THE SYNTHESIS OF CARBAPENEM AND CARBACEPHEM DERIVATIVES BY A COMBINATION OF 4CC WITH THE CHEMISTRY OF OXAZOLES AND N-BOC-CARBONAMIDES

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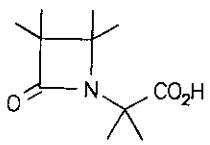
Dedicated to the memory of Professor T. Kametani.

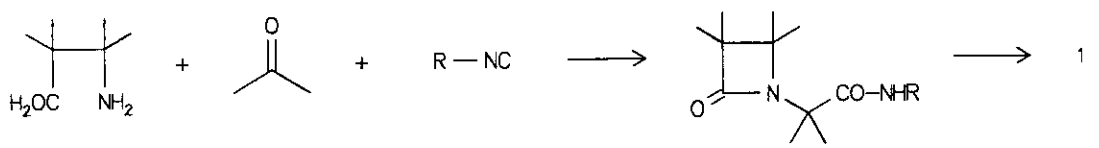
Abstract - A synthetic approach to carbapenem and carbacephem derivatives is described. It is based on the formation of the N-carboxymethyl- ß-lactam system by a four component condensation, the cleavage of a carbonamide via the N-Boc-carbonamides and esters, and the masking of a carboxyl group as its 4,5-diphenyloxazolyl derivative that is convertible to an N,N-dibenzoylamide by photooxidation.

With very few exceptions, the substructure **1** is the characteristic common feature of the ß-lactam antibiotics, one of the favored research topics of Kametani et al.[1]



1

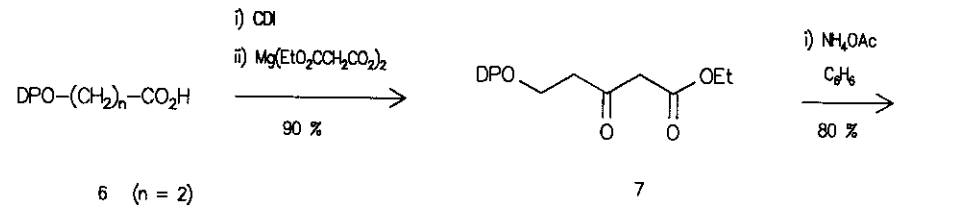
In some of the most effective synthetic approaches to the β-lactam antibiotics, the key step is a four component condensation (4CC, Ugi reaction),[2] **2 + 3 + 4 -> 5.**



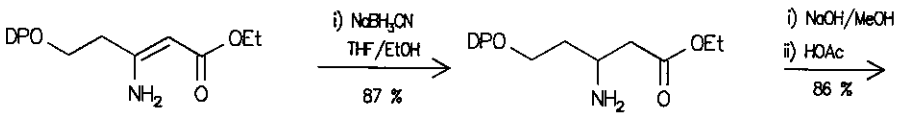
2 **3** **4** **5**

In the present paper we describe a 4CC based synthetic route that may serve for the preparation of a

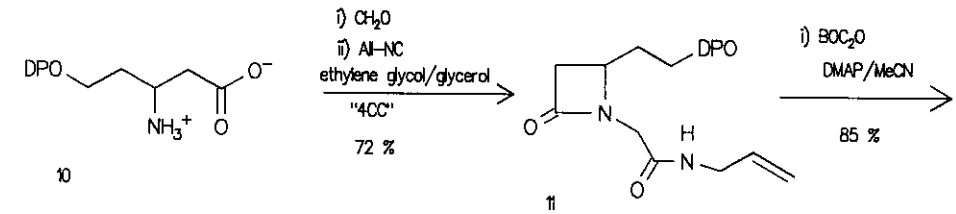
variety of carbapenems and carbacephems.



