# SYNTHESIS OF SOME NEW 6-SUBSTITUTED CARBAPENEM DERIVATIVES

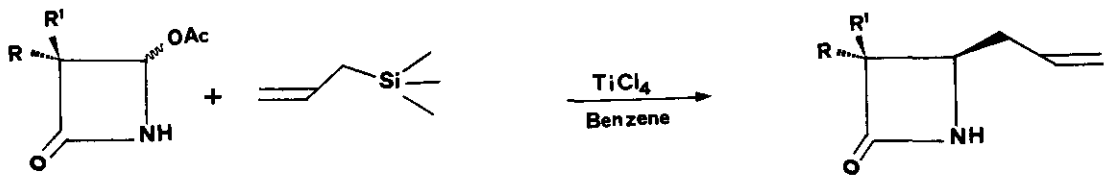
Kapa Prasad*, Kurt Adlgasser, Rajiv Sharma and Peter Stütz

Sandoz Research Institute, Brunnerstraße 59, A-1235 Vienna, Austria

Abstract- Carbapenem acetonyl esters 9-12 and sodium salts 13-15 were prepared utilizing 3-substituted 4-acetoxyazetidinones as starting materials.

The potent antibacterial activity displayed by thienamycin[1] has generated a great deal of interest in this area recently. Several examples exist in the literature, related to the carbapenem family of antibiotics, which have been isolated from various Streptomyces strains. It has been demonstrated that the nucleus of these antibiotics, i.e. 1-carba-2-penem-3-carboxylic acid[1], is primarily responsible for the high antimicrobial activity. For example, 6-α(R)-hydroxyethyl-1-carba-2-penem-3-carboxylic acid[1] possesses bioactivity which is comparable to that of thienamycin. In this communication, we wish to report the synthesis of carbapenem derivatives related to PS-5[2] and PS-6[2], utilising 3-substituted 4-acetoxyazetidinones as starting materials.

Scheme 1

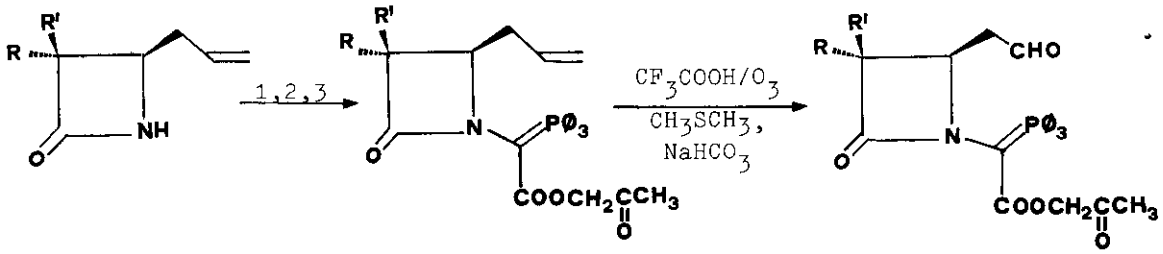



| | | | |
|---|---|---|---|
| 1 | R = $CH_2CH_3$, | R' = H | 5 |
| 2 | R = $CH_2CH_2OAc$, | R' = H | 6 |
| 3 | R = Isopropyl, | R' = H | 7 |
| 4 | R = $CH_3$, | R' = $CH_3$ | 8 |

The key step in our synthesis involves allylation at C-4 of various 4-acetoxyazetidinones, as shown in Scheme-1. We found the above reaction to be quite general for the carbon extension. For example, treatment of the azetidinones 1-4[3] with allyltrimethylsilane in the presence of titanium tetrachloride in benzene afforded the respective allyl derivatives 5-8[4]. It must be pointed out, that recently several reports have appeared in the literature[5] regarding C-C bond formation at C-4 of acetoxyazetidinone using silanes and Lewis acids.

