Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Synthesis of New β-Lactams

J. C. Lancelot [a] , B. Letois [a] , C. Saturnino [a] , D. Perrine [b] & M. Robba [a]

[a] Laboratoire de Chimie Thérapeutique, U.F.R. des Sciences Pharmaceutiques, 1, rue Vaubénard, 14032, CAEN Cedex, FRANCE

[b] Laboratoire de Zoologie-Parasitologie, U.F.R. des Sciences Pharmaceutiques, 1, rue Vaubénard, 14032, CAEN Cedex, FRANCE

Published online: 23 Sep 2006.

To cite this article: J. C. Lancelot , B. Letois , C. Saturnino , D. Perrine & M. Robba (1993) Efficient Synthesis of New β-Lactams, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:11, 1535-1542, DOI: 10.1080/00397919308011248

To link to this article: http://dx.doi.org/10.1080/00397919308011248

SYNTHETIC COMMUNICATIONS, 23(11), 1535-1542 (1993)

EFFICIENT SYNTHESIS OF NEW β-LACTAMS .

J.C.LANCELOT* , B.LETOIS* , C.SATURNINO* , D.PERRINE** and M.ROBBA*†.

*Laboratoire de Chimie Thérapeutique ,

**Laboratoire de Zoologie-Parasitologie ,

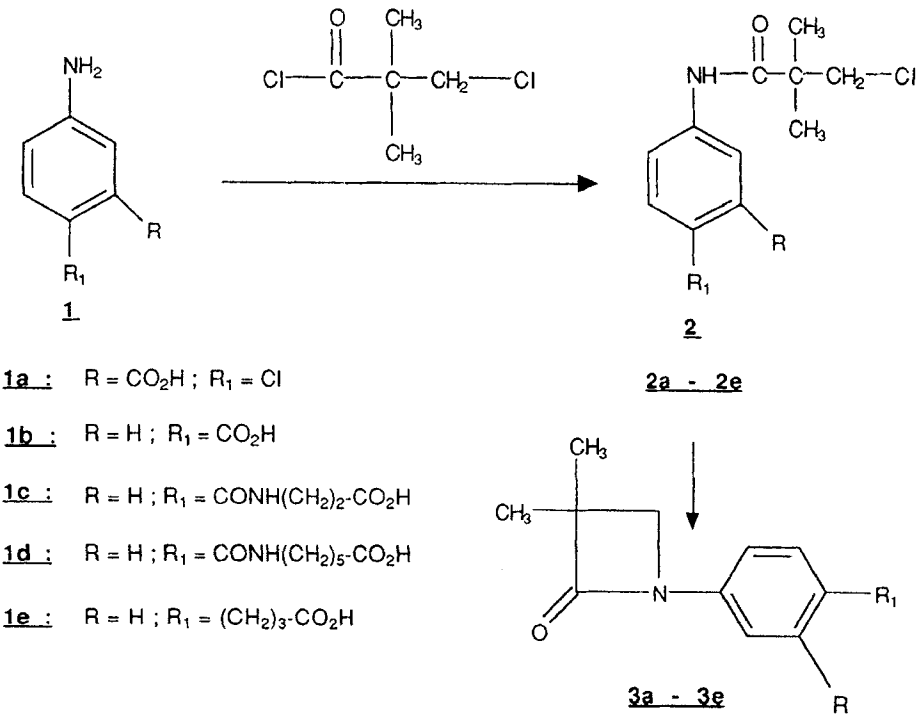
U.F.R. des Sciences Pharmaceutiques ,

1 , rue Vaubénard , 14032 CAEN Cedex , FRANCE .

Abstract : The synthesis of β-lactams was carried out by N-arylpropionamide cyclisation in a mixture of N,N-dimethylformamide and anhydrous sodium carbonate under nitrogen atmosphere with 50 to 90% yield .