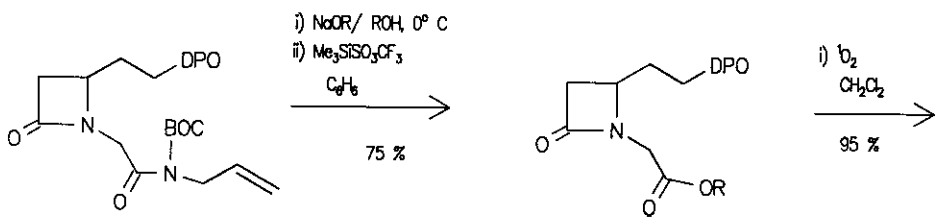
6 (n = 2) 7



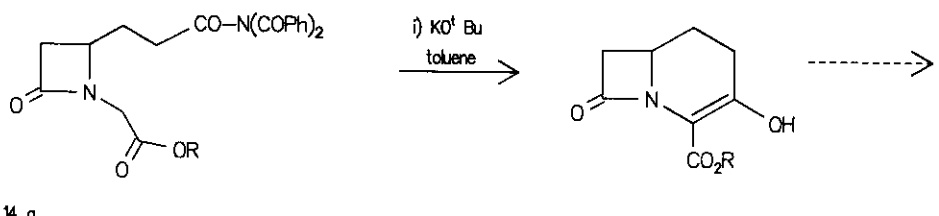
8 9



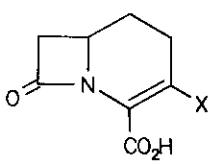
10 11



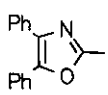
12 13 a (R= Me)
13 b (R= allyl)



14 a 15 a



16 (X= OR,SR,Cl)

(DPO =  , CDI = carbonyldiimidazole

, All = allyl , BOC = tert. butoxycarbonyl)

The synthesis begins with **6**, n=2, which is readily available from benzoin and succinic anhydride.[3] The intermediate **8** is of particular interest to future ß-lactam syntheses, because its stereoselective reduction leads to chiral **9**; its acetylation in the α-position of the ester group[4] can be exploited for thienamycine syntheses. The 4CC **10** -> **11** proceeds best in a (3 + 5) mixture of ethylene glycol and glycerol. This solvent is superior to trifluoroethanol, hitherto the "magic solvent" of such 4CC.[5] In methanol, generally the favored solvent of such 4CC,[6] only a minor amount of **11** is obtained by 4CC of **10** with formaldehyde and allyl isocyanide. The attempted conversion of **11** into **13 b** by the nitrosation[7] method did not succeed, whereas **13 a** and **b** are easily obtained from **11** through introduction an N-Boc-group by the method of Ragnarsson and Grehn,[8] followed by cleavage of **12** according to Grieco et al.[9] The transformation of **13** into the carbacephems **16** via **14**[10] and **15** is at the stage of preliminary experiments, as well as similar syntheses of carbapenem derivatives from **6**, n=1, in analogy to the synthesis of Hatanaka et al.[11]

EXPERIMENTAL

General: ^{1}H-Nmr (360 MHz) spectra as well as the ^{13}C-nmr spectra (90 MHz) were recorded on a Bruker AM 360. Chemical shifts are reported in ppm downfield from internal TMS. Infrared spectra were obtained on a Perkin-Elmer Model 257. Mass spectra were recorded on a Varian CH5 MAT (70 eV). Melting points were taken on a Büchi SMP-20 (uncorrected).

Ethyl 5-(4,5-diphenyl-2-oxazolyl)pentan-3-onate (7).

At 25°C and under a blanket of N_2 31.1 g (0.190 mol) of carbonyldiimidazole (CDI) are added to a solution of 48.0 g (0.160 mol) of ß-(4,5-diphenyl-2-oxazolyl)propionic acid **6**, n=2, in 200 ml of dry THF. After 6 h a suspension of 46.5 g (0.350 mol) of magnesium monoethyl malonate[12] in 200 ml of THF is added to the aforementioned solution and is stirred overnight. The solvent is evaporated and the residue is partitioned between 400 ml of 1 N HCl and 200 ml of ether. The ether phase is washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Evaporation leaves a yellow residue which is recrystallized from ether. **Yield:** 53.8 g (90.4%), colorless crystals of mp 61-61.5°C . $C_{22}H_{21}NO_4$ (363) ; **ms (m/z)** : 363(M^+); **^{1}H-nmr**($CDCl_3$): δ= 1.26 (t, 3H, J= 7.0 Hz, $-CH_3$); 3.15 (s, 4H, $-CH_2-CH_2-$); 3.56 (s, 2H, $-CH_2CO_2-$); 4.19 (q, 2H, J= 7.0 Hz, $-OCH_2-$); 7.35 (m, 6H, Ar); 7.54 - 7.60 (m, 4H, Ar) ; **^{13}C-nmr**($CDCl_3$): δ= 14.1 ($-CH_3$); 22.1 ($-CH_2-$); 39.2 ($-CH_2-$); 49.4 ($-CH_2-$); 61.5 ($-OCH_2-$); 126.4-128.6 (Ar-CH); 132.5 (Ar-C); 135.1 (-C=C); 145.8 (-C=C-); 161.9 (-N=C-O-); 167.0 ($-CO_2-$); 200.8 (-CO-).

Ethyl 5-(4,5-diphenyl-2-oxazolyl)-3-amino-2-pentenoate (8).

