity of the reaction, even when the reaction conditions favoured the trans stereochemistry[3b].

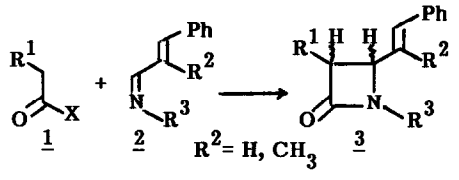
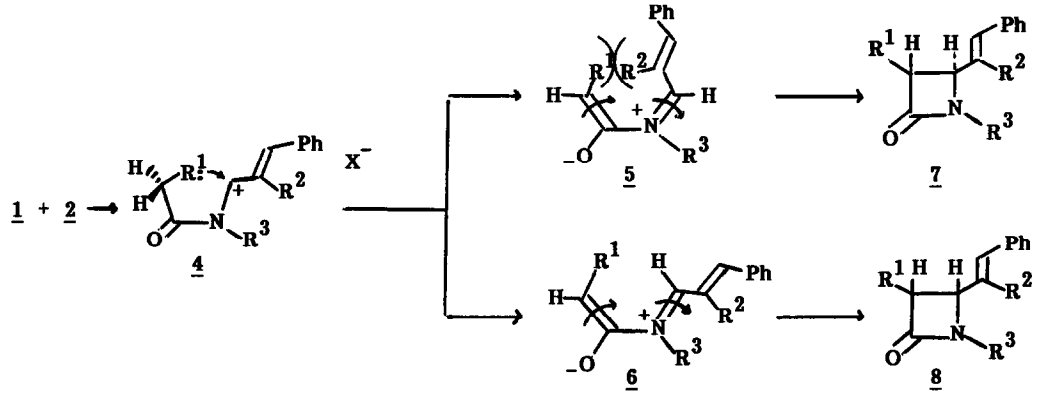


Table 1. cis : trans distribution in β-lactams **3**

Entry	Product **3**			Configuration [a]		m.p.(ºC) [d]
	R^1	R^2	R^3	cis : trans [b]	cis : trans [c]	
1	Phth	H	4-$CH_3OC_6H_4$	95 : 5 (45)	90 : 10	178-179
2	Phth	CH_3	4-$CH_3OC_6H_4$	———	100 : 0 (64)	105-107
3	Phth	H	4-$Me_3SiOC_6H_4$	50 : 50	———	——
4	Phth	CH_3	4-$Me_3SiOC_6H_4$	———	100 : 0 (50)[f]	172-174
5	MeO	H	4-$CH_3OC_6H_4$	———	90 : 10 (40)	146-149
6	MeO	CH_3	4-$CH_3OC_6H_4$	100 : 0 (60)	100 : 0 (40)	117-118
7	PhO	H	4-$CH_3OC_6H_4$	100 : 0 (45)	———	180-182
8	PhO	CH_3	4-$CH_3OC_6H_4$	100 : 0 (70)	———	157-158
9	ε [e]	CH_3	4-$CH_3OC_6H_4$	100 : 0 (50)	———	150-151

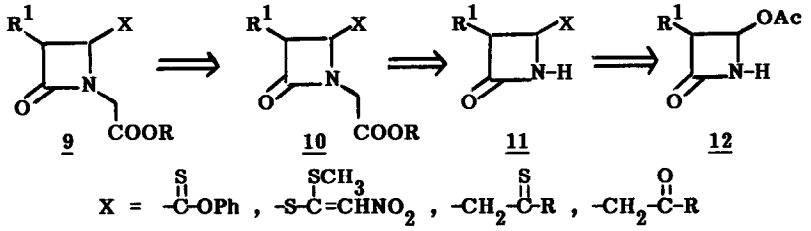
a) Cofiguration of C-3 and C-4 protons in all these β-lactams was determined by nmr spectroscopy. The numbers in parentheses indicate isolated yields of the β-lactam. b) The acid halide was added to a solution of the imine and triethylamine. c) Triethylamine was added to a solution of the acid halide and the imine. d) Melting point of the cis isomer. e) From Dane salt of aminoacetic acid and phenyl dichlorophosphate reagent, see ref. 10. f) The β-lactam was isolated with the free hydroxyl group.

