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THE CARBONYL-CARBONYL COUPLING ROUTE TO PENEMS : A STEPWISE ANALYSIS

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Abstract : Preparation and reactivity of novel azetidinyl(phosphoranylidene)acetates implicated in penem synthesis is discussed

Recently, a novel route to the valuable penem antibiotics FCE 22101 and FCE 22891[1] entailing the reductive coupling of dicarbonyl precursors was worked out in our laboratories[2]. In spite of parallelisms between this CO/CO condensation and the Schering CO/CS coupling[3], which reportedly proceeds through a carbene-CS insertion without allowing isolation of any stable intermediate, we were led by simple a priori considerations[4] to dismiss an analogous carbene-CO addition[5], and consequently undertook a close experimental analysis of the reaction pathway. An intervening paper by Sankyo chemists describing similar penem-forming reactions[6] prompts us to report our independent studies on mechanism and scope of phosphite-mediated reductive olefinations of this type.

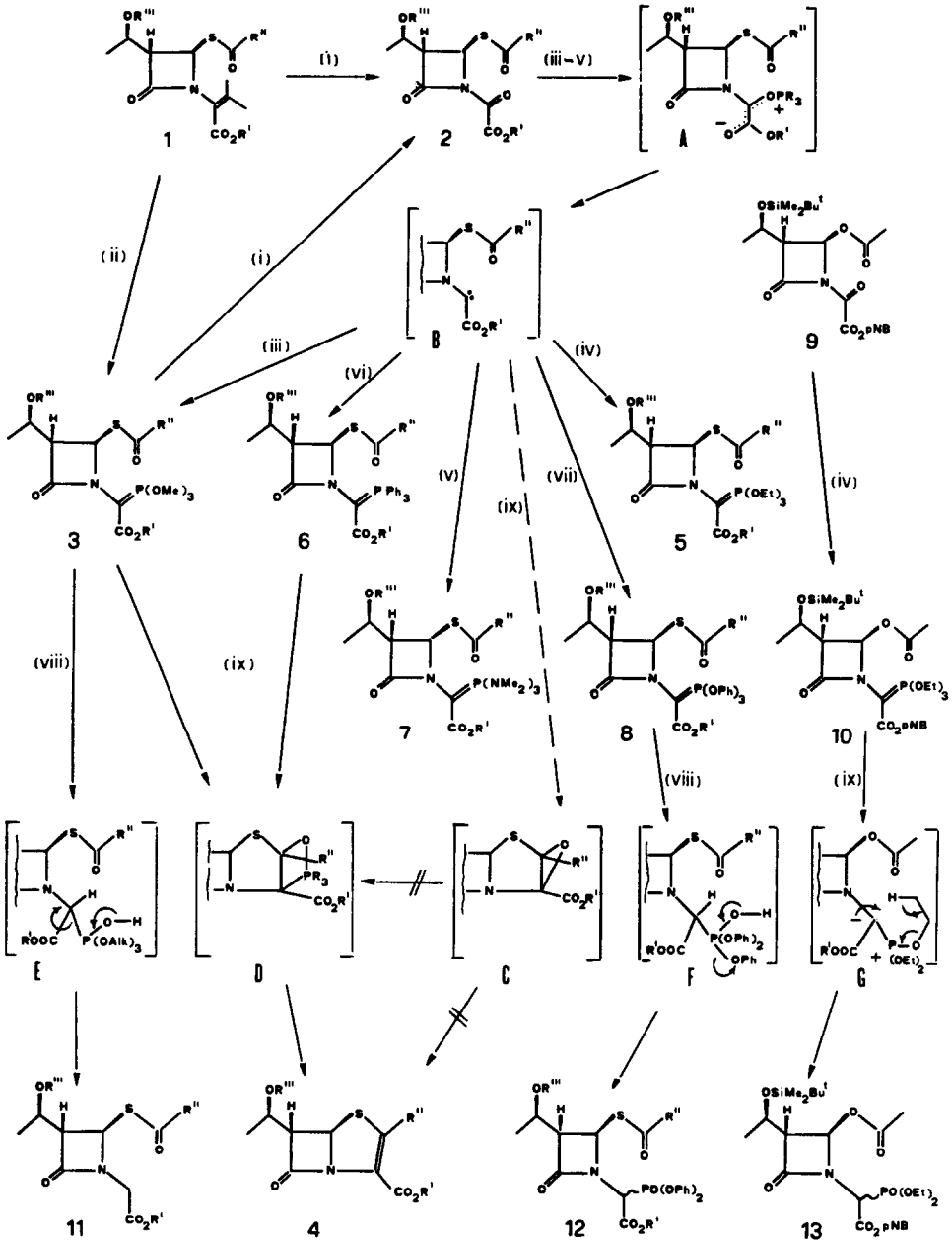
In our search for reaction intermediates, it was felt that an electron-withdrawing substituent on the carboxyl group could enhance the reactivity of the oxalimide carbonyl towards the phosphite, while possibly retarding any further reaction (species A in the Scheme); trichloroethyl esters were thus specifically selected as prototypical substrates. Sure enough, mere addition of excess trimethylphosphite (octadeuterotoluene, n.m.r. tube) to 2 (R'~R''' as shown) brought about its conversion into a new trimethoxyphosphorous derivative, with simultaneous release of $PO(OMe)_3$, at a fast enough rate to be monitored by consecutive instrumental scannings. Full spectroscopic[7] and chemical evidence (reversion to the starting oxamide 2 upon ozonation; conversion to the penem 4 by plain heating in neat xylene) completed the structural assignment of the new product as the phosphite ylide 3 and its recognition as a true intermediate in the penem-forming ring closure, along what amounts to a modified Wittig-type reaction.