To the solution of 47.5 g (0.130 mol) of **7** in 150 ml of benzene are added 20.1 g (0.260 mol) of ammonium

acetate and 0.5 ml of acetic acid. After 3 h of heating under reflux, the solvent is evaporated. The residue is dissolved in 300 ml of ether, washed with water, then evaporated to 150 ml and left to crystallize at 0°C. **Yield:** 37.9 g (80%); mp 88-89°C (ether); **^{1}H-nmr** ($CDCl_3$): δ = 1.25 (t, 3H, J= 7.0 Hz, $-CH_3$); 2.72 (t(AA'BB'), 2H, J= 7.2 Hz, $-CH_2-$); 3.11 (t(AA'BB'), 2H, J= 7.2 Hz,$-CH_2-$); 4.15 (q, 2H, J= 7.0 Hz, $-OCH_2-$); 4.64 (s, 1H, =CH-); 6.80 (br, 2H, $-NH_2$); 7.35 (m, 6H, Ar); 7.54 -7.60 (m, 4H, Ar).

Ethyl 5-(4,5-diphenyl-2-oxazolyl)-3-aminopentanoate (9).

At 0°C conc. hydrochloric acid (ca. 10 ml) is added dropwise to a stirred solution of 46.0 g (0.127 mol) of **8** , 8.5 g (0.135 mol) of $NaBH_3CN$ and 2 mg of Bromokresol Green in 100 ml of THF and 50 ml of EtOH, until the color turns permanently yellow (ca. 1.5 h). After pouring into 500 ml of 0.1 N NaOH, the product is extracted with ether. Evaporation in vacuo yields a pale yellow oil that is spectroscopically pure. **Yield:** 40.0 g (87%); **^{1}H-nmr**($CDCl_3$): δ = 1.25 (t, 3H, J= 7.0 Hz, $-CH_3$); 1.85 (br, 2H, $-NH_2$); 2.05 (m, 2H, $-CH_2$); 2.35 (dd, 1H, J= 15.8 Hz, J= 8.7 Hz, $-CH_2-CO_2-$); 2.55 (dd, J= 15.8 Hz, J= 4.2 Hz, $-CH_2-CO_2-$); 3.00 (m, 2H, $-CH_2-$); 3.31 (m, 1H, -CH-); 4.14 (q, 2H, J= 7.0 Hz, $-OCH_2-$); 7.33 (m, 6H, Ar); 7.54-7.60 (m, 4H, Ar); **^{13}C-nmr**($CDCl_3$): δ = 14.2 ($-CH_3$); 24.9 ($-CH_2-$); 34.5 ($-CH_2-$); 42.6 ($-CH_2-CO_2-$); 47.8 (-CH-); 60.4 ($-OCH_2-$); 126.4 - 128.7 (Ar-CH); 129.8 (Ar-C); 132.4 (Ar-C); 135.0 (-C=C-); 145.2 (-C=C-); 163.0 (-O-C=N-); 172.3 ($-CO_2-$); ir (film): 3480 cm^{-1}(m); 3060(m); 2980(s); 1740(vs); 1550(s).

5-(4,5-Diphenyl-2-oxazolyl)-3-aminopentanoic acid (10).

The solution of 36.4 g (0.100 mol) of **9** and 11.8 g (0.29 mol) of NaOH in 150 ml of methanol was refluxed for 4 h. The solvent is evaporated in vacuo, and the residue is dissolved in 120 ml of water and 300 ml of ethyl acetate. Acetic acid is added to the mixture until pH=6.0 is reached. On standing at 0°C *overnight crystallization takes place.* The crystals are collected and washed with 200 ml of ethyl acetate , 300 ml of cold water and 150 ml of acetone, then dried in vacuo over P_2O_5. **Yield:** 30.1 g (87.8%); mp 180-181°C (with decomp). $C_{20}H_{20}N_2O_7$ (336); **ms (m/z)** : 248 ($M^+-C_3H_6NO_2$) 0.7% ; 105 ($PhCO^+$) 3.8%; 91 ($PhCH_2^+$) 2.8%; 77 ($C_6H_5^+$) 2.1% ;60 ($C_2H_4O_2^+$) 79.5% ; 45 (CO_2H^+) 92% ;43 ($C_2H_5N^+$) 100%; **^{1}H-nmr**(CD_3CO_2D): δ = 2.31 (m, 2H, $-CH_2-$); 2.85 (m, 2H, $-CH_2-$); 3.15 (pseudo-t, 2H, $-CH_2-$); 3.92 (m, 1H, -CH-); 7.40 (m, 6H, Ar); 7.68 (m, 4H, Ar); 11.25 (br, 1H, $-CO_2H$); **^{13}C-nmr**(CD_3CO_2D): δ = 24.7 ($-CH_2-$); 30.0 ($-CH_2-$); 36.9 ($-CH_2-CO_2$); 49.5 (-CH-); 127.3-129.7 (Ar-CH); 129.9 (Ar-C); 132.2 (Ar-C); 135.2 (-C=C-); 146.5 (-C=C-); 164.1 (-O-C=N-); 177.9 ($-CO_2H$).

2-[2-(4,5-Diphenyl-2-oxazolyl)-ethyl]-1-(N-allylcarbamoylmethyl)azetidinone (11).

At 25°C 1.55 ml (18.4 mmol) of allyl isocyanide are added to a solution of 5.50 g (16.4 mmol) of **10**

and 2.2 ml (25.7 mmol) of 35% aqueous formaldehyde in 150 ml of 1,2-ethanediol and 250 ml of glycerol. After 2.5 h 200 ml of water are added, and the product is extracted with ethyl acetate. The solvent is evaporated in vacuo. The residue is redissolved in ethyl acetate and filtered through a 3 cm layer of silica gel. The solvent is evaporated. The residue crystallizes on treatment with hexane/acetone (10:1). **Yield**: 5.0 g (74%) ; mp 101-102°C; $C_{25}H_{25}N_3O_3$ (415) ; **ms (m/z)** : 415 (M^+); ^{1}**H-nmr**($CDCl_3$): δ = 2.10 (m, 1H, $-CH_2-$); 2.42 (m, 1H, $-CH_2-$); 2.68 (dd, 1H, J= 14.4 Hz, J= 2.0 Hz, $-CH_2-CO-N-$); 2.91 (t, 2H, J= 6.7 Hz, $-CH_2-$); 3.12 (dd, 1H, J= 14.4 Hz, J= 4.7 Hz, $-CH_2-CO-N-$); 3.81 (d, 1H, J= 16.6 Hz, $-CO-N-CH_2-CO-$); 3.86 (t, 2H, J= 6.7 Hz, $-CH_2-CH=$); 3.92 (m, 1H, -CH-); 4.00(d, 1H, J= 16.6 Hz, $-CO-N-CH_2-CO-$); 5.13 (m, 2H, $=CH_2$); 5.75 (m, 1H, -CH=); 6.71 (t, 1H, J= 5.7 Hz, -NH); 7.33 (m, 6H, Ar); 7.55 - 7.60 (m, 4H, Ar); ^{13}**C-nmr**($CDCl_3$): δ = 24.4 ($-CH_2-$); 30.0 ($-CH_2-$); 41.9 ($-N-CH_2-CON-$); 42.6 ($-CH_2-C=$); 45.0 ($-CH_2-CON-$); 52.5 (-CH-); 116.6 ($=CH_2$); 126.4 - 128.8 (Ar-CH); 128.9 (Ar-C); 132.3 (Ar-C); 133.6 (-CH=); 135.1 (-C=C-); 145.5 (-C=C-); 161.7 (-N=C-O-); 167.3 (-CO-N-); 167.8 (-CO-N-); **ir**($CHCl_3$): 3420 cm^{-1} (m); 3310 (s); 3010 (vs); 1750 (vs); 1670 (vs); 1535 (s).

2-[2-(4,5-Diphenyl-2-oxazolyl)-ethyl]-1-[(N-Boc-N-allyl)carbamoylmethyl]azetidinone (12).

At 25°C 3.40 g (15.7 mmol) of Boc_2O are added to a stirred suspension of 5.0 g (12.05 mmol) of 11 and 0.190 g (1.6 mmol) of DMAP in 30 ml of dry acetonitrile. After 4.5 h the solvent is removed in vacuo, the residue is dissolved in ether and washed subsequently with 1N $NaHSO_4$ solution and saturated $NaHCO_3$ solution. The ether solution is evaporated in vacuo. The residue crystallizes from ether/hexane (5:1). **Yield** : 5.28 g (85%) ; mp 90-91°C; ^{1}**H-nmr**($CDCl_3$): δ = 1.52 (s, 9H, $-CMe_3$); 2.11 (m, 1H, $-CH_2-$); 2.44 (m, 1H, $-CH_2-$); 2.70 (dd, 1H, J= 14.6 Hz, J= 2.3 Hz, $-CH_2-CON-$); 2.93 (t, 2H, J= 7.5 Hz, $-CH_2-$); 3.15 (dd, 1H, J= 14.6 Hz, J= 5.1 Hz, $-CH_2-CON-$); 4.05 (m, 1H, -CH-); 4.23 (d, 2H, J= 5.8 Hz, $-CH_2-CH=$); 4.28 (d, 1H, J= 18.8 Hz, $-N-CH_2-CO-$); 4.78 (d,1H, J= 18.8 Hz, $-N-CH_2-CO-$); 5.13 (m, 2H, $=CH_2$); 5.75 (m, 1H, -CH=); 7.35 (m, 6H, Ar); 7.55-7.60 (m, 4H, Ar).

