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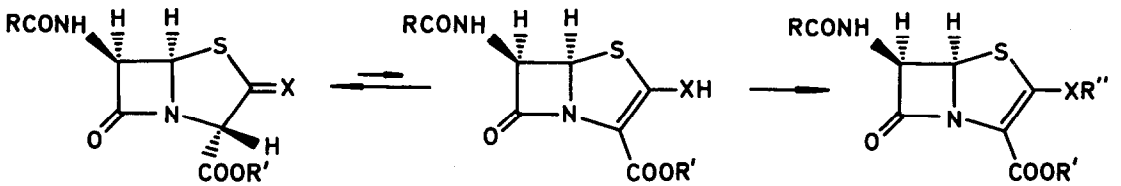
A GENERAL ROUTE TOWARD 2-OXO-, 2-THIOXO- AND 2-IMINOPENAMS AND THEIR CONVERSION INTO 2-ALKOXY-, 2-ALKYLTHIO- AND 2-AMINOPENEMS

Marc COSSEMENT, Jacqueline MARCHAND-BRYNAERT,
Sophie BOGDAN and Léon GHOSEZ*

Laboratoire de Chimie Organique de Synthèse
Université Catholique de Louvain, Place Louis Pasteur, 1,
B-1348 LOUVAIN-LA-NEUVE, BELGIUM.

Summary : A convenient methodology is described which allows the preparation of 2-oxo-, 2-thioxo- and 2-iminopenams from a single precursor readily prepared from penicillin G. These penams have been converted into the corresponding 2-hetero-substituted penems.

Most synthesis of penems are still based on the intramolecular thiocarbonyl Wittig cyclization developed by Woodward and his colleagues[1,2]. However this methodology appears to be not readily applicable to the synthesis of penems 1 bearing heterosubstituents at C-2.[3] We have proposed an alternative approach toward such penems.[4] It is based on the irreversible quenching of the "enol tautomers" 2 of penams 3 bearing an exocyclic C=X double bond (Scheme 1). This has been already illustrated by the synthesis of 2-alkoxypenems 1 (X=O).[5]

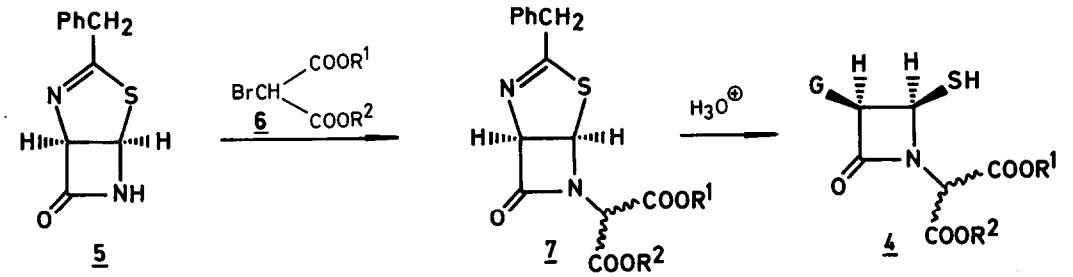


3 2 1

Scheme 1.

We describe here a more general route toward a variety of penams 3 and the corresponding penems 1 from a common intermediate 4 readily prepared from penicillin G.

Alkylation of compound 5[6] with bromomalonates 6[7] (2 equiv. Triton B, DMF, -30°C to 20°C) yielded the N-substituted β-lactams 7a (73%) and 7b (65%, two diastereoisomers) (Scheme 2). Hydrolysis of 7 (35% $HClO_4$ or 1N HCl, CH_3OH, 20°C, 30 min) liberated quantitatively the G side-chain and the thiol group[8] to give the compounds 4 which were directly exposed to various bis-electrophiles (Scheme 3).



G = $PhCH_2CONH-$

a : $R^1 = R^2 = CH_2Ph$

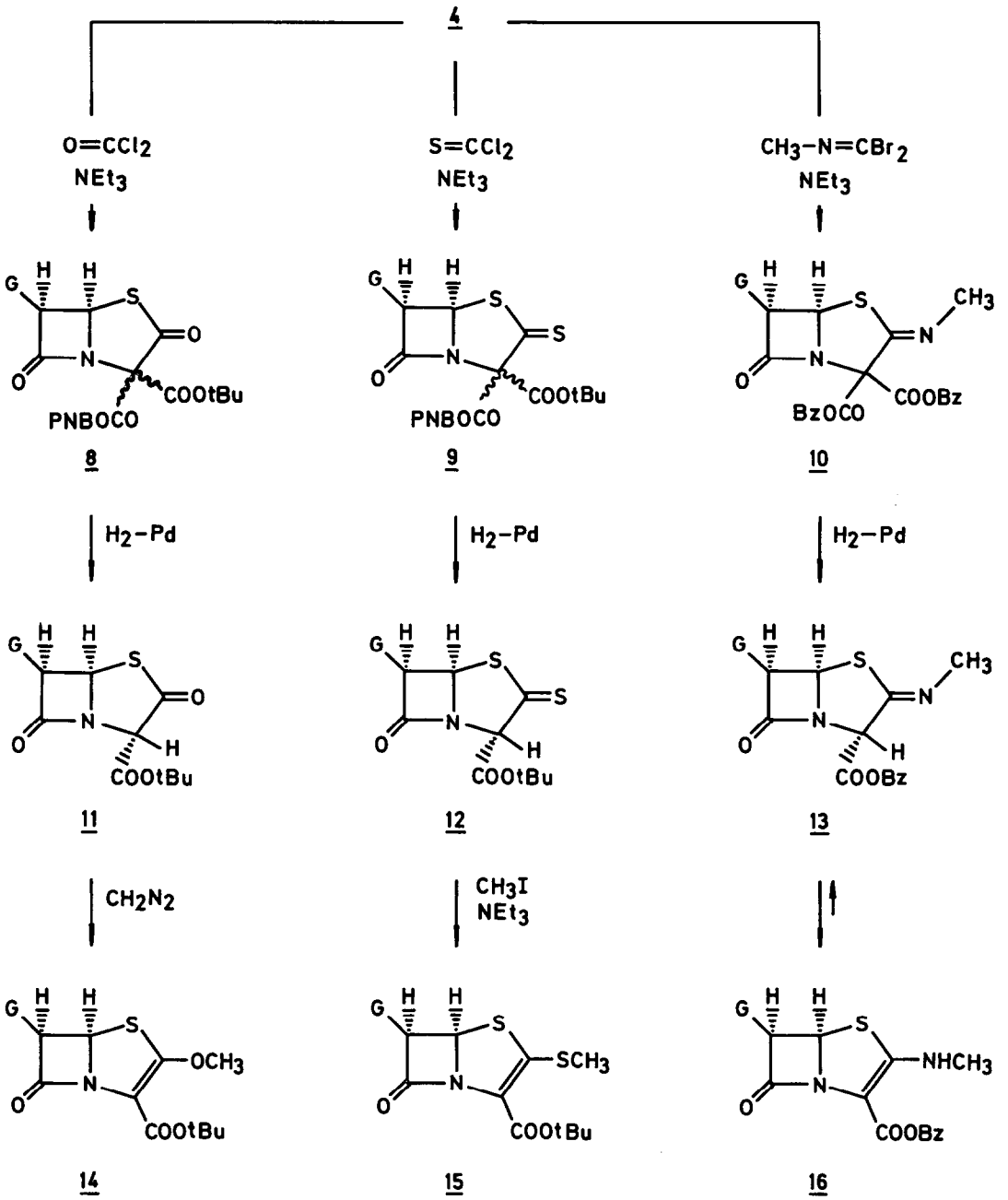
b : $R^1 = tBu$; $R^2 = CH_2$-(p-NO_2-C_6H_4)

Scheme 2.

Reaction of 4b with phosgene (1 equiv.) and thiophosgene (1 equiv.) in the presence of triethylamine (2 equiv. CH_2Cl_2, -60°C to 0°C) yielded compounds 8 (two diastereoisomers, 53% after chromatography, $\nu_{C=O}$ 1808 cm^{-1}) and 9 (red solid, two diastereoisomers, 59% after chromatography, $\nu_{C=O}$ 1806 cm^{-1}). Dibromo-N-methylimine reacted under the same conditions with 4a to give the bicyclic compound 10 (20% after chromatography, $\nu_{C=O}$ 1803 cm^{-1}).