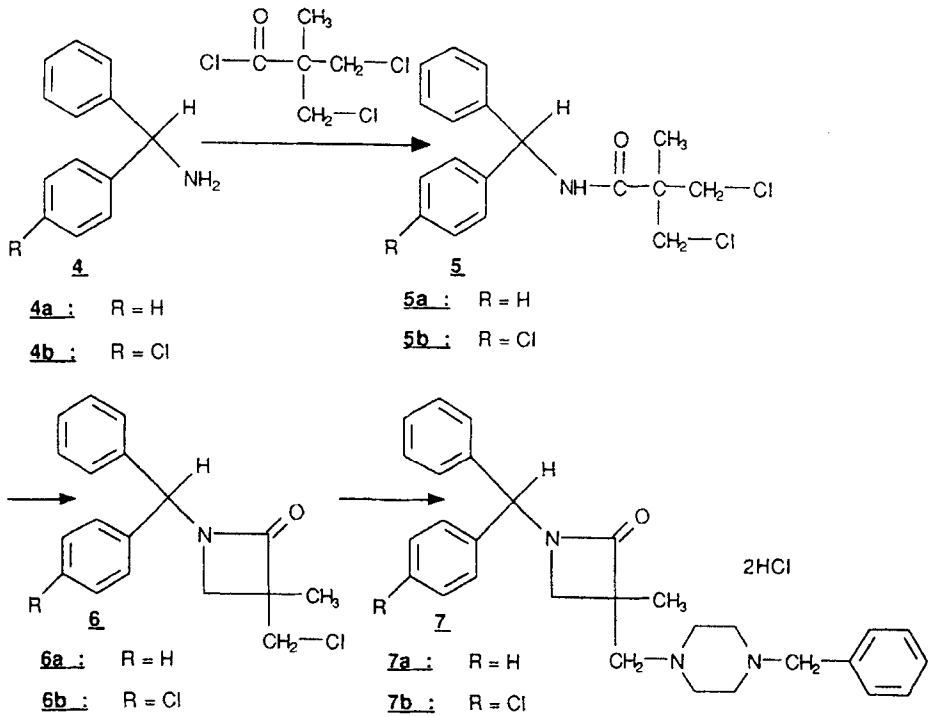
Synthesis of β-lactams is accessible through several methods under anhydrous conditions [1] . Some β-lactam syntheses were shown to be carried out from β-haloacylchlorides and α-aminoacid derivatives in a mixture of benzene and 40% sodium hydroxide with a phase transfer catalysis (KAY [2]) . Yamazaki [3] performed preparation of β-lactams from N-alkyl-β-halocarboxamides [4] by using potassium hydroxide as phase

†To whom correspondence should be addressed



Scheme 1

transfer . In the present paper , we report the preliminary results of an easy synthesis leading to new β-lactams without the use of phase transfer catalysis for cyclisation . Firstly , we perfected a rapid synthesis of propionamide derivatives **2a** - **2e** . That was achieved with 60 to 70% yields by condensing diversely substituted aniline **1a** - **1e** and 3-chloro-pivaloyl chloride under reflux in dioxane for 1 hour in presence of one pyridine equivalent . The benzhydryl derivatives **4a** - **4b** , in presence of 3,3'-di-chloropivaloyl chloride and through the same reacting conditions led to expected propionamide compounds **5a** - **5b** . These compounds



Scheme 2

were cyclized in β-lactams **3a** - **3c** and **5a** - **5b** by heating at 140°C in dimethylformamide in presence of one sodium carbonate equivalent with 70 to 90% yields after the solution was acidified at pH = 4 by diluted *hydrochloric acid* . The 3-chloromethyl-3-methyl-N-benzhydryl-2-oxoazetidines **6a** - **6b** heated in dimethylformamide with benzylpiperazine and sodium carbonate , led to dihydrochlorides **7a** - **7b** with 70% yields , after acidification .

The structures of these derivatives agreed with their ^1H NMR spectra while *the elemental analysis* agreed with the theoretical values with an 0,30%

accuracy . Because these N- and C-substituted β-lactams have shown antibacterial effects against Gram$^+$ bacteria , these preliminary results have to be completed by new synthesises of β-lactam derivatives having various chains with intent to improve the antibacterial activity .

Experimental :

Melting points were determined on Kofler type WME apparatus and are uncorrected. IR. spectra were recorded on Philips P.U.spectrometer . ^{1}H NMR spectra were recorded on Varian E.M.390 spectrometer at 90 MHz in hexadeuteriodimethylsulfoxide with tetramethylsilane as an internal reference . Chemical Shifts are expressed as δ (ppm) relative to TMS . The 3-chloropivaloyl chloride and 3,3'-dichloropivaloyl chloride started from the commercially Aldrich Limited .

N-(4-chloro-3-carboxyphenyl)-3-chloro-2,2-dimethylpropionamide **2a** : General procedure

A solution of 10 g (0.05 mole) of 5-amino-2-chlorobenzoic acid **1a** and 8.99 g (0.058 mole) of 3-chloropivaloyl chloride in 120 mL dioxane was refluxed with 5 ml pyridine under nitrogen atmosphere for 1 hr . The solvent was evaporated in vacuo and the residue dissolved in water and extracted with ether . The solvent was removed to leave a solid 12.50 g (75%) , m.p. : 54°C of **2a** (Crystallized from ether-hexane) . The yields and conditions for the isolated products **1a** - **1e** , **5a** - **5b** are summarized in the table 1 . ^{1}H NMR (DMSO-d_6) : δHAr : 7.56 and 7.36 ; δNH : 9.16 ; δCH_2 : 3.83 ; δ$(CH_3)_2$: 1.40 .

Table 1

Entry	Reaction time (hr)	ir (KBr) (υcm^{-1})	m.p. (°C)	Yield (%)	^1H NMR/TMS (δ) ppm.
2b	1	3300(NH); 1685, 1660(CO)	227	60	δNH: 9.66(s,1H);δAr: 7.93 (m,4H); δCH_2: 3.93(s,2H); $\delta(CH_3)_2$: 1.33(s,6H); δOH: 12.16 (m,1H) .
2c	1	3300(NH); 1690, 1645, 1610(CO)	190	70	δNH: 9.33(s,1H), 8.26(t,1H); δAr: 7.60(m,4H); δCH_2: 3.70 (s,2H); $\delta(CH_2)_2$: 3.30, 2.40 (m,4H) ; $\delta(CH_3)_2$: 1.20(s,6H); δOH: 11.49 (s,1H) .
2d	1	3360, 3280 (NH); 1700, 1625(CO)	113	65	δNH: 9.46(s,1H), 8.30(t,1H); δAr: 7.76(m,4H); δCH_2: 3.86 (s,2H); $\delta(CH_2)_5$: 3.26, 2.20, 1.56(m,10H); $\delta(CH_3)_2$: 1.30 (s,6H); δOH: 11.62 (s,1H) .
2e	1	3340(NH); 1720, 1660(CO)	124	78	δNH: 9.13(s,1H); δAr: 7.43,7.00 (d.d,4H); δCH_2Cl: 3.76(s,2H); $\delta(CH_2)_3$: 2.46, 2.13, 1.76 (m,6H); $\delta(CH_3)_2$: 1.23(s,6H)
5a	1	3310(NH); 1640(CO)	176	70	δNH: 8.60(d,1H); $\delta(C_6H_5)_2$: 7.13(m,10H); δCH: 6.10 (d,1H); $\delta(CH_2)_2$: 3.83(d,4H); δCH_3: 1.26(s,3H) .
5b	1	3310(NH); 1630(CO)	142	75	δNH: 8.30(d,1H); δC_6H_5 , C_6H_4 :7.13(m,9H); δCH: 6.06 (d,1H); $\delta(CH_2)_2$: 3.71(d,4H); δCH_3: 1.16(s,3H) .

N-(3,3-dimethyl-2-oxoazetidinyl) phenyl-para-butyric acid **3e** : General procedure

A mixture of 10 g (0.0336 mole) of 4-[p- (3-chloro-2,2-dimethylpropionamidophenyl)] butyric acid **2e** , sodium carbonate 8.19 g (0.0772 mole) and 30 mL of dimethylformamide was heated at 160°C with stirring under nitrogen for 1 hr . Water (100 mL) was added , and the mixture acidified (pH = 4) by slow addition of concentrated HCl under cooling with an ice-water bath . The aqueous solution was extracted with ether (150 mL) , and evaporated to dryness . The dry residue was washed twice with ether-hexane , to give in **3e** (6.20 g ; 71%) as a white solid , m.p. : 66°C .

^{1}H NMR (DMSO-d_6) : δHAr : 7.20 ; δCH_2 : 3.48 ; δ$(CH_2)_3$: 2.56, 2.23, 1.86 ; δCH_3 : 1.36 ; δOH : 12.00 .

The isolated products **3a** - **3d** , **6a** - **6b** are summarized in the table 2 .

3-methyl-2-(4'-benzyl-1'-methylpiperazinyl)-N-(benzhydrylamido)-2-oxoazetidine dihydrochloride **7a** .

To a solution of 5 g (0.0167 mole) of 3-methyl-3'-chloromethyl-N-(benzhydryl-amino)-2-oxoazetidine **6a** in 35 mL dry N,N-dimethylformamide was added 1.77 g (0.0167 mole) of sodium carbonate and 2.93 g (0.0167 mole) of benzylpiperazine . The mixture was stirred at 160°C for 1 hr . The solution was poured into ice/water (150 mL) and extracted with ethylacetate (150 mL) . The extract were dried (Na_2SO_4) , the solvent was removed under reduced pressure . The oil 5.25 g (0.0119 mole , 72 %) was dissolved in isopropanol (30 mL) and (5 mL) hydrochloric acid and was converted to the dihydrochloride salt **7a** (4.20 g ; 69%) as a white solid ,

