Tetrahedron Letters,Vol.25,No.11,pp 1151-1154,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

FROM PENICILLIN TO PENEM AND CARBAPENEM. V[1)]

SYNTHESIS OF CARBAPENAM SKELETON BY (3 + 2) CYCLIZATION

Katsumi Fujimoto, Yuji Iwano, and Koichi Hirai*

Chemical Research Laboratories, Sankyo Co., Ltd.
1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140, Japan

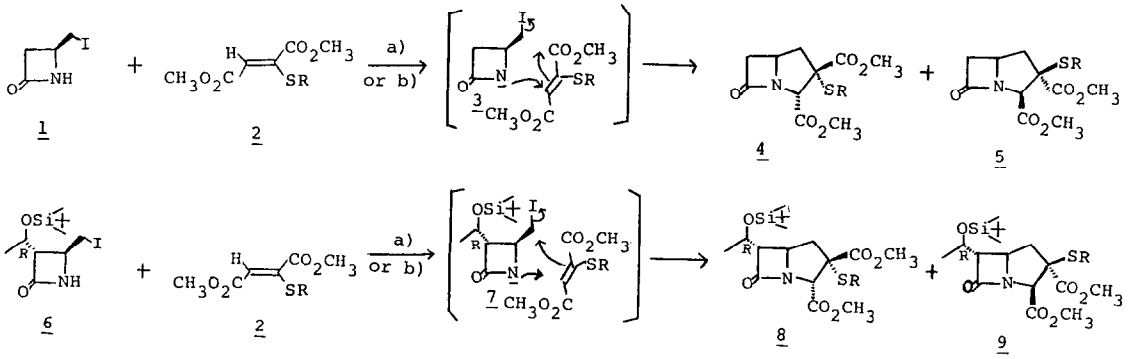
Summary : The carbapenam derivatives were prepared by the new type of (3+2) cyclization[2)] of 4-iodomethyl-2-azetidinones (1 and 6) and 2-thiosubstituted dimethylfumarate derivatives (2, R= CH_3, C_6H_5).

The representative methods for the construction of the carbapenam (or carbapenem) skeleton are currently thought to be the next two ; the first one is the internal Wittig type of reaction between C_2 and C_3 originally developed by Woodward in the field of penem synthesis[3)], and the second one is the Merck method of the carben insertion reaction between C_3 and N_4-H to build up the 2-oxocarbapenam molecule[4)]. Beside these several other methods are reported, and one of wich is the aldol type reaction between C_1 and C_2[5a)] or C_2 and C_3 under basic conditions[5b-d)]. We have already succeeded in the synthesis of Δ^1-carbapenem by aldol condensation between C_1 and C_2 using dialdehyde intermediate[5a)], and our continuing interest to construct the cabapenam molecule by ring closure between C_1 and C_2 prompted us to describe here our new method for the synthesis of this unique molecule.

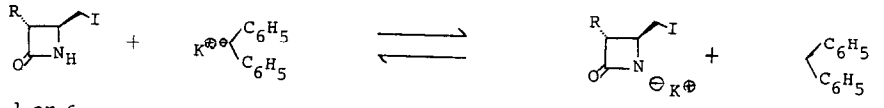
It is reasonably assumed that the nitrogen in the azetidinone molecule is nucleophilic enough to attack the ß-position of the α,β-unsaturated cabonyl compound (the Michael reaction) and when the azetidinone molecule has any electrophilic center in itself the resulting carbanion at the α-position has a chance to capture the electrophilic center to give the cyclic compound[6)]. Under these working hypotheses we investigated the reaction of 4-iodomethyl-2-

azetidinone (1)[7] and dimethyl 2-phenylthiofumarate (2, R= C_6H_5) under basic conditions. To the cooled suspension of potassium hydride in THF at -78°C were added 0.67 eq. of 4-iodomethyl-2-azetidinone (1) in THF and one equivalent of 18-crown-6 successively. The whole mixture was stirred for ten min at the same temperature and then one equivalent of dimethyl 2-phenylthiofumarate[8] in THF solution was added. Stirring was continued for 3 hr (during this time the reaction temperature rose to 0°C), and then aqueous ammonium chloride solution was added. The products were extracted with ethyl acetate. After evaporation of the solvent the products were separated on rapid chromatography (silica gel, cyclohexane : ethyl acetate= 2 : 1). The desired compounds (4 and 5 (1 : 1), R= C_6H_5) were purified on silica gel TLC (Rf= 0.3 and 0.35, acetone : ethyl acetate : n-hexane= 1 : 2 : 8) in 27% yield. One of the diastereomers (5) crystallized, Rf= 0.3, mp 136-138°C. IR (KBr) ν cm^{-1} : 1765, 1740. NMR ($CDCl_3$ TMS) : δ 2.22(1H, dd, J= 10, 14Hz), 2.74(1H, dd, J= 5, 14Hz), 2.8-3.3(2H, m), 3.46(3H, s), 3.5-3.9(1H, m), 3.88(3H, s), 4.69(1H, s), 7.0-7.7(5H, m). *Anal.* Calcd for $C_{16}H_{17}NO_5S$: C, 57.47: H, 4.82: N, 4.19: S, 9.59. Found: C, 57.36: H, 4.39: N, 4.20: S, 9.63. The other diastereomer (4), Rf= 0.35, NMR ($CDCl_3$) : δ 2.2-3.3(4H, m), 3.48(3H, s), 3.86(3H, s), 3.2-4.3(1H, m), 5.28(1H, s), 7.3-7.8 (5H, m).

The compound 6 which has the hydroxyethyl substituent at 3-position of azetidinone gave the corresponding cyclized compounds (8 and 9, R= C_6H_5) under the same conditions in 15% isolated yield.



