Tetrahedron Letters,Vol.24,No.44,pp 4837-4838,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A SIMPLE SYNTHESIS OF (±)-1-CARBACEPHEM DERIVATIVES

Minoru Hatanaka and Toshiyasu Ishimaru
The Institute of Scientific and Industrial Research, Osaka University,
Mihogaoka, Ibaraki, Osaka 567, Japan

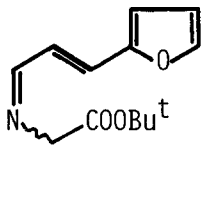
Summary: The Dieckmann condensation of the phenylthioester of 4-(1-t-butoxycarbonylmethyl-3-phenoxyacetamido-azetidin-2-one-4-yl)butylic acid affords a simple route to 3-substituted-8-oxo-7-phenoxyacetamido-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acids.

1-Carbacephems, in which the sulfur atom at the 1-position of cephalosporin is replaced by methylene, have been shown to have comparable antibacterial activity with the corresponding cephalosporins[1]. Moreover, recent success on 1-oxa analogue of cephalosporins[2] has stimulated renewed interest in synthesis of 1-carbacephem derivatives[3]. Although most of the previous syntheses have used internal Wittig cyclization, this method seemed to be inconvenient in order to prepare 1-carbacephems bearing heterosubstituents at C-3[3]. We have recently reported an efficient synthesis of carbapenem using Dieckmann condensation as a key step[4]. Now we represent that this method provides a simple procedure for synthesis of 3-hydroxy-(±)-1-carbacephem 7, which could be converted into various 1-carbacephem derivatives.

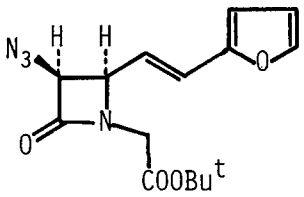
The Shiff's base 1, prepared quantitatively from 3-(2-furyl)acrylaldehyde and t-butyl glycinate, reacted with azidoacetyl chloride (Et_3N, CH_2Cl_2, -20°C) to give the cis-azetidinone 2[5,6,7] (72%). Catalytic reduction (Pd-$SrCO_3$) of 2 and successive acylation with phenoxyacetyl chloride afforded 3 (68%), which was then subjected to ozonolysis yielding 4 (76%). The acid 4 was converted quantitatively into the phenylthioester 5 (PhSH, DCC, CH_2Cl_2).

In subsequent cyclization step, internal N-acylation might be competitive side reaction. Indeed, treatment of 5 with equimolar amount of lithium bis-trimethylsilylamido effected smoothly internal N-acylation even at -78°C to give 6. However, the desired Dieckmann cyclization to form 7 was accomplished highly regioselectively when 3 molar amounts of the base were added at once at -78°C to a solution of 5 in THF. This results indicate that carbanion generation undergoes rapidly prior to attack of the amido anion to the phenylthiocarbonyl, spontaneously followed by C-acylation. Although 3-hydroxy-1-carbacephem derivative has been reported to be too unstable to be isolated[3a], pure 7 was obtained as white crystalline powder in 64% yield after flash chromatography of the crude product.

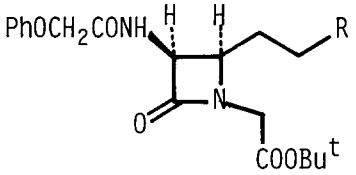
The compound 7 is useful intermediate to prepare various 1-carbacephem derivatives. Treatment of 7 with diazomethane in the usual manner[3a] gave quantitatively the 3-methoxy-1-carbacephem 8. Moreover, 7 was converted into 9 which possessed aminoethylthio substituent as found in thienamycin by use of the published procedure[8] [(1) $(PhO)_2P(O)Cl$, i-Pr_2NEt, CH_3CN, 0°C, (2) $(CH_3)_3SiSCH_2CH_2NHCOOPNB$, i-$Pr_2NEt$, 20°C]. Removal of the protecting groups [(1) CF_3COOH, (2) H_2 / Pd-C] gave 10, which had considerable activity toward gram positive organisms.



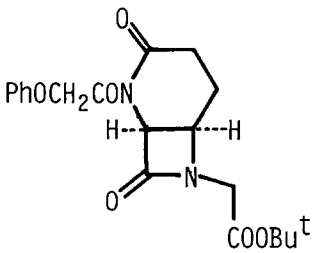
1



2

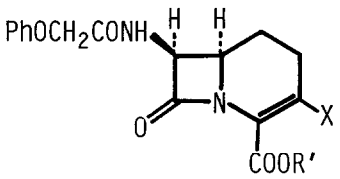


3. R = 2-Furyl
4. R = COOH
5. R = COSPh



6

PNB = p-nitobenzyl



7. X = OH, R′ = Bu^t
8. X = OMe, R′ = Bu^t
9. X = $SCH_2CH_2NHCOOPNB$, R′ = Bu^t
10. X = $SCH_2CH_2NH_2$, R′ = H

References and Notes

1. R.N. Guthikonda, L.D. Cama, and B.G. Christensen, J. Am. Chem. Soc., 96, 7585 (1974); R. A. Firestone, J.L. Fahey, N.S. Maciejiwicz, G.S. Patel, and B.G. Christensen, J. Med. Chem., 20, 551 (1977).
2. Y. Hamashima, H. Matsumura, S. Matsuura, W. Nagata, M. Narisada, and T. Yoshida, "Recent advances in the chemistry of β-lactam antibiotics", Chem. Soc. Spec. Publ., 1980, No. 5.
3. a) S. Uyeo and H. Ona, Chem. Pharm. Bull., 28, 1563 (1980); b) T. Hirata, T. Ogasa, A. Sato, S. Kobayashi, Y. Ono, C. Shiraki, F. Suzuki, K. Mochida, I. Matsukuma, S. Yoshiiye, S. Tomioka, and K. Tamaki, 4th International Conference on Organic Synthesis, Tokyo, Aug. 1982, Abstr., p.173; I. Matsukuma, S. Yoshiiye, K. Mochida, S. Hashimoto, T. Hirata, and K. Sato, The 103rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1983, Abstr., p. 299.
4. M. Hatanaka, Y. Yamamoto, H. Nitta, and T. Ishimaru, Tetrahedron Lett., 22, 3883 (1981).
5. All compounds are racemic mixtures, but only one enantiomer is depicted for convenience.
6. All new compounds were satisfactorily characterised by microanalytical and / or spectroscopic data.
7. Selected physical data. 2: ν (CH_2Cl_2) 2100, 1770 and 1740 cm^{-1}; δ ($CDCl_3$) 4.90 (1H, d, J=5.4 Hz, H-3). 3: mp 106-108°. 4: mp 154-156°. 5: ν (CH_2Cl_2) 3400. 1765. 1740 and 1690 cm^{-1}. 6: mp 172-173°; ν (CH_2Cl_2) 1775 and 1725 cm^{-1}; δ ($CDCl_3$) 1.47 (9H, s), 1.90 (2H,m), 2.67 (2H, m), 3.92 (2H, s), 4.45 (1H, m), 5.18 (2H, s), 6.06 (1H, d, J=5.4 Hz), and 6.84-7.42 (5H, m). 7: mp 118-121°; ν (CH_2Cl_2) 3400, 1768, 1693 and 1655 cm^{-1}; δ ($CDCl_3$) 1.44-2.15 (2H, m), 1.56 (9H, s), 2.49(2H, m), 3.85 (1H, m), 4.54 (2H, s), 5.29 (1H, dd, J=4.4 and 6.8 Hz), and 6.70-7.40 (5H, m). 8: mp159-162°; ν (CH_2Cl_2) 3400, 1770 and 1695 cm^{-1}; δ ($CDCl_3$) 3.76 (3H, s, OMe). 9: ν (CH_2Cl_2) 3400. 1772, 1730 and 1695 cm^{-1}; δ ($CDCl_3$) 1.25-2.15 (2H, m), 1.54 (9H, s), 2.56 (2H, m), 2.87 (2H, m), 3.34 (2H, m), 3.89 (1H, m), 4.53 (2H, s), 5.18 (2H, s), 5.38 (1H, dd, J=4.7 and 7.0 Hz), and 6.84-8.33 (9H, m).
8. I. Shinkai, R.A. Reamer, F.W. Hartner, T. Liu, and M. Sletzinger, Tetrahedron Lett., 23, 4903 (1982).

(Received in Japan 11 July 1983)