Since, it is generally agreed that the acid chloride-imine reaction or equivalent proceeds through a dipolar intermediate of type 5 and 6, rather than by a concerted[2+2]addition[5], a satisfactory explanation of these results could be the following one:

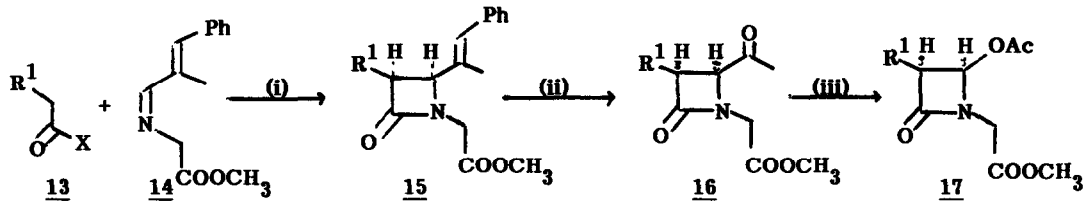


Abstraction of C_3 proton in the transition state 4 would give two zwitterions 5 and 6. These zwitterions upon conrotatory ring closure lead to the corresponding trans and cis β-lactams 7 and 8 respectively. When cinnamaldehyde Schiff bases were involved in the cycloaddition process, intermediates 5 and 6 may be formed, as judged by the results obtained, however, when $R^2=CH_3$, zwitterion 6 is greatly favoured since the R^1/R^2 interaction is relieved and therefore the cis-β-lactam 8 results as the exclusive reaction product. Therefore, starting from carboxylic acids carrying heteroatoms with a pair of free electrons at the α-position and 2-methylcinnamylideneamines, now, seems to be possible to predict the stereochemistry of the resulting β-lactam[6]. Furthermore, it is worthy of note that these β-lactams 8 could serve as precursors of 4-acetoxyazetidin-2-ones 12 since the N-substituent on these β-lactams 8 can be N-dearylated by means of Kronenthal's method[7].

These 4-acetoxyazetidin-2-ones 12 are known as useful building blocks of penem and carbapenem derivatives because they are easily convertible into various kinds of intermediates[8]. Recently, several research groups[9] have described methodologies for obtaining 4-unsubstituted-1-alkoxycarbonylmethylazetidin-2-ones 10 as the last synthetic target for making 9.



We have found that β-lactams of type 10 (X=OAc) can be prepared, stereospecifically, from β-lactams 15, by a double oxidation sequence as shown in scheme 1. Thus, when the Schiff base 14, derived from 2-methylcinnamaldehyde and methyl glycinate, was allowed to react with phthalimidoacetic acid 13a, phenyl dichlorophosphate reagent and triethylamine, the cis-β-lactam 15a was obtained in 66% yield as single isomer, as expected by the above observations. Oxidation of 15a was achieved by means of potassium permanganate in the presence of NaH_2PO_4 in aqueous acetone-dioxane at room temperature to give 16a in 80% yield. Using the same procedure, but starting from 15b as crude product, the yield of 16b decreased to 34%; however, ozonolysis of the crude compound 15b in dichloromethane as solvent at -70ºC afforded the desired β-lactam 16b in 55% overall yield. We also have found that the corresponding trans isomers can be obtained by isomerization of these 4-acyl-β-lactams with 1,8-diazabicyclo (5.4.0) undec-7-ene (DBU) as catalyst. Thus, 16b upon treatment with DBU for 60 min at room temperature yielded a mixture of cis and trans isomers in a molar ratio 65:35; when the reaction was allowed to stand at room temperature overnight an equimolar mixture of 16b and 18b was



a: R^1= Phth , b: R^1= PhO

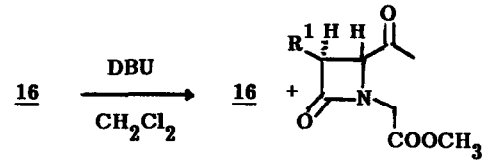
Scheme 1. (i) $PhOPOCl_2$, CH_2Cl_2, NEt_3, r.t. 20-24h; (ii) $KMnO_4$, NaH_2PO_4, H_2O-Me_2CO, r.t. or O_3, CH_2Cl_2, -70ºC, then Me_2S or Pyr; (iii) MCPBA, Bz, 80ºC.

obtained. Interesting, **16a** upon treatment with DBU for 24h yielded a mixture of cis and trans isomers in a molar ratio 10/90 . Under these conditions no isomerization was observed when **15a** was subjected to treatment with DBU.

Table. Isomerization of **16**

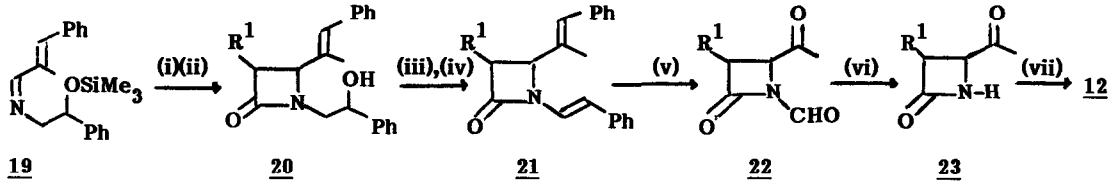
16	time	Product distribution[a] (%) **16**	**18**
a	24h	10	90
b	1h	65	35
	24h	50	50

a) Determined by nmr spectroscopy



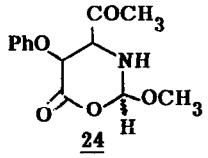
Finally, Baeyer-Villiger oxidation on these β-lactams **16** was carried out in refluxing benzene for 4-6hr by means of m-chloroperbenzoic acid (MCPBA) to give, after work-up, the expected 4-acetoxy-β-lactams **17** .

Next, we extended our study to the synthesis of N-unsubstituted 4-acetoxyazetidin-2-ones **12**. For this purpose, we selected as starting materials the β-lactams **20** prepared by reaction between the corresponding acetic acid and the Schiff base **19** promoted by phenyl dichlorophosphate reagent. As was expected, these β-lactams also showed cis stereochemistry at C_3-C_4 protons. These β-lactams **20** upon treatment[11] with triphenylphosphine dibromide, followed by dehydrobromination by means of DBU in benzene yielded the corresponding N-styryl- β-lactams **21** .



Scheme 2. (i) RCH_2COOH, NEt_3, $PhPPOCl_2$, r.t. 20-24h; (ii) 1N HCl, Me_2CO; (iii) Ph_3PBr_2, CH_2Cl_2; (iv) DBU, Bz, reflux, 15min ; (v) O_3, CH_2Cl_2, -70ºC; (vi) MeOH, NEt_3 ; (vii) MCPBA, CH_2Cl_2, r.t.

Simultaneous ozonolysis of the two double bonds on these β-lactams afforded the expected 4-acetyl--N-formylazetidin-2-ones **22**, (**22a** in 98% yield and **22b** in 80% yield). N-Deformylation was carried out under mild conditions by a simple modification of the known method[12]. Thus treatment of **22a** in methanol with a catalytic amount of triethylamine yielded **23a** in 85% yield; using sodium methoxide in place of triethylamine only a 50% yield of **23a** was obtained. Isomerization of **23a** by means of DBU in dichloromethane as solvent for 24h at room temperature, gave the trans isomer in a molar ratio 10:90 (cis : trans). When **22b** was subjected to N-deformylation with methanol and triethylamine as catalyst, compound **24**[13] m.p: 118-120ºC was isolated: ^{1}H-NMR ($CDCl_3$) δ ppm: 10.25 (m,1H,NH), 8.35(d,J=4Hz,1H,OCHO), 7.5-6.8 (m,5H,arom.), 5.3(s_b,2H,CH,CH), 3.65(s,3H,OCH_3), 2.25(s,3H,CH_3); IR(nujol) ν cm^{-1}: 3250 (NH), 1750, 1720 (C=O), along with the corresponding β-lactam **23b**, m.p. 149-149.5ºC, ^{1}H-NMR ($CDCl_3$)δppm:7.4-7.0 (m,5H,arom.), 6.6(s_b,1H,NH), 5.5(d,d, J=5Hz, J'=2Hz, 1H,CH), 4.55(d, J=5Hz, 1H, CH), 1.9(s,3H,CH_3).



24

Since β-lactams **23** can be easily converted into the corresponding 4-acetoxy-derivatives under Baeyer-Villiger conditions[3d,e] our procedure constitutes an atractive easy route to intermediates of β-lactam antibiotics. It is worthy of note that from this approach optically active compounds could be obtained from optically active Schiff bases of type **19**.

In conclusion, we have found easy alternatives for the synthesis of a wide variety of building blocks of bicyclic β-lactam compounds. Total synthesis of β-lactam antibiotics starting from these compounds[14] would be presented in the near future, as well as the scope of our method for producing cis-β-lactams starting from Schiff bases derived from 2-methylcinnamaldehyde and related aldehydes.

REFERENCES AND NOTES

1.- Contribution nº 60 in the series Reagents and Synthetic Methods. For the contribution nº 59 see J.M.Aizpurua , C. Palomo An.Quim. in press. The present work has been supported by Comision Asesora de Investigación Científica y Técnica (Project 994/84). A grant from Ministerio de Educación y Ciencia to F.P. Cossío is gratefully acknowledged.

2.- a) A.Arrieta, J.M. Aizpurua, C. Palomo, Synth.Commun., 12, 967 (1982); b) A.Arrieta,J.M.Aizpurua, C.Palomo, Tetrahedron Lett., 25, 3365 (1984).

3.- a) A.K.Bose, G.Spiegelman, M.S.Manhas, Tetrahedron Lett, 3167 (1971); b) A.K. Bose, Y.H.Chiang, M.S. Manhas, Tetrahedron Lett, 4091 (1972); c) A.K. Bose, B. Dayal, H.P.S. Chawla, M.S.Manhas, Tetrahedron Lett, 2823 (1972); d) A.K. Bose,J.C. Kapur, S.D.Sharma, M.S. Manhas,Tetrahedron Lett, 2319 (1973); e) A.K. Bose, B. Anjaneyulu, S.K. Battacharya, M.S.Manhas, Tetrahedron, 23,4769(1967).

4.- a) A. Arrieta, B.Lecea, C.Palomo,J.Chem.Soc.Perkin I, in press; b) H.W.Moore, G.Hughes, K. Srinivasachar, M.Fernandez, N.V. Nguyen, D. Schoon, A. Tranne, J.Org.Chem., 50, 4231(1985).

5.- T.W.Doyle, B. Belleau, B. Luh, C.F. Ferrari, M.P. Cunningham, Can.J.Chem.,55, 468 (1977).

6.- At this stage, we also have found that reaction between thiophenoxyacetic acid and imines **2** leads to the formation of the corresponding trans β-lactams. Such stereospecificity is not clear at present; see also, M.S. Manhas, S.S. Bari, B.M. Bhawal, A.K. Bose, Tetrahedron Lett, 25, 4733 (1984).

7.- D.R. Kronenthal, C.Y. Han, M.K. Taylor, J.Org.Chem., 47, 2765 (1982).

8.- a) For a review, see: T. Kametani, Heterocycles, 17, 463 (1982); b) Y. Ueda, S.C. Maynard,Tetrahedron Lett, 26, 6309 (1985); c) D.H. Hua, A. Verma, Tetrahedron Lett, 26, 547 (1985).

9.- a) W.J. Leanza, F.DiNino, D.A. Muthard, R.R. Wilkening, K.J. Wildonger, R.W.Ratcliffe, B.G. Christensen, Tetrahedron, 39, 2505 (1983); b) G. Johnson, P.M.Rees, B.C. Ross,J.Chem.Soc.Chem. Commun, 970 (1984); c) M.Hatanaka, H.Nitta, T.Ishimaru,Tetrahedron Lett,2387(1984); d) M. Hatanaka, T.Hishimaru, Tetrahedron Lett, 24, 4837 (1983); e) S. Hanessian, A. Bedeschi, C.Battistini, N.Mongelli, J.Am.Chem.Soc., 107, 1438 (1985).

10.- A. Arrieta, F.P. Cossío, C. Palomo, Tetrahedron Lett, 41, 1703 (1985).

11.- F.P. Cossío, C. Palomo, Tetrahedron Lett, 26, 4235 (1985).

12.- D. Häbich, Angew.Chem.Int.Ed.Engl., 22, 711 (1985).

13.- An analogous structure has been proposed when a β-lactam is formed by direct cyclization of β--amino acids, see: J.C. Sheehan, E.J. Corey, Org.Reactions, 9, 388 (1957).

14.- All the synthetic β-lactams are racemic mixtures. All new compounds had satisfactory microanalytical data and their proton magnetic resonance spectra ($CDCl_3$,ppm) fitted the assigned structures. Selected physical data includes: **15a** m.p. 191-194ºC(EtOH), δ 7.80(m,4H,arom.), 7.21(m,5H,arom.), 6.53 (m,1H,CH=), 5.55(d,J=6Hz,1H,CH), 4.78(d,J=6H,1H,CH), 4.35(d,d,J=20Hz,CH_2), 3.74(s,3H,CH_3), 1.60 (m,3H,=C-CH_3). **16a** m.p. 210-213ºC (EtOH), δ: 7.98(m,4H,arom.), 5.80(d,J=7Hz,1H,CH), 4.85(d, J=7Hz,1H,CH), 4.43(d,d,2H,J=18Hz,CH_2), 3.81(s,3H,CH_3), 2.16(s,3H,CH_3); **17a** m.p. 145ºC (EtOH), δ : 7.92(m,4H,arom.), 6.35(d,J=4Hz)1H,CH), 5.76(d,J=4Hz,1H,CH), 4.24(d,d,J=18Hz,2 H,CH_2), 3.82 (s,3H,CH_3), 1.97(s,3H,CH_3); **16b** m.p. 55-58ºC (CCl_4), δ : 7.28(m,5H,arom.), 5.55(d,J=6Hz,1H,CH), 4.86(d,J=6Hz,1H,CH), 4.28(d,d,J=18Hz,2H,CH_2), 3.72(s,3H,CH_3),2.20(s,3H,CH_3); **17b** m.p: 83.5ºC (CCl_4), δ: 7.18(m,5H,arom.), 6.40(d,J=4Hz,1H,CH), 5.42(d,J=4Hz,1H,CH), 4.10(d,d,J=18Hz,2H,CH_2), 3.73(s,3H,CH_3), 2.00(s,3H,CH_3), **22a** m.p: 186-190ºC, δ : 8.9(s,1H,CHO), 7.8(s_b,4H,arom.), 5.8(d,J=7Hz, 1H,CH), 4.85(d,J=7Hz,1H,CH), 2.0(s,3H,CH_3); **22b** m.p: 110-112ºC, δ: 8.95(s,1H,CHO), 7.5-6.8(m,5H, arom.),5.6(d,J=6Hz,1H,CH), 4.95(d,J=6Hz,1H,CH),2.25(s,3H,CH_3).

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