An Efficient Method for the Preparation of Carbapenem Derivatives with C-2 Carbon Side Chains from PS-5 and OA-6129 Compounds

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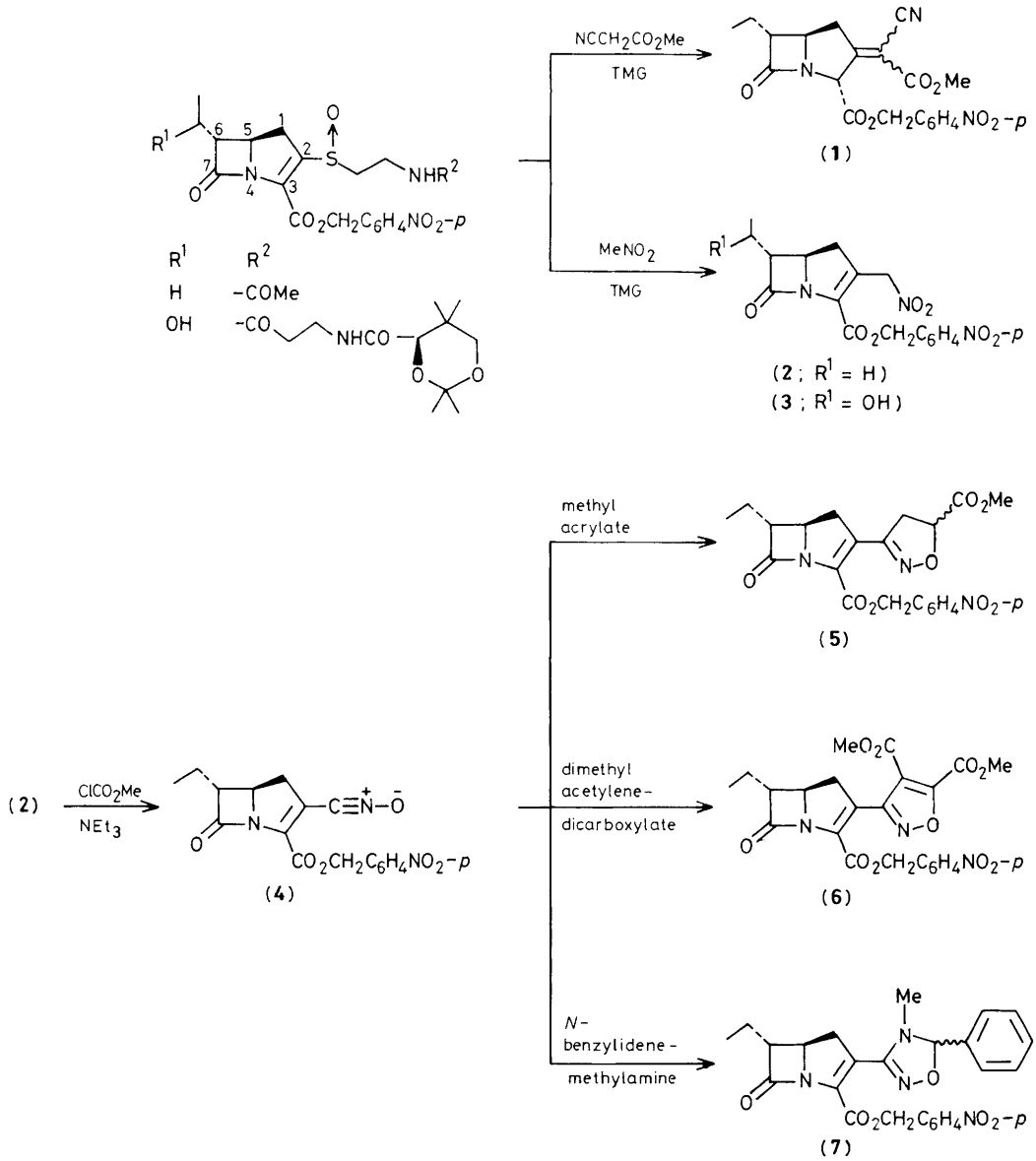
Treatment of *S*-oxides of PS-5 and OA-6129 esters with nitromethane gives 2-(nitromethyl)carbapenems which are converted into nitrile oxides leading to isoxazolyl, isoxazolinyl, or isoxadiazolinyl derivatives.

We have already established a new versatile method for displacement of the C-2 sulphur side chains of naturally-occurring carbapenems by a variety of thiols *via* the corresponding *S*-oxides.[1]

Recently we have found that the sulphinyl group at the C-2 position can be replaced by active methylene compounds such as nitromethane or methyl cyanoacetate. When the *S*-oxide of PS-5 *p*-nitrobenzyl ester in dimethyl formamide (DMF) was treated (−35 °C for 1.5 h) with methyl cyanoacetate (10 equiv.) as a nucleophile in the presence of tetramethyl guanidine (TMG, 9 equiv.) as a base, a compound possessing the cyanoacetyl side chain at C-2 was obtained as a mixture of the geometrical isomers in 56% yield. The structure of the compound (**1**) was determined by mass spectrometry [*m/z* 413 (*M*)] and by observation of the C-3 proton [δ 5.75 and 5.48 (isomeric ratio 5 : 1) d, $J_{1\beta,3}$ 2.0 Hz] in the n.m.r. spectrum. The use of strong bases such as NaH, NaOMe, or KOBu^t in DMF resulted in the rupture of the β-lactam ring.



2-(Nitromethyl)carbapenems, (**2**) and (**3**),† were prepared in 58 and 54% isolated yields, respectively, by treatment (−25 °C, 30 min) of the sulphoxides of PS-5 and isopropylidene-OA-6129B2 *p*-nitrobenzyl esters[2] with nitromethane as a solvent in the presence of TMG. These nitromethyl compounds were so unstable towards acids that the purification could be achieved by extraction with organic solvents and column chromatography on Bio-Beads S-X3[3] instead of silica gel.

† *Spectroscopic data:* (**2**) $\lambda_{max.}$ (CH_2Cl_2), nm (ε) 268 (12 100); $\nu_{max.}$ ($CHCl_3$), cm^{-1} 1780 (β-lactam), 1725 (ester), 1555, 1520, 1350 (nitro); ^1H n.m.r. ($CDCl_3$, Me_4Si) δ 3.02 (2H, d, *J* 9 Hz, 1-H_2), 3.22 (1H, m, 6-H), 4.02 (1H, dt, *J* 3, 9 Hz, 5-H), 5.31 (1H, d, *J* 15.5 Hz, C*H*H–NO_2), 5.78 (1H, d, *J* 15.5 Hz, CH*H*–NO_2). (**3**) $\lambda_{max.}$ (CH_2Cl_2), nm (ε) 268 (13 100); $\nu_{max.}$ ($CHCl_3$), cm^{-1} 1780 (β-lactam), 1720 (ester), 1555, 1520, 1350 (nitro); ^1H n.m.r. ($CDCl_3$) δ 2.98 (2H, d, *J* 9 Hz, 1-H_2), 3.30 (1H, m, 6-H), 3.85—4.35 (2H, m, 5-H, 8-H), 5.29 (1H, d, *J* 15 Hz, C*H*H–NO_2), 5.66 (1H, d, *J* 15 Hz, CH*H*–NO_2). (**4**) (purified by silica gel column chromatography) $\lambda_{max.}$(CH_2Cl_2), nm (ε) 324 (10 600), 267 (12 000); $\nu_{max.}$($CHCl_3$), cm^{-1} 2295 (nitrile), 1792 (β-lactam), 1730 (ester); ^1H n.m.r. ($CDCl_3$) δ 2.98 (1H, dd, *J* 10, 19 Hz, 1-*H*H), 3.17 (1H, dd, *J* 10, 19 Hz, 1-H*H*), 3.28 (1H, m, 6-H), 4.08 (1H, dt, *J* 3, 10 Hz, 5-H). (**5**) $\lambda_{max.}$ (THF), nm (ε) 325 (12 300), 269 (12 000), 262.5 (14 200), 257.5 (13 600), 251 (12 200); $\nu_{max.}$ ($CHCl_3$), cm^{-1} 1785 (β-lactam), 1740 (ester); ^1H n.m.r. ($CDCl_3$) δ 3.0—3.8 (5H, m, 1-H_2, 6-H, 4′-H_2), 3.75 (3H, s, OMe), 3.93 (1H, dt, *J* 3, 9 Hz, 5-H), 5.10 (1H, m, 5′-H); *m/z* 443 (*M*). (**6**) $\lambda_{max.}$ (THF), nm (ε) 268 (13 400), 260 (12 900), 253 (12 000), 248 (11 300); $\nu_{max.}$ ($CHCl_3$), cm^{-1} 1790 (β-lactam), 1740 (ester); ^1H n.m.r. ($CDCl_3$) δ 3.27 (3H, m, 1-H_2, 6-H), 3.73 (3H, s, OMe), 3.97 (3H, s, OMe), 4.1 (1H, dt, *J* 3, 9 Hz, 5-H); *m/z* 499 (*M*). (**7**) $\lambda_{max.}$ (THF), nm (ε) 270 (11 000), 264 (10 700), 261 (10 000), 255 (8800); $\nu_{max.}$ ($CHCl_3$), cm^{-1} 1790 (β-lactam), 1735 (ester); ^1H n.m.r. ($CDCl_3$) δ 2.50 (3H, s, NMe), 3.16 (3H, m, 1-H_2,6-H), 4.06 (1H, m, 5-H), 5.83 and 5.90 (1H, s respectively, 5′-H); *m/z* 476 (*M*).

Compound (**2**) was allowed to react (0 °C, 30 min) with methyl chloroformate (2 equiv.) in the presence of triethylamine (2 equiv.) in DMF, leading to a nitrile oxide (**4**)† which, without purification, was trapped with 1,3-dipolarophiles to afford isoxazolyl, isoxazolinyl, and isoxadiazolinyl derivatives. Namely, the cycloaddition reaction (room temp., 4 h) of (**4**) to methyl acrylate (3 equiv.) provided an isoxazoline compound (**5**) in 51% isolated yield from PS-5 ester sulphoxide. The use of dimethyl acetylenedicarboxylate (1.5 equiv.) or *N*-benzylidenemethylamine (4 equiv.) under the same reaction conditions gave the corresponding isoxazolyl or isoxadiazolinyl compound (**6**)† or (**7**)† in 36 or 34% isolated yield, respectively, from the sulphoxide.

These carbapenem derivatives having the carbon side chains at C-2 showed substantial antimicrobial activities against *Comamonas terrigena* B-996 and *Staphylococcus aureus* 209P on bioassay agar plates containing horse serum.

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