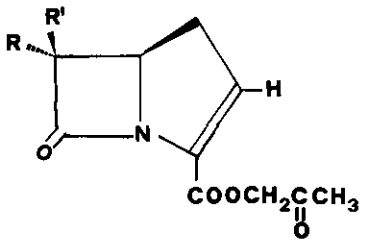
A typical experimental procedure for the reaction described in Scheme-1 is as follows: A solution of 3-ethyl-4-acetoxyazetidinone (1.10 g; 7 mmol), titanium tetrachloride (0.88 ml; 8 mmol) and allyltrimethylsilane (1.26 ml; 8 mmol) in benzene (10 ml) was stirred under an inert atmosphere at ambient temperature. After 16 h., the reaction mixture was cooled to $0^{o}C$, diluted with ether (100 ml) and washed with brine. The dried organic layer was filtered and evaporated to leave a gum. Chromatography of the residue on $SiO_2$ using toluene/EtOAc (1:2) as an eluent system gave 494 mg (50 % yield) of azetidinone 5.

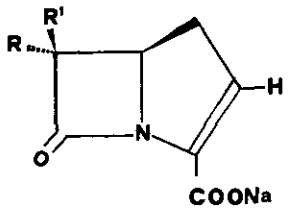
Scheme-2




1. Acetonyl glyoxylate; 2. $SOCl_2/NEt_3$ and 3. triphenyl phosphine.

The conversion of the azetidinones 5-8 into the corresponding phosphoranes was performed in a three step sequence[6] using acetonyl glyoxylate[7], as shown in Scheme-2. Ozonolysis of the phosphoranes in $CH_2Cl_2$ at $-40^{o}C$, in the presence of trifluoroacetic acid, followed by treatment with dimethyl sulfide and washing with aqueous sodium bicarbonate gave the respective aldehydes. These underwent an intramolecular Wittig reaction[8] on heating in dichloromethane to give the carbapenem esters 9-12[9] respectively.





| | | | |
|---|---|---|---|
| 9 R = $CH_2CH_3$, | R'=H | 13 R = $CH_2CH_3$, | R' = H |
| 10 R = $CH_2CH_2OAc$, | R' = H | 14 R = Isopropyl, | R' = H |
| 11 R = Isopropyl, | R' = H | 15 R = $CH_3$, | R' = $CH_3$ |
| 12 R = $CH_3$, | R' = $CH_3$ | | |

Acetonyl esters 9, 11 and 12 upon treatment with one equivalent of 1 N sodium hydroxide solution in dioxane at 5°C afforded the respective sodium salts 13, 14 and 15 in quantitative yields; their spectroscopic features are described below.

Compound 13: Amorphous solid; IR(KBr): 1751, 1621, 1586, 1406, and 1259 $cm^{-1}$; NMR($D_2O$): 1.00 (3H, t, J = 7 Hz), 1.76 (2H, m), 2.84 (2H, m), 3.27 (1H, m), 4.07 (1H, dt, J = 9 and 3 Hz) and 6.26 br (1H, t, J = 3 Hz) ppm.

Compound 14: Amorphous solid; IR(KBr): 1750, 1625, 1590, 1405 and 1250 $cm^{-1}$; NMR($D_2O$): 0.98 (3H, d, J = 7 Hz), 1.02 (3H, d, J = 7 Hz), 2.06 (1H, m), 2.82 (2H, m), 3.15 br (1H, dd, J = 8 and 3 Hz), 4.11 (1H, dt, J = 10 and 3 Hz) and 6.26 br (1H, t, J = 3 Hz) ppm.

Compound 15: Amorphous solid; IR(KBr): 1750, 1620, 1590, 1405, 1280 and 1255 $cm^{-1}$; NMR($D_2O$): 1.23 (3H, s), 1.43 (3H, s), 2.76 (2H, m), 4.12 (1H, dd, J = 11 and 10 Hz) and 6.28 (1H, t, J = 3 Hz) ppm.

The acetonyl ester 12 and the salt 15 were devoid of any biological activity. However, compounds 9-11, 13 and 14, under the same in vitro screening, exhibited significant bioactivity.

ACKNOWLEDGEMENT: The authors are grateful to Prof. A. Vasella, University of Zürich, for valuable suggestions and Dr. G. Schulz and his co-workers (SFI) for the recording and discussion of the NMR spectra.