There are several striking points in this sequence. First, trimethylphosphite acted both as a carbene-generator (2→B) and as a carbene-trapper (B→3); the question arose whether different phosphorous compounds can play either role efficiently. Qualitatively, it was found that only air sensitive[8] reagents act in this way; air-stable ones, as triphenylphosphite and

4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.1]octane (ETPB) failed to react with oxamide 2 even in refluxing $CHCl_3$; phosphines (PBu_3 and, to a much slower rate, PPh_3) gave complex mixtures of non ß-lactam products, while hexamethylphosphoroustriamide, though destructive as well, could be driven to yield the expected ylide 7 ($\leqslant$10%) under strictly controlled conditions (-70° to 25°, overnight). Then, to assess the ability of the above reagents to behave as carbene-trappers, species B was generated in the presence of the reagent to be tested (competitive trapping). Typically, a mixture of the latter (excess) and oxoamide 2 was exposed to dropwise addition of $P(OMe)_3$ ($\leqslant$1 mol equiv.). This procedure proved fascinating and not devoid of preparative value; phosphorane 6 (a key intermediate in classical multistep routes) and 8 (to our knowledge, the first arylphosphite ylide ever reported) were obtained in reasonable yields thereupon. The easy access to the classical triphenylphosphorane 6 and to the new ylides 3,5,7,8 opened by the above routes gave us the welcome opportunity of comparing their reactivity in the Wittig condensation to penem 4 (130°, xylene). Whilst 7 and 8 decomposed without cyclizing, 3 and 5 gave comparable results (55%, 3h), and the smoothest outcome was obtained from 6 ($\sim$70%, 1.5 h)[9]; when dealing with stabilized phosphoranes this makes sense, since electron-withdrawing (-I) substituents on the phosphorous are known to stabilize the ylene vs. the ylide form.[10, 11]

Additional interesting traits of the new ylides emerged from their treatment under thermolitic and hydrolitic conditions; Arbuzov rearrangement[12] and, resp., conversion into phosphonates[12b, 13] were expected. However, the former reaction pattern was never evident; instead, the 4-acetoxy derivative 10, which could be thermolysed without interfering cyclization (125°, 10 h), gave the phosphonate 13, presumably through a pericyclic ß-elimination (species G). Phosphonates, on the other hand, which were anticipated as hydrolysis products, were obtained only from the triphenoxyphosphorane 8, undoubtedly by virtue of a good leaving group being present (8 → 12, prolonged exposure to moist air or silica[14]; species F suggested); trialkoxyphosphoranes 3, 5, 10 rather lose trialkylphosphate to give azetidinylacetates, as testified by the remarkable conversion of 3 into 11 ($CDCl_3/D_2O$, n.m.r. tube, 72 h; deuterium incorporation in the acetate methylene simultaneously occurring). Nevertheless, compound 3 proved stable to washings with pH 7.4 phosphate buffer; this was enough to elicit a convenient one-pot procedure from 1 to 3 [O_3, -78°; then $P(OMe)_3$ 10 equiv., overnight r.t.; removal of excess reagent in vacuo and of $PO(OMe)_3$ by aq. work-up], devised after the observation that phosphites can serve the extra purpose of reducing ozonides.[15]

The limited stability of phosphite ylides, the manifold reactivