SYNTHESIS OF NEW PENEM DERIVATIVES: N-SUBSTITUTED ANALOGS OF FCE 22101

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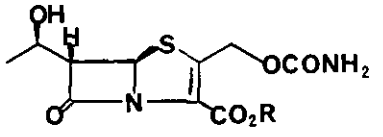
Abstract - New penem derivatives, analogs of FCE 22101 with N-substitution at the carbamoyl moiety, have been synthesized by using a new catalytic action of 4-dimethylaminopyridine.

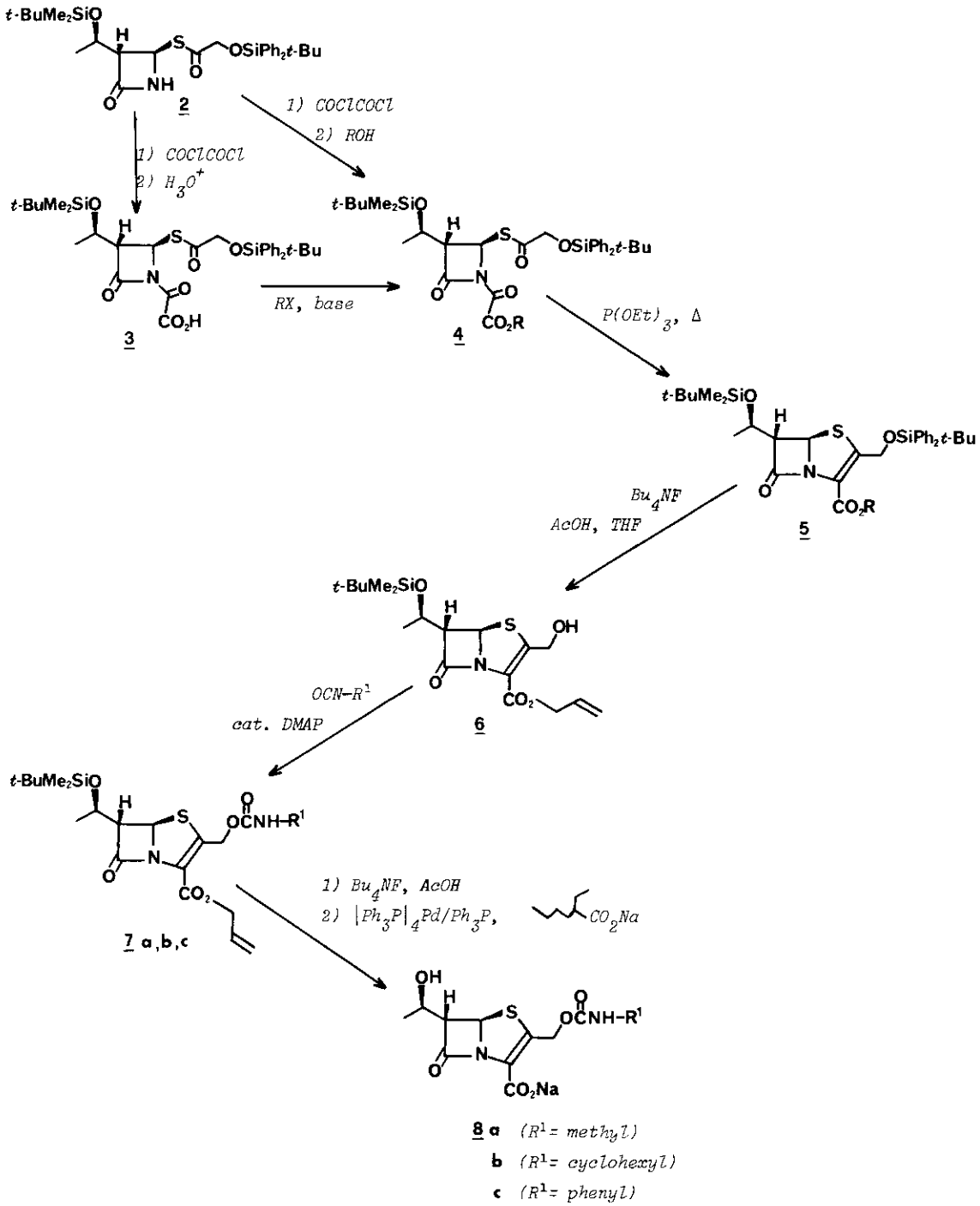
Our interest in the synthesis of penem antibiotics induced us to prepare new analogs of FCE 22101[1] (1a) as well as to design convenient modifications of previous synthesis.[1-3] We considered a logical trend investigating the effects of N-substituent at the carbamoyl moiety upon the biological activity. Methyl, cyclohexyl and phenyl groups were chosen as representative examples of the substituent.



1a : R = Na (FCE 22101)
1b : R = CH_2OCOCH_3 (FCE 22891)

The Scheme shows the synthesis of the target compounds 8a-c starting from the N-unsubstituted derivative 2.[1] The proper functionalization at the azetidinone nitrogen was provided by treatment with oxalyl chloride and diisopropylethylamine in CH_2Cl_2, soon followed by addition of allyl alcohol. The crude oxalimido derivative 4 was directly cyclized to the penem structure (compound 5, R = allyl) by our recently reported method[3] in a 50% overall yield. After selective deprotection of the primary hydroxyl group,[1,2] the introduction of N-substituted carbamoyl moiety involved reaction of the allylic alcohol 6 with the suitable isocyanate. The catalytic action of 4-dimethylaminopyridine (DMAP) proved essential for such a reaction. Indeed treatment of the hydroxy compound 6 with 1.1 molar equivalent of methyl isocyanate and 20-30% (by moles) of DMAP in ethanol free dichloromethane (2 h at reflux temperature) afforded the N-methylcarbamoyl derivative 7a[4] crystallized from isopropyl ether in 60% yield. By using the same reaction conditions, the N-cyclohexylcarbamoyl derivative 7b[4] was obtained in 60% yield after column chromatography. In the case of the phenyl analog it was necessary to increase the reaction temperature by using chloroform (ethanol free) as refluxing solvent. All the other conditions were unchanged and, after an aqueous acid work-up, crystallization from cyclohexane afforded the N-phenylcarbamoyl derivative 7c[4] in 50% yield.

S C H E M E


t-BuMe2SiO
OSiPh2t-Bu
2
1) COClCOCl
2) ROH
1) COClCOCl
2) H3O+
3
RX, base
4
P(OEt)3, Δ
5
Bu4NF
AcOH, THF
6
OCN-R1
cat. DMAP
7 a,b,c
1) Bu4NF, AcOH
2) [Ph3P]4Pd/Ph3P,
CO2Na
8 a (R1 = methyl)
b (R1 = cyclohexyl)
c (R1 = phenyl)

Usual deblocking reactions[1,5,6] afforded the final target compounds 8a[7] and 8c.[9] Since 8b was obtained in very poor yield by this route, the sequence was repeated by utilizing the corresponding p-nitrobenzyl ester, getting better results in the last deprotecting reaction (by hydrogenolysis)[1] to 8b.[8] The N-methyl derivative 8a showed an antibacterial activity similar to that of FCE 22101; on the contrary, 8b and 8c were much less active.

The acetoxymethyl ester FCE 22891 (1b)[1,3] is a promising prodrug of 1a. The two-step acylation procedure outlined in the Scheme allowed the development of a different approach in which the enzymatically labile moiety is already incorporated in the azetidinone N-appendage before the formation of the penem ring. The N-unsubstituted azetidinone 2 was acylated with oxalyl chloride (one molar equivalent with diisopropylethylamine and $CaCO_3$ in CH_2Cl_2) going on to the fairly stable oxo-acid intermediate 3[10] (by acid or basic hydrolytic work-up). The subsequent esterification step was performed with bromomethyl acetate (with $NaHCO_3$ in DMF or with TEA in CH_2Cl_2) leading to the oxalimido derivative 4 (R = CH_2OCOCH_3), directly cyclized to the penem 5 (R = CH_2OCOCH_3) (40% overall yield from 2). Successively, selective deprotection of the primary hydroxyl group, carbamoylation and final deprotection afforded FCE 22891 (1b).