Hydrogenolysis (Pd 10% on C, AcOEt, 20°C) of the p-nitrobenzyl esters of 8 and 9 was accompanied by the spontaneous decarboxylation of the resulting acids to yield the known[5] 2-oxopenam ester 11 (48% after chromatography) and the new[9] 2-thioxopenam ester 12 (35% after chromatography).[10] We had already shown[5] that 11 could readily be converted into 2-methoxypenem 14 on treatment with diazomethane but did not react with methyliodide and triethylamine at room temperature. In contrast 12 readily reacted under these conditions to yield the penem derivative 15 (46% yield after chromatography at -40°C, unstable at room temperature).[11]

Hydrogenolysis of 10 under the standard conditions gave consistently 15-25% yield of 2-iminopenam 13. A significant amount of starting material 10 was recovered. Examination of the spectral properties[12] of 13 revealed the presence of both 2-iminopenam 13 and 2-aminopenem 16 tautomers in an approximate ratio of 1:2. This contrasts with the behaviour of 11 and 12 which do not show any detectable "enol" or "enethiol" content. Clearly, in 13, the extra-strain provided by the additional sp^2 center is outweighed by the stabilisation resulting from the better conjugation in 16.


4
O=CCl2
NEt3
S=CCl2
NEt3
CH3-N=CBr2
NEt3
PNBOCO
COOtBu
8
PNBOCO
COOtBu
9
BzOCO
COOBz
10
H2-Pd
H2-Pd
H2-Pd
11
12
13
CH2N2
CH3I
NEt3
14
15
16

Scheme 3.

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This work was generously supported by the "Institut pour l'Encouragement de la Recherche Scientifique dans l'industrie et l'Agriculture" (fellowships to M.C. and S.B.), the "Fonds National de la Recherche Scientifique" (fellowship to J.M.-B.) and the "Service de la Programmation de la Politique Scientifique" (grant 79/84-13).

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(7) 6a was prepared from malonic acid by esterification ($PhCH_2Br$, 2 equiv./NEt_3, 2 equiv./DMF, 20°C) and subsequent bromination (Br_2, 1 equiv./hν, $CHCl_3$); 6b was obtained after monoesterification of malonic acid with p-nitrobenzylalcohol (<1 equiv., iC_3H_7-N=C=N-iC_3H_7, THF-CH_2Cl_2, 20°C), followed by bromination (Br_2, 1 equiv./ CH_2Cl_2, reflux) and esterification with isobutylene (excess) under pressure (H_2SO_4 catalysis/CH_2Cl_2, 20°C).

(8) M. Narisada, H. Onoue, M. Ohtani, F. Watanabe, T. Okada and W. Nagata, Tetrahedron Letters, 20, 1755 (1978).

(9) Thioxopenams without acylamino side chains have been recently described : T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura, T. Miyadera, J. Chem. Soc. Chem. Commun., 713 (1982); M. J. Daniels, G. Johnson, B.C. Ross, M. A. Yeomans, J. Chem. Soc., Chem. Commun., 1119 (1982).

(10) IR (CH_2Cl_2, cm^{-1}): 3410, 1803, 1740, 1690; ^{1}HNMR ($CDCl_3$, 60 MHz,δ) 1.46 (s,9), 3.56 (s,2), 5.1 (s,1), 5.76 (dxd, 1, J=4 and 7 Hz), 6.11 (d,1, J=4 Hz), 6.85 (br d, 1, J=7 Hz), 7.25 (s,5).

(11) IR (CH_2Cl_2, cm^{-1}): 3420, 1801, 1685 (br); ^{1}HNMR ($CDCl_3$, 60 MHz,δ): 1.5 (s,9), 2.46 (s,3), 3.65 (s,2), 5,7 (dxd, 1, J=4 and 7.5 Hz), 5.86 (d,1,J=4 Hz), 6.87 (br d, 1, J=7.5 Hz), 7.35 (s,5); UV (dioxane): λm 332 nm (ε=12700).

(12) IR (CH_2Cl_2, cm^{-1}) : 3410 (w), 3295 (w), 1800 (s), 1745 (w), 1685 (s), 1655 (m), 1580 (m); ^{1}HNMR ($CDCl_3$, 200 MHz,δ) 13 : 3.09 (d,3, J=1Hz), 3.54 (s,2), 5.04 (q,1, J=1 Hz), 5.13 (br s,2), 5.63 (d, 1, J=4.1 Hz), 5.72 (dxd, 1, J=4.1 and 8.4 Hz), 6.23 (br d, 1, J=8.4 Hz), ∿7.25 (m,10); 16 : 2.88 (d,3, J=5.1 Hz), 3.54 (s,2), ∿5.14 (ABq, 2, J=13 Hz), 5.57 (dxd,1, J=3.5 and 7.1 Hz), 5.67 (d,1,J=3.5 Hz), 6.47 (br d, 1, J=7.1 Hz), ∿7.25 (m,10), 7.37 (br q, 1, J=5.1 Hz).

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