Tetrahedron Letters,Vol.26,No.35,pp 4239-4242,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

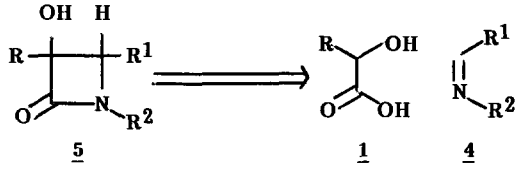
STEREOSELECTIVE ANNELATION OF TRIMETHYLSILOXYACETIC ACIDS AND IMINES INTO 3-HYDROXY- β-LACTAMS[1]

Fernando P. Cossío and Claudio Palomo*

Kimika Organikako Departamendua. Kimika Fakultatea.
Euskal Herriko Unibertsitatea. Altza. Donostia. Spain.

Abstract: Stereoselective synthesis of variously substituted 3-hydroxy-β-lactams can be achieved by the annelation of Schiff bases with trimethylsiloxyacetic acids promoted by phenyl dichlorophosphate reagent. A potential synthesis of N-unsubstituted β-lactams is made.

In recent years monocyclic β-lactams have become a center of attention in many laboratories. Suitable substituted monocyclic β-lactams can be converted to bicyclic or polycyclic β-lactams including naturally ocurring 6-hydroxypenams, 7-hydroxycephems, cephamicins and their analogs[2]. The first naturally occurring member of this series to be reported in the literature[3a] was Wildfire toxin, Tabtoxin 5a, for which the firt total synthesis was recently developed[3b]. As part of a program devoted to the synthesis of 3-substituted β-lactam derivatives[4] we report here on a general method for the synthesis of 3-hydroxy-β-lactams of type 5. The disconnection approach of these β-lactams 5 leads to suitable starting materials, the hydroxyacetic acids 1. From this approach the acid chloride-imine method is not applicable because hydroxyacetyl chloride is not commercially available and not simple to prepare. An alternative pathway includes the use of reagents for activating the carboxyl group in the starting acetic acid, but however this method is not applicable when active bifunctional compounds are involved[5]. To avoid these drawbacks, protection of the hydroxyl group is required and several alcoxyacetic acids[6a] andacyloxyacetic acids[6b] have been used to form after acid-cleavage the corresponding 3-hydroxy-β-lactams. From this acid hydrolysis, epimerization, opening of the β-lactam ring[6b] and side reactions can be expected. Also, Bose and coworkers[6c] indicated that the scope of these procedures for hydrolysis appears to be limited. Within recent years, silylation as a protective method in the synthesis of organic compounds has been increasing in use[7]. The easy removal of the trimethylsilyl group under very mild conditions has promted us to investigate the synthetic potential of this protecting group as source of the hydroxyl function. Two papers[8] have revealed that trimethylsiloxyacetates 2 underwent easy silatropic rearrangement into the corresponding trimethylsiloxyacetic acids 3. However, synthetic applications of them have not been yet investigated.



5 1 4

a R: $CH_2CH_2CH(NH_2)CONHCH(COOH)CH(CH_3)OH$
$R^1=R^2$: H

α-Hydroxy-β-lactams

Our finding is that trimethylsiloxyacetic acids 3 together with Schiff bases 4 and triethylamine in the presence of phenyl dichlorophosphate reagent leads to an efficient mild method for the synthesis of a wide range of 3-hydroxy-β-lactams 5. In a typical experiment, a mixture of hydroxyacetic acid (1.14 g, 15 mmol), triethylamine (2.8 ml, 20 mmol) and trimethylchlorosilane (2.1 ml, 18 mmol) in benzene (25 ml) was stirred at room temperature for 15-20 h. The resulting mixture was diluited with dichloromethane (25 ml) and then diphenylimine (1.81 g, 10 mmol), triethylamine (6.3 ml, 45 mmol) and phenyl dichlorophosphate (2.25 ml, 15 mmol) were consecutively added at 0-5ºC. The mixture was stirred overnight at room temperature, washed with water (2x30 ml) and the organic layer was dried with sodium sulfate. Evaporation of the solvent gave a red-brown oil which was purified by column chromatography (Silica gel 70-230 mesh, 25 cm. Eluent: AcOEt-hexane 1:5), affording firstly trans-3-hydroxy-1,4-diphenyl-2-azetidinone (0.24 g, 10%) m.p. 178-180ºC (from ethanol-hexane Lit 180-181ºC)[9] and then cis-3-hydroxy-1,4-diphenyl-2-azetidinone (0.84 g, 35%) m.p. 202-203ºC (from ethanol-hexane. Lit 206-207ºC)[9]. Some examples are given in table 1 to illustrate this unusual approach. Examination of the table shows that trans/cis relation decreases when the size of the substituents at C-1 and C-4 increases. Thus, this reaction was stereospecific and a single isomer was obtained when bulky substituents were involved. These compounds were characterized by pmr spectroscopy and elemental analysis. The infrarred absorption for the OH and CO groups was at 3340 and 1730 cm^{-1} respectively.

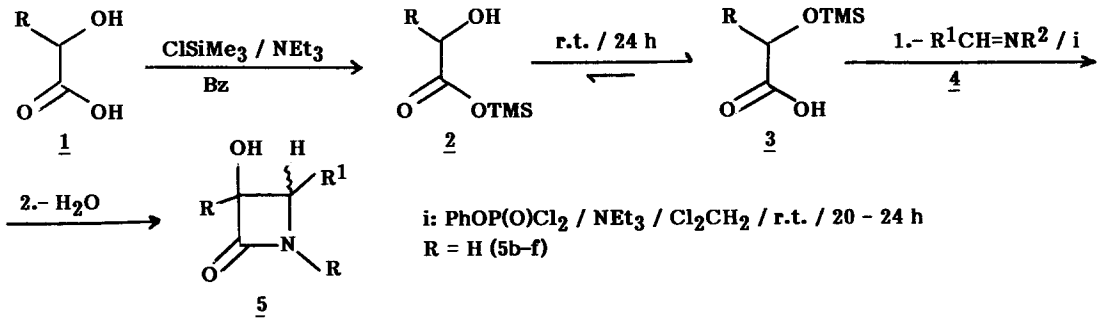


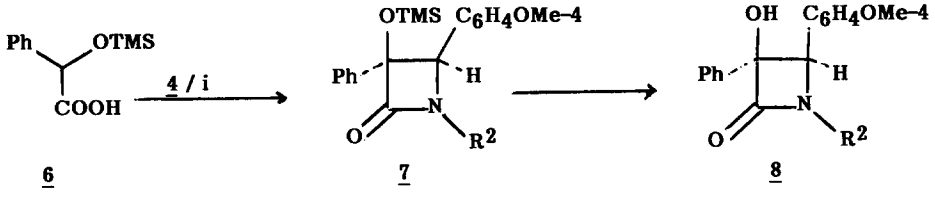
Table 1. Preparation of α-hydroxy-β-lactams 5

Compound[d]	R	R^1	R^2	Yield (%)[b]		m.p. (°C)	
				cis [a]	trans [a]	cis	trans
5b	H	C_6H_5	C_6H_5	35	10	202-203 [e]	178-181 [e]
5c	H	C_6H_5	4-$MeOC_6H_4$	41	8	210-212	155-156
5d	H	4-$MeOC_6H_4$	4-MeC_6H_4	55	6.5	135-137	101-104
5e	H	4-$MeOC_6H_4$	4-$MeOC_6H_4$	65	—	136-138 [e]	——
5f [c]	H	4-$MeOC_6H_4$	$CH_2CH(OH)C_6H_5$	50	—	126-130	——

a) Configuration determined by pmr spectroscopy. b) isolated by column chromatography (silica gel 70-230 mesh. Eluent : EtOAc-hexane 1:5). c) see note 11. d) all new compounds gave satisfactory spectroscopic data and elemental analyses. e) see ref. 9

α-Trimethylsiloxy-β-lactams

We next examined the method from α-hydroxyphenylacetic acid (amigdalic acid) 6 and have found that the corresponding α-trimethylsiloxy-β-lactams 7 were isolated instead the unprotected β-lactams 8. However, hydrolysis of these compounds was easily carried out under different conditions and without concomitant side reactions.



6 7 8

Table 2. β-lactams 7 and 8 prepared [12]

R^2	Product [a]	Yield (%)	m.p.°C
C_6H_5	7a	82	154-155
C_6H_5	8a	100	198-199
4-$MeOC_6H_4$	7b	71	134-135
4-$MeOC_6H_4$	8b	80	167-168
$CH(C_6H_5)_2$	7c	55	144-145
$CH(C_6H_5)_2$	8c	100	170-171

a) A single isomer was formed, determined by tlc and pmr analysis. The infrarred absorption for the OH and CO groups was at 3500 and 1740-1750 cm^{-1} respectively.