REFERENCES AND NOTES


1. L.D.Cama and B.G.Christensen in "ß-lactam antibiotics", ed. by S. Mitsuhashi, Springer-Verlag Berlin, 1981, p 164.
2. Y.Fukagawa, K.Okamura, N.Shibamoto and T.Ishikura in "ß-lactam antibiotics", ed. by S. Mitsuhashi, Springer-Verlag Berlin, 1981, p 158.
3. Azetidinones 1 and 3 were made according to ref. T.Kametani, T.Honda, A.Nakayama, Y.Sakai, T. Mochizuki,and K.Fukumoto, J. Chem. Soc. Perkin I, 1981, 2228. Compound 2 is a novel azetidinone (K. Prasad, unpublished results) and compound 4 was prepared according to ref. K.Clauss, D.Grimm and G. Prossel, Ann., 1974, 539.
4. Spectral properties:
   Compound 5: oil; IR($CH_2Cl_2$): 3430 and 1750 $cm^{-1}$; NMR($CDCl_3$): 1.00 (3H, t, J = 7 Hz), 1.72 (2H, m), 2.38 (2H, m), 2.76 (1H, m), 3.37 (1H, m), 5.14 (2H, m), 5.76 (1H, m) and 6.14 br (1H) ppm.
   Compound 6: oil; IR($CH_2Cl_2$): 3430, 1760 and 1740 $cm^{-1}$; NMR($CDCl_3$): 1.94-2.52 (4H, m), 2.08 (3H, s), 2.90 (1H, m), 3.48 (1H, m), 4.20 (2H, m), 5.15 (2H, m), 5.70 (1H, m) and 5.98 br (1H) ppm.
   Compound 7: oil; IR($CH_2Cl_2$): 3430 and 1755 $cm^{-1}$; NMR($CDCl_3$): 0.98 (3H, d, J = 7 Hz), 1.07 (3H, d, J = 7 Hz), 2.02 (1H, m), 2.36 (2H, m), 2.63 (1H, m), 3.43 (1H, m), 5.14 (2H, m) and 5.58-6.05 br (2H, m) ppm.
   Compound 8: oil; IR($CH_2Cl_2$): 3435 and 1750 $cm^{-1}$; NMR($CDCl_3$): 1.20 (3H, s), 1.33 (3H, s), 2.32 (2H, m), 3.39 (1H, dd, J = 10 and 6 Hz), 5.13 (2H, m) and 5.78 br (2H, m) ppm .
5. a) S.Karady, J.S.Amato, R.A.Reamer and L.M.Weinstock, J. Am. Chem. Soc., 103, 6765 (1981). b) P.J. Reider, R.Rayford and E.J.J.Grabowski, Tetrahedron Letters, 23, 379 (1982). c) G.A.Kraus and K. Neuenschwander, J. Chem. Soc. Chem. Commun., 1982, 134.
6. R.B.Woodward, K.Heusler, I.Ernest, K.Burri, R.J.Friary, F.Haviv, W.Oppolzer, R.Paioni, K.Syhora, R. Wenger and J.K.Whitesell, Nouveau J. Chim., 1, 85 (1977).
7. H.R.Pfaendler, J.Gosteli and R.B.Woodward, J. Am. Chem. Soc., 101, 6306 (1979).
8. A.J.G.Baxter, K.H.Dickinson, P.M.Roberts, T.C.Smale and R.Southgate, J. Chem. Soc, Chem. Commun., 1979, 236.
9. Physical and spectral properties:
   Compound 9: mp 97-98°C; UV(dioxane) $\lambda$max(ε): 353 (2778) and 278 (4729) nm; IR($CH_2Cl_2$): 1775 and 1725 $cm^{-1}$; NMR($CDCl_3$): 1.06 (3H, t, J = 7.2 Hz), 1.90 (2H, m), 2.23 (3H, s), 2.82 (1H, m, J = 19, 2.7 Hz), 2.98 (1H, m, J = 19, 3, 9.5 Hz), 3.17 (1H, m, J = 7.2, 3, 0.5 Hz), 4.06 (1H, m, 9.5, 8.7, 3 Hz), 4.74 (1H, d, J = 17 Hz), 4.84 (1H, d, J = 17 Hz) and 6.62 (1H, m, J = 3, 2.7, 0.5 Hz) ppm . The spectral properties for compounds 10 (oil), 11 (mp 90-92°C) and 12 (mp 117-119°C) were in good agreement with their structures.


Received, 21st June, 1982