On the other hand the reaction of 2-methylthiofumarate (2, R= CH_3) with the same azetidinone derivatives (1 and 6) did not give the expected cyclized products. So we checked the base effect on our cyclization ; DBU, KF, triphenylmethylpotassium, and LDA failed to afford the desired compound. At this stage we took advantage of the generation of the nitrogen anions (3 and 7) by proton abstraction from 1 and 6 by diphenylmethane carbanion (pKa = 33) and the equilibrium between these two species.



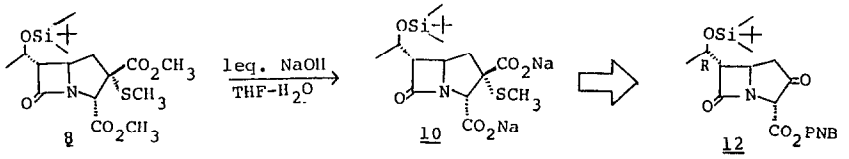
1 or 6 3 or 7

The THF solution of diphenylmethane (1 eq.) and 18-crown-6 (1 eq.) was added to the suspension of potassium hydride in THF at r.t. and stirred for 2.5 hr, then cooled to -40°C. To the mixture was added (3S,4S)-3-[(R)-1'-t-butyldimethylsilyloxyethyl]-4-iodomethyl-2-azetidinone (6)[1] (0.96 eq.). After stirring for 2 hr at -40~-20°C the reaction was quenched with aqueous ammonium chloride. The reaction mixture was extracted with ethyl acetate, and the products were separated on rapid chromatography (methylene chloride : cyclohexane= 10 : 1). The desired cyclized compound (8 and 9 (2 : 1), R= CH_3) were purified further on silica gel TLC (Rf= 0.6 and 0.65, ether : cyclohexane= 1 : 1) in 18% yield. Compound 8 R= CH_3, Rf= 0.65, IR ($CHCl_3$) ν cm^{-1} : 1772, 1735, NMR ($CDCl_3$) : δ 0.05(6H, s), 0.88(9H, s), 1.19(3H, d, J= 6.6Hz), 2.16(3H, s), 2.1-2.5(1H, m), 2.7-3.2(2H, m), 3.79(3H, s), 3.80(3H, s), 3.8-4.4(2H, m), 5.34(1H, s) Compound 9 R= CH_3, Rf= 0.6, IR (neat) ν cm^{-1} : 1770, 1735. NMR ($CDCl_3$) : δ 0.04(6H, s), 0.84(9H, s), 1.15(3H, d, J= 6Hz), 2.10(3H, s), 2.18(1H, d, J=12.6Hz) 2.71(1H, dd, J= 6, 12.6Hz), 3.08(1H, dd, J= 3, 6Hz), 3.3-3.8(1H, m), 3.77(3H, s), 3.83(3H, s), 3.8-4.4(1H, m), 4.69(1H, s).

Under the same conditions the compound 1 gave the carbapenams (4 and 5, R= CH_3) in 9% yield. Compound 4 R= CH_3, NMR ($CDCl_3$) : δ 2.14(3H, s), 2.43(1H, dd, J= 6, 15Hz), 2.87(1H, dd, J= 1, 6Hz), 2.9-3.6(2H, m), 3.76(3H, s), 3.80(3H, s), 3.8-4.4(1H, m), 5.31(1H, s).

The purified compound (8, R= CH_3) was carefully hydrolyzed with sodium hy-

droxide in THF-water for 20 hr[9] to disodium salt (10). Compound 10, NMR (D_2O, DSS) : δ 0.17(6H, s), 0.93(9H, s), 1.28(3H, d, J= 5.4Hz), 2.10(3H, s), 2.0-2.5 (3H, m), 5.36(1H, s).



We are now concentrated in the conversion of this compound (10) to 2-oxo-carbapenam derivative (12) *via* Trost's oxydative decarboxylation method[10]. Compound 12 is an important intermediate for the synthesis of thienamycin and the related carbapenem antibiotics[4].

REFERENCES

1) Part IV, K. Hirai, Y. Iwano, and K. Fujimoto, Tetrahedron Lett., 1982, 4025.

2) a) K. Hirai, J. Soc. Org. Synth. Chem., Tokyo, 38, 97(1980). b) M. Ono, *ibid*., 39, 827(1981).

3) I. Ernest, J. Gosteli, C. W. Greengrass, W. Holic, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, J. Am. Chem. Soc., 100, 8214(1978).

4) R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, Tetrahedron Lett., 1980, 31.

5) a) K. Hirai, K. Fujimoto, Y. Iwano, T. Hiraoka, T. Hata, and C. Tamura, Tetrahedron Lett., 1981, 1021. b) M. Shibuya and S. Kubota, *ibid*., 1981, 3611. c) M. W. Foxton, R. C. Mearman, C. E. Newall, and P. Ward, *ibid*., 1981, 2497. d) M. Hatanaka, Y. Yamamoto, H. Nitta, and T. Ishimaru, *ibid*., 1981, 3883.

6) N. F. Osborne, J. Chem. Soc. Perkin 1, 1980, 150.

7) T. Tanaka and T. Miyadera, Heterocycles, 19, 1497(1982).

8) W. E. Truce and R. B. Kruse, J. Am. Chem. Soc., 81, 5372(1959).

9) S. Oida, A. Yoshida, and E. Ohki, Chem. Pharm. Bull., 28, 3494(1980).

10) B. M. Trost and Y. Tamaru, J. Am. Chem. Soc., 99, 3101(1977).

(Received in Japan 13 December 1983)