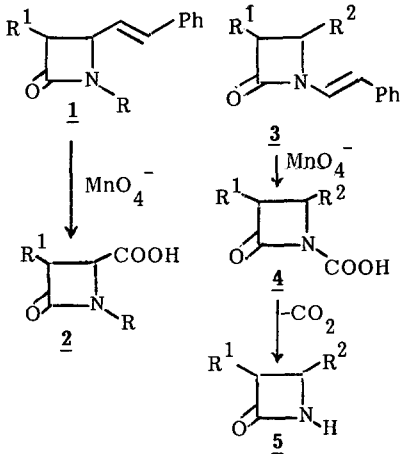
Tetrahedron Letters,Vol.26,No.35,pp 4235-4238,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A NOVEL SYNTHETIC APPROACH TO N-UNSUBSTITUTED β-LACTAMS[1]

Fernando P. Cossío and Claudio Palomo*
Kimika Organikako Departamendua, Kimika Fakultatea. Euskal Herriko
Unibertsitatea. Altza. Donostia. Spain.

Abstract: A convenient simple route to N-unsubstituted β-lactams is described. Formation of unusual N-styryl--β-lactams is the key of the method.

Synthesis of N-unsubstituted β-lactams have received increased attention in the past few years and specially with the advent of the third generation of β-lactam antibiotics[2]. We have been interested, therefore, in converting easily synthesized monocyclic β-lactams to the corresponding N-unsubstituted derivatives. Manhas and Bose[3] have reported that permanganate oxidation of β-lactams of type 1 give the corresponding 4-carboxy-2--azetidinones 2. We expected that under the same conditions β-lactams 3 afforded the N-unsubstituted β-lactams 5. Unfortunately, the direct disconnection approach of these β-lactams 3 leads to an unusual synthon, the vinylamine 9 (**Analysis 1**). However, we have found that by means of a simple functional group interconversion, (**Analysis 2**), these β-lactams 3 can be easily synthesized from the readily available 2-phenylethanolamine 13. In a typical example β-lactam 11a was prepared by our method[4], by reaction of phenoxyacetic acid 6 and the silylated Schiff base 12, formed from anisaldehyde and 2-phenylethanolamine 13, induced by phenyl dichlorophosphate reagent. Only a single isomer was obtained in 91% isolated yield (m.p. 175-177ºC). Treatment of the resulting free hydroxy β-lactam 11a or its trimethylsilyl ether with sodium iodide/trimethylchlorosilane[5] (molar ratio substrate/NaI/ClSiMe$_3$ = 1/3/3) in refluxing acetonitrile for 25 min, gives the corresponding β-lactam 10a in 88% yield. The crude iodo--compound was treated in benzene as solvent with 1,8-diazabicyclo (5.4.0)undec-7-ene (DBU) (molar ratio, substrate/DBU = 1/2) and the resulting mixture was refluxed for 30 min; then, the DBU.HI precipitated was filtered off. After work-up the crude N-styryl-β-lactam 3a was "in situ" oxidized by means of potassium permanganate affording the N-unsubstituted β-lactam 5a (40% overall yield 11→5 after recrystallization from ethanol, m.p. 167-168ºC, NMR δppm: 8.5,5.6 and 5.1 J_{AB} = 5 Hz, J_{AX} = 2 Hz, J_{BX} ≃ 0 Hz).



Analysis 1

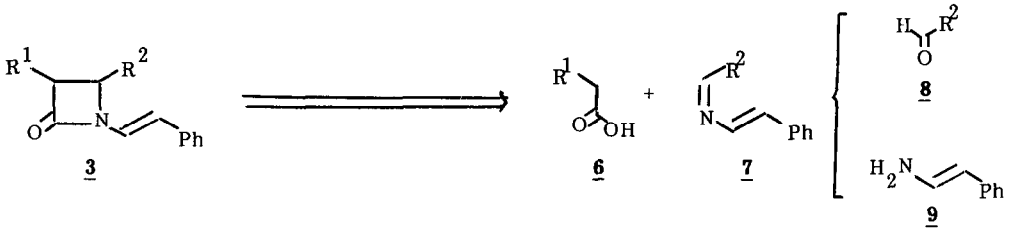
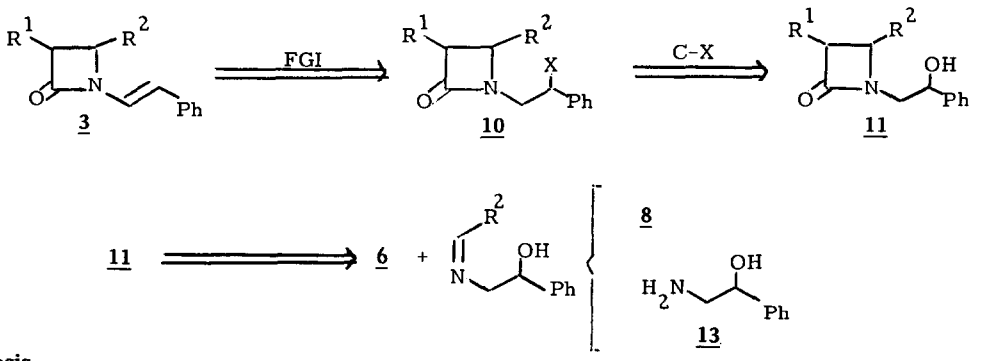


Table . β-lactams prepared

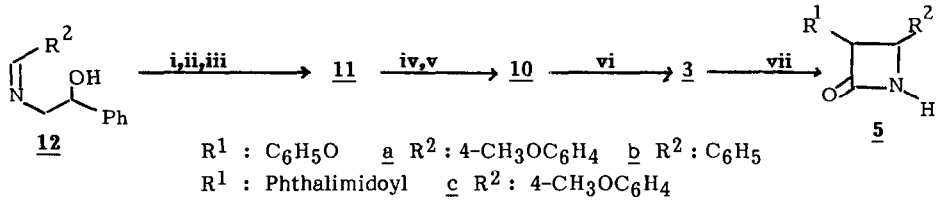
Compound [g]	% Yield	M.p.(ºC) [a] (lit.)	^{1}H-N.M.R. data (δ ppm, $CDCl_3$)
10a	85	146-150	7.4-6.6(m,14H,arom.); 5.3(d,J= 5 Hz,1H,COCH); 5.4-4.8(m,1H,CHBr) 5.1(d,J= 5 Hz,1H,NCH); 4.3-3.4(m,2H,CH_2); 3.7(s,3H,OCH_3)
3a	90	168-171	7.4-6.7(m,15H,=CH,arom.); 5.8(d,J= 14 Hz,1H,=CH); 5.4(d,J= 5 Hz, 1H,CH); 5.2(d,J= 5 Hz,1H,CH); 3.7(s,3H,OCH_3)
5a	62	165-166 (166-167) [b]	see text
10b	86	184-185	7.3-6.5(m,15H,arom.); 5.4(d,J= 5 Hz,1H,CH); 5.1(d,J= 5 Hz,1H,CH); 5.5-4.8(m,1H,CHBr); 4.4-4.0,3.7-3.2(m,2H,CH_2Br)
3b	98	160-164	7.3-6.6(m,16H,arom,=CH); 5.8(d,14H,=CH); 5.4(d,J= 5 Hz,1H,CH); 5.2(d,J= 5 Hz,1H,CH)
5b	77	174-176	7.3-6.4(m,11H,arom,NH); 5.4(dd,J= 2 Hz,J'= 5 Hz,1H,CH); 4.9(d,J= 5 Hz,1H,CH)
10c	64	193-196	7.6-6.5(m,13H,arom.); 5.3(d,J= 5 Hz,1H,CH); 5.1(d,J= 5 Hz,1H,CH); 5.5-4.9(m,1H,CHBr); 4.5-3.4(m,2H,CH_2CBr); 3.6(s,3H,OCH_3)
3c	94 [c]	syrup	7.6-6.5(m,14H,arom,=CH); 5.9(d,J= 14 Hz,=CH); 5.5(d,J= 5 Hz,1H, CH Z); 5.2(s_b,2H,CH E; 1H,CH Z); 3.7(s,3H,OCH_3 E); 3.5 (s, 3H, OCH_3 Z)
5c	40 [c]	——	8.3(s_b,1H,NH); 7.5-6.3(m,8H,arom.); 5.1(dd,J= 5 Hz, J'= 2 Hz,1H,CH, Z); 4.7(d,J= 2 Hz,1H,CH E); 4.6(d,J= 2 Hz,1H,CH E); 4.5-4.7(unresolved signal,1H,CH Z); 3.4(s,3H,OCH_3 E); 3.2(s,3H,OCH_3 Z)
17d	50 [d]	142-144	7.3-6.4(m,16H,arom,NH); 5.5(dd,J= 5 Hz,J'= 10 Hz,1H,CHCO); 4.8 d,J= 5 Hz,1H,CH); 5.1-4.7(m,1H,CH); 4.2(d,J= - 14 Hz,1H,OCHCO); 3.9(d,J= - 14 Hz,1H,OCHCO); 4.0-2.9(m,2H,NCH_2)
19d	64 [e]	165-167	7.6-6.3(m,17H,arom,NH,=CH); 5.8(d,J= 16 Hz,1H,=CH); 5.6(dd,J= 5 Hz,J'= 10 Hz,1H,CHCO); 5.2(d,J= 5 Hz,1H,CH); 4.3(d,J= - 14 Hz,1H, OCHCO); 4.0(d,J= - 14 Hz,1H,OCHCO)
20d	80	134-135 (134-136) [f]	7.3-6.4(m,12H,arom,NH,NH); 5.6(dd,J= 5 Hz,J'= 10 Hz,1H,CH), 5.0 d,J= 5 Hz,1H,CH); 4.3(d,J= - 14 Hz,1H,OCHCO); 4.0(d,J= - 14 Hz, 1H,OCHCO)
17e	47 [d]	128-130	7.4-6.5(m,15H,arom,NH); 5.5(dd,J= 5 Hz,J'= 10 Hz,1H,CHCO); 4.8 d,J= 5 Hz,1H,CH); 5.2-4.7(m,1H,CH); 4.3(d,J= - 14 Hz,1H,OCHCO); 4.2(d,J= - 14 Hz,1H,OCHCO); 3.7(s,3H,OCH_3); 4.3-2.9(m,2H,NCH_2); 2.2(s_b,1H,OH)
19e	53 [e]	146-147	7.3-6.5(m,16H,arom,NH,=CH); 5.8(d,J= 16 Hz,1H,=CH); 5.7(dd,J= 5 Hz,J'= 10 Hz,1H,CHCO); 5.2(d,J= 5 Hz,1H,CH); 4.3(d,J= -14 Hz,1H, OCHCO); 4.1(d,J= - 14 Hz,1H,OCHCO); 3.7(s,3H,OCH_3)
20e	75	154-155	7.3-6.4(m,11H,arom,NH,NH); 5.5(dd,J= 5 Hz,J'= 10 Hz,1H,CH); 4.9 (d,J= 5 Hz,1H,CH); 4.3(d,J= -14 Hz,1H,OCHCO); 4.1(d,J= -14 Hz,1H, OCHCO); 3.7(s,3H,OCH_3)

a) A single spot was detected by tlc analysis except for 5c which showed two spot corresonding to Z and E isomers; b) A.K. Bose et al. Tetrahedron Lett. 3851 (1973); c) both isomers Z (25%) and E (75%) were obtained after work-up. The Z-E ratio was determined by pmr analysis; d) overall yield from the corresponding imine 14; e) overall yield from 17 ; f) A.K. Bose et al. Synthesis 543 (1979); g) for preparation of β-lactams 11 see ref. 4.

Analysis 2



Synthesis

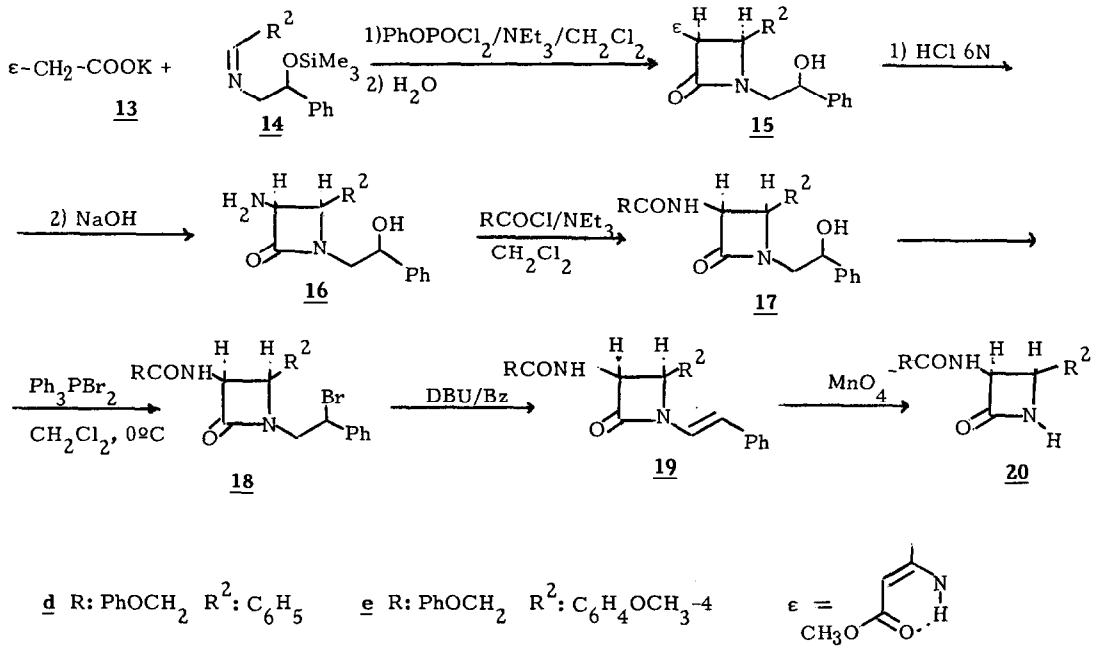


R^1 : C_6H_5O a R^2 : 4-$CH_3OC_6H_4$ b R^2 : C_6H_5
R^1 : Phthalimidoyl c R^2 : 4-$CH_3OC_6H_4$

i: $ClSiMe_3/NEt_3/CH_2Cl_2$/r.t.; **ii:** $R^1CH_2COOH/NEt_3/PhOP(O)Cl_2$; **iii:** H_2O;
iv: $ClSiMe_3/NEt_3/CH_3CN$/r.t.; **v:**NaX/$ClSiMe_3$/reflux; **vi:**DBU/Bz/reflux;
vii: $MnO_4K/(CH_3)_2CO/H_2O$.

An alternative analogous procedure can be also developed from the corresponding bromides 10(X:Br),thus, treatment of β-lactam 11 with phosphorus tribromide molar ratio 1:2, in refluxing benzene for 15 min affords the corresponding bromide 10 in 60-85% yield. Dehydrobromination of 10 by means of DBU in the same solvent gave the expected N-styryl β-lactam 3 in 95% yield. Selected examples were prepared by this method as shown in the Table. It is worthy of note that, Schiff bases 12 involving a bulky silyl ether and phenyl groups[6] allows an stereospecific formation of β-lactams 11 as precursors of the N-unsubstituted β-lactams 5.