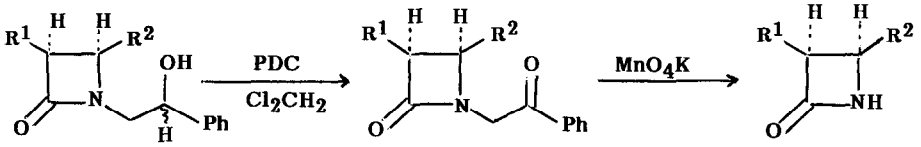
Table 3. Deprotection of 7a into 8a

Conditions	T°C	time(h)	Yield(%)
Acetone/water	25	48	—— [a]
Acetone/water	70	4	—— [a]
HF/MeOH/CH_2Cl_2	25	2	100
HCl 1N/Acetone	25	2	100

a) No hydrolysis was produced.

N-H Azetidinones

Another interesting finding of this preliminary investigation is that the use of Schiff bases derived from aldehydes and the commercially available 2-phenyl-ethanolamine leads to a stereospecific formation of precursors of N-unsubstituted β-lactams. Thus, under similar conditions to those used for the preparation of β-lactam 5f (Table 1), the β-lactam 9 was prepared in 91 % yield (m.p. 175-177 ºC). PDC oxidation of 9 affords β-lactam 10 in 60 % yield (m.p. 99-100 ºC). When this β-lactam 10 was subjected to permanganate oxidation in acetone-water the corresponding N-unsubstituted β-lactam 11 was obtained in moderate yield. Attempts to apply this method from 9 were unsuccesful and side reactions predominated.



9 10 11

R^1 : PhO , R^2 : $C_6H_4OCH_3$-4 , 11 m.p. 166-167 ºC (60 %)

Related 3-substituted-β-lactams

Since a hydroxyl group can be easily transformed to acyloxy and alkyloxy groups, various β-lactam derivatives should be available from the method described above. Furthermore, the one step synthesis of α-hydroxy--β-lactams allows a readily accessto azetidine-2,3-diones, known as useful intermediates for the synthesis of β-lactam antibiotics[10].

Summary

Although this investigation is still in its preliminary stages, the results obtained from the readily available hydroxyacetic acids suggest that the procedure herein described constitutes a useful and convenient strategy for the direct synthesis of 3-hydroxy-β-lactams and related compounds of biological interest such 5a. We are continuing to study the scope of the method and we will report the results in due curse.

REFERENCES AND NOTES

1 .- Reagents and Synthetic Methods 53. Agrant from Ministerio de Educación y Ciencia to F. P. Cossío is gratefully acknowledged. This work was in part supported by Gema-Liessa (Spanish) and Lonza A.G. (Swiss).

2 .- a) A. K. Mukerjee, A. K. Singh, Synthesis, 547 (1975); b) ibid., Tetrahedron, 34, 1731 (1978); c) A. K. Bose, M. S. Manhas, Lect. Heterocycl. Chem., 3, 43 (1976); d) P. G. Sammes (Ed.), "Topics in Antibiotic Chemistry" Vol. 4, Ellis Harward Limited, New York, 1980.

3 .- a) W. W. Stewart, Nature (London), 229, 174 (1971); b) J. E. Baldwin, P. D. Bailey, G. Gallacher, H. Otsuka, K. A. Singleton, Ph. H. Wallace, Tetrahedron, 40, 3695 (1984).

4 .- a) J. M. Aizpurua, I. Ganboa, F. P. Cossío, A. Gonzalez, A. Arrieta, C. Palomo, Tetrahedron Lett., 25, 3905 (1984); b) A. Arrieta, F. P. Cossío, C. Palomo, Tetrahedron, 41, 1703 (1985).

5 .- Attempts to apply this method to the preparation of 3-hydroxy-β-lactams from hydroxyacetic acids and Schiff bases were unsuccesful: side reactions predominated and no hydroxy-β-lactam could be isolated.

6 .- a) A. K. Bose, Y. H. Chiang, M. S. Manhas, Tetrahedron Lett., 4091 (1972); b) A. K. Bose, B. Lal, B. Dayal, M. S. Manhas, Tetrahedron Lett., 2633 (1974); c) A. K. Bose, M. S. Manhas in ref. 2c p. 51.