Table 2

Entry	Reaction time (hr)	ir (KBr) (υcm^{-1})	m.p. (°C)	Yield (%)	^{1}H NMR/TMS (δ) ppm.
3a	1	1725, 1690(CO)	226	70	δAr: 7.66, 7.43(m,3H); δCH_2: 3.50(s,2H); $\delta(CH_3)_2$: 1.33 (s,6H); δOH: 12.22 (s,1H) .
3b	1	1750, 1670(CO)	235	90	δAr: 7.90(d,2H), 7.33(d,2H); δCH_2: 3.53(s,2H); $\delta(CH_3)_2$: 1.33 (s,6H); δOH: 12.56(s,1H).
3c	1	3300(NH); 1740, 1680(CO)	170	87	δAr: 7.80(d,2H); 7.33(d,2H); δNH: 8.40(t,1H); δOH: 12.20 (s,1H); δCH_2: 3.50(s,2H); $\delta(CH_2)_2$: 3.30, 2.40(m,4H); $\delta(CH_3)_2$: 1.30 (s,6H) .
3d	1	3300(NH); 1730, 1700(CO)	140	85	δNH: 8.33(t,1H); δOH: 12.00 (s,1H); δAr: 7.83(d,2H); 7.33 (d,2H); δCH_2: 3.50 (s,2H); $\delta(CH_2)_5$: 3.16, 2.13, 1.60 (m,10H); $\delta(CH_3)_2$: 1.26(s,6H)
6a	1	1750(CO)	122	92	δAr: 7.20(m,10H); δCH: 5.95 (s,1H); δCH_2: 3.73(s,2H); δCH_2Cl: 3.21, 2.90(q.q,2H); δCH_3: 1.25(s,3H) .
6b	1	1750(CO)	88	83	δAr: 7.20(m,9H); δCH: 5.96 (s,1H); δCH_2: 3.73(s,2H); δCH_2Cl: 3.20, 2.96(q.q,2H); δCH_3: 1.23(s,3H) .

m.p. : 165°C . ^{1}H NMR (DMSO-d_6) : δNH$^+$: 3.96 ; δHAr : 7.50 , 7.20 ;

δCH : 5.88 ; δCH_3 : 1.33 ; δCH_2 : 4.28 , 3.40 and 3.26 .

The yield and the reaction condition for obtaining the 3-methyl-3-(4'-benzyl-1'-methylpiperazinyl)-N-(4-chlorobenzhydrylamido)-2-oxoazetidine dihydrochloride **7b** (6 g , 72% and m.p.: 170°C) werethe same as **7a** .

^{1}H NMR (DMSO-d_6) : δHNH$^+$: 3.96 ; δHAr : 7.56 , 7.23 ; δCH : 5.90 ;

δCH_3 : 1.33 ; δCH_2 : 4.30 , 3.40 and 3.26 .

References

1. a/ Sheehan, J.C. , and Corey , E.J. , Organic Reactions , 9 , 388 , 1957 ; b/ Manhas, M.S., and Bose, A.K. , "β-lactams : Natural and synthetic", Wiley-interscience , New York , 1969 ; c/ Mukerjee, A.K., and Singh, A.K.,Synthesis , 547 , 1975 ; d/ Sommes, P.G. , Chem.Rev., 76 , 1 , 1976 ; e/ Wasserman, H.H. , Hlasta, D.J. , Trempor, A.W. , and Wu, J.C. , Tetrahedron Lett. , 549 , 1979 ; f/ Okawara, T. , Matsuda, T. , and Furukawa, M. , Chem.Pharm.Bull., 30 , 1225 , 1982; g/ idem ibid. , 30 , 1574 , 1982.

2. Fletcher, S.R. , and Kay, I.T. , Chem.Commun. , 903 , 1978 .

3. a/ Takahata, H. , Ohnishi, Y., and Yamazaki , T. , Heterocycles , 14 , 467 , 1980 ; b/ Takahata, H. , Ohnishi, Y., Tsurutani, K., and Yamazaki, T. , Chem.Pharm.Bull., 29 , 1063 , 1981 .

4. a/ Rhinesmith , H.S. , Organic Reactions , 2 , 177 , 1943 . b/ Bocchi V., Casnati G.,Dossena, A., and Marchelli R. , Synthesis , 957, 1979 ; c/ Nitecki D.E., Halpern B., and Westley, J.W., J.Org.Chem., 33 , 864 , 1968 ; d/ Yamamoto, Y. , Yatagai, H., and Maruyama, K. Chem.Commun., 835, 1980 ; e/ Phillips, B.A., and Crowell, N.H., J.Heterocyclic.Chem., 795; 1973 ; f/ Hatenaka, N., Abe, R., and Ojima, I., Chem. Letters , 1927 , 1981; g/ Liu, H.J., Sabesan, S.I. , Can.J.Chem. , 58 , 2645 , 1980 ; h/ Mukerjee, A.K. , Tetrahedron , 34 , 1731 , 1978 .

(Received in UK 16 December 1992)