2-[2-(4,5-Diphenyl-2-oxazolyl)-ethyl]-1-(methoxycarbonylmethyl)azetidinone (13a).

At 0°C a solution of 0.11 g (2.13 mmol) of sodium methoxide in 2.0 ml of dry methanol is added to 1.00 g (1.94 mmol) of 12 in 5.0 ml of dry methanol. After 3 min this reaction mixture is poured into 15 ml of water, and then extracted with ether. The ether phase is washed with water, dried over $MgSO_4$, and evaporated in vacuo. The resulting oil is dissolved in 10 ml of benzene, and a solution of 6.3 ml (1.90 mmol) of a 0.3 N benzene solution of $Me_3SiOSO_2CF_3$[13] is added at 25°C. After 5 min the solvent is evaporated. The residue is dissolved in ether, washed with water, and dried over $MgSO_4$. Evaporation of the solvent leaves a pale yellow oil. **Yield** : 0.58 g (77%); $C_{23}H_{22}O_2N_2$ (390); **ms (m/z)**: 390 (M^+); ^{1}**H-nmr**($CDCl_3$): δ = 2.05 (m, 1H, $-CH_2-$); 2.35 (m, 1H, $-CH_2-$); 2.70 (dd, 1H, J= 15.0 Hz, J= 2.4 Hz, $-CH_2-CO-N-$); 2.90 (t, 2H, J= 7.5 Hz, $-CH_2-$); 3.15 (dd, 1H, J= 15.0 Hz, J= 5.0 Hz, $-CH_2-CON-$); 3.69

(s, 3H, -OMe); 3.82 (d, 1H, J= 18.1 Hz, -N-CH_2-CO_2-); 3.95 (m, 1H, -CH-); 4.20 (d, 1H, J= 18.1 Hz, -N-CH_2-CO_2-); 7.35 (m, 6H, Ar); 7.55-7.60 (m, 4H, Ar); ^{13}C-nmr($CDCl_3$): δ = 24.4 (-CH_2-); 30.0 (-CH_2-); 41.8 (-CH_2-CO-N-); 42.8 (-N-CH_2-CO_2-); 51.8 (-OMe); 52.3 (-CH-); 126.4-128.7 (Ar-CH) ; 128.8 (Ar-C); 132.3 (Ar-C); 135.2 (-C=C-) ; 145.5 (-C=C-); 161.8 (-N=C-O-); 167.2 (-CON-); 168.7 (-CO_2-).

2-[2-(N,N-Dibenzoyl)carbamoylethyl]-1-(methoxycarbonylmethyl)azetidinone (14 a)

A solution of 1.70 g (4.35 mmol) of **13 a** in 110 ml of dry dichloromethane was oxygenated for 3 h in the presence of 100 mg of Sensitox (Rose Bengal polymer) during irradiation with a tungsten halogen lamp (650 w) according to the procedure of Wasserman et al.[10] The Sensitox was removed by filtration. The solvent was evaporated. A yellow oil was obtained. (It was directly used for the synthesis of **15 a** by cyclisation with potassium t-butoxide in toluene at 0°C)

Yield : 1.75 g (95 %); ^{1}H-nmr($CDCl_3$): δ = 2.05 (m, 1H, -CH_2-); 2.28 (m, 1H, -CH_2-); 2.70 (dd, 1H, J= 14.7 Hz, J= 2.2 Hz, -CH_2-CO-N-CH_2-); 2.96 (m, 2H, -CH_2-CO-N-); 3.18 (dd, 1H, J= 14.7 Hz, J= 4.9 Hz, -CH_2-CO-N-CH_2-); 3.76 (s, 3H, -OMe); 3.80 (d, 1H, J= 18.1 Hz, -CH_2-CO_2Me); 3.94 (m, 1H, -CH-); 4.18 (d, 1H, J= 18.1 Hz, -CH_2-CO_2Me); 7.42 (pseudo-t, 4H, Ar); 7.56 (pseudo-t, 2H, Ar); 7.78 (d,4H, J= 7.4 Hz, Ar).

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