The wide utility of our method is exemplified by the synthesis of 3-phenoxyacetamido-4-phenyl-2-azetidinone, a compound reported to show anti-β-lactamase activity[7]; thus, the potassium salt of (α-methyl-β-methoxycarbonyl)-vinylaminoacetic acid 13 was allowed to react with phenyl dichlorophosphate[4] and triethylamine in the presence of the corresponding trimethylsiloxy Shiff base 14 to form the corresponding α-vinylamino-β--lactam 15 as single stereoisomer. The vinylamino group of 15 was cleaved under mild acid condition to produce the free amino compound 16 which was directly acylated to 17. When 17 was subjected to bromination with phosphorus tribromide very low yield of the corresponding bromo compound 18 was obtained and side reactions predominated. However, we have found that the desired bromides 18 can be obtained in high yields by treatment of 17 with triphenylphosphine dibromide[8] at 0ºC for 30 min in dichloromethane as solvent. Dehydrobromination of 17 by means of DBU and permanganate oxidation of the N-styryl-β-lactam 19 affords the N-unsubstituted β-lactam 20 in excellent yield. An additional important aspect is that analytically pure products



d R: $PhOCH_2$ R^2: C_6H_5 e R: $PhOCH_2$ R^2: $C_6H_4OCH_3$-4

are obtained by very easy work-up in all sequences of the method. Therefore, the method described here may prove to be a useful alternative strategy to other recent methods developed for the same purpose[9].

REFERENCES AND NOTES

1. Considered as Reagents and Synthetic Methods 50. This work was in part supported by GEMA S.A.-LIESSA S.A. (Spanish). A grant from Ministerio de Educación y Ciencia to F.P. Cossío is gratefully acknowledged. We are grateful to BASF S.A. (Spanish) for financial support (supply of triphenylphosphine).
2. a) R.B. Morin, H. Gormán, Ed. "Chemistry and Biology of β-Lactam Antibiotics" Academic Press, Vol. 1, New York, 1982; b) P.G. Sammes, Ed. "Topics in Antibiotic Chemistry" Vol. 3, Ellis Howood Ltd. 1980; c) J. O'Sullivan, E.P. Abraham, "Antibiotics" Vol. IV, Ed. J.W. Corcoran, Springer-Verlag, Berlin, 1981.
3. A.K. Bose, M.S. Manhas, S.G. Amin, J.C. Kapur, J. Kreder, L. Mukkavilli, B. Ram, J.E. Vicent, **Tetrahedron Lett.** 2771 (1979).
4. a) J.M. Aizpurua, I, Ganboa, F.P. Cossío, A. González, A. Arrieta, C. Palomo, **Tetrahedron Lett. 25,** 3905 (1984); b) A. Arrieta, F.P. Cossío, C. Palomo, **Tetrahedron, 41,** 1703 (1985).
5. a) G.A. Olah, S.C. Narang, G.B. Gupta, R. Malhotra, **J.Org.Chem. 44,** 1247 (1979); b) idem, **J.Org.Chem. 45,** 1638 (1980).
6. We are continuing to study the scope of the method and its utility from bulky chiral Schiff bases **12** according to the observations of Manhas and Bose; see A.K. Bose, M.S. Manhas, J.M. Van der Veen, S.S. Bari, D.R. Wagle, **Tetrahedron Lett. 26,** 33 (1985) and ibid "Recent Advances in the Chemistry of β-Lactam Antibiotics" Third International Symposium, 1984, The Royal Society of Chemistry,Burlington House, London.
7. British Patent, 1301720 (1973); **Chem. Abs. 76,** 723809 (1973).
8. L.Horner, H.Oediger, H.Hoffman, **Justus Liebigs.Ann.Chem. 626,** 26 (1959).
9. a) D.R.Kronenthal, C.Y.Han, M.K.Taylor, **J.Org.Chem. 47,** 2765(1982); b) A.K.Bose, M.S.Manhas, J.E.Vincent, K.Gala, I.F.Fernández, **J.Org.Chem. 47,** 4075(1982); c) T.Fukuyama, A.A. Laird, C.A. Schimdt, **Tetrahedron Lett. 42,** 4709 (1984).

(Received in UK 25 June 1985)