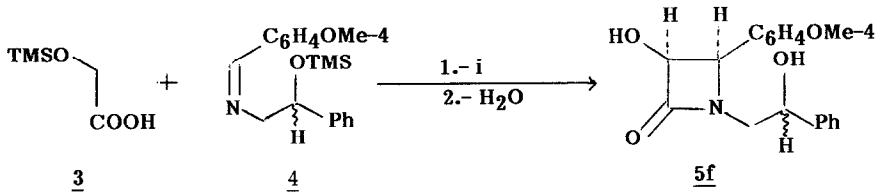
7 .- a) B. E. Cooper, Chem. Ind. (London), 794 (1978); b) T. W. Greene, "Protective Groups in Organic Synthesis" Academic Press, New York, 1981.

8 .- a) F. A. Henglein, G. Abelsnes, H. Heneka, K. L. Lienhard, Pr. Nakhre, K. Scheinost, Makromol. Chem., 24, 1 (1957), b) A. L. Palomo, An. Quim., 77c, 35 (1977).

9 .- M. S. Manhas, H. P. S. Chawla, S. G. Amin, A. K. Bose, Synthesis, 407 (1977).

10.- a) Y. S. Lo, J. C. Sheehan, J. Am. Chem. Soc., 94, 8253 (1972); b) ibid., J. Org. Chem., 38, 3227 (1973); c) M. S. Manhas, S. S. Bari, B. M. Bhawal, A. K. Bose, Tetrahedron Lett., 25, 4733 (1984).

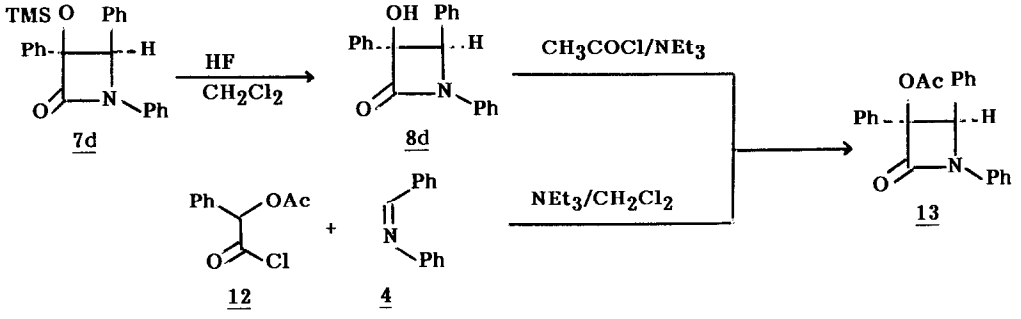
11.- Formation of β-lactam 5f was carried out by protection of both hydroxyl groups in the starting materials. Without protection of the Schiff base 4 the β-lactam 5f could not be isolated.



3 4 5f

5f.- IR ($CHCl_3$) ν cm^{-1} : 3600-3100 (OH); 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm: 7.3-6.7 (m, 9 H, arom.); 4.9 (d, J=5 Hz, 1 H, CH); 5.0-4.7 (m, 1 H, CHPh); 4.6 (d, J=5 Hz,1 H CH); 3.7 (s, 3 H, OCH_3); 4.0-2.8 (m, 4 H, CH_2, OH, OH).

12.- In order to obtain information about the configuration of β-lactams 7 and 8 we examined the method from the acid 6 and diphenylimine, and the resulting β-lactam 7 was hydrolized into 8 and then acylated to 13. Since Bose and coworkers[6b] have revealed that the reaction between O-acetyl-amigdalyl chloride and Schiff bases was sterospecific and gives Z isomers, the stereochemistry of compounds 7 and 8 was deduced by direct comparison of physical and spectral properties of 13 obtained by means of both methods.



7d 8d 13 12 4

7d.- m.p.(ºC): 153-154; IR ($CHCl_3$) ν cm^{-1} : 1740 (C=O); ^{1}H-NMR ($CDCl_3$) δ ppm: 7.7-7.2(m,15H,arom.); 5.2(s,1H,CH); 0.0(s,9H,CH_3Si).

8d.- m.p.(ºC): 190-191; IR ($CHCl_3$) ν cm^{-1} : 3540 (OH), 1750 (C=O); ^{1}H-NMR($CDCl_3$) δ ppm : 7.6-7.0(m,15H,arom.); 5.15(s,1H,CH); 3.05 (s,1H,OH).

13.- m.p.(ºC): 220-221; IR ($CHCl_3$) ν cm^{-1} : 1750 (C=O); ^{1}H-NMR ($CDCl_3$) δ ppm: 7.7-7.0 (m,15H,arom.); 5.65 (s,1H,CH); 1.55 (s,3H,CH_3CO).

(Received in UK 3 July 1985)