REFERENCES AND NOTES

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2. M. Foglio, C. Battistini, F. Zarini, C. Scarafile and G. Franceschi, *Heterocycles* 1983, *20*, 1491.
3. C. Battistini, C. Scarafile, M. Foglio and G. Franceschi, *Tetrahedron Lett.*, 1984, *25*, 2395.
4. These intermediates showed correct UV, IR and ^{1}H-NMR spectral data, in agreement with their structures.
5. V.M. Girijavallabhan, A.K. Ganguly, S.W. McCombie, P. Pinto and R. Rizvi, *Tetrahedron Lett.*, 1981, *22*, 3485.
6. P.D. Jeffrey and S.W. McCombie, *J. Org. Chem.*, 1982, *47*, 587.
7. Compound 8a. UV (95% EtOH): λ_{max} 304 nm (ε 5670). P.M.R. (200 MHz, D_2O), δ (p.p.m.): 1.30 (d, J = 6.5 Hz, 3H, $\underline{CH_3}CH$); 2.73 (s, 3H, $NH\text{-}\underline{CH_3}$); 3.90 (dd, J = 1.6, 6.0 Hz, 1H, H-6); 4.24 (dq, J = 6.0, 6.5 Hz, H-8); 5.07, 5.36 (two d, J = 14.6 Hz, 2H,  $\underline{CH_2}$-OCO); 5.65 (d, J = 1.6 Hz, 1H, H-5).
8. Compound 8b. UV (95% EtOH): λ_{max} 306 nm (ε 7600). P.M.R. (200 MHz, D_2O + DMSO), δ (p.p.m.): 1.32 (d, J = 6.4 Hz, 3H, $\underline{CH_3}CH$); 1.19 - 1.39, 1.57 - 1.92 (two m, 10H, cyclohexyl protons); 3.38 (m, 1H, cyclohexyl tertiary proton) 3.88 (dd, J = 1.5, 6.2 Hz, 1H, H-6); 4.23 (dq, J = 6.2, 6.4 Hz, 1H, H-8); 5.11, 5.40 (two d, J = 14.7 Hz, 2H,  $\underline{CH_2}$-OCO); 5.65 (d, J = 1.5 Hz, 1H, H-5).
9. Compound 8c. UV (95% EtOH): λ_{max} 301 nm (ε 6100). P.M.R. (200 MHz, D_2O), δ (p.p.m.): 1.21 (d, J = 6.4 Hz, 3H, $\underline{CH_3}CH$); 3.82 (dd, J = 1.5, 5.6 Hz, 1H, H-6); 4.15 (dq, J = 5.6, 6.4 Hz, 1H, H-8); 5.09, 5.40 (two d, J = 14.5 Hz, 2H,  $\underline{CH_2}OCO$); 5.58 (d, J = 1.5 Hz, 1H, H-5); 7.33 (m, 5H, aromatic protons).

10. Compound 3. IR ($CHCl_3$) ν (cm^{-1}): 1815, 1750, 1715. P.M.R. (200 MHz, $CDCl_3$), δ (p.p.m.): 0.08 (s, 6H, $Si(\underline{CH_3})_2$); 0.85 (s, 9H, $Me_2\underline{Si}-C(\underline{CH_3})_3$); 1.12 (s, 9H, $Ph_2\underline{Si}-C(\underline{CH_3})_3$); 1.28 (d, J = 6.5 Hz, 3H, $\underline{CH_3}CH$); 3.62 (m, 1H, H-6), 4.3 - 4.6 (m, 3H, $CO\underline{CH_2}OSi$ and H-8); 6.12 (m, 1H, H-5); 7.4 - 7.9 (m, 10H, $Si\underline{Ph_2}$); 9.52 (bs, 1H, $CO\underline{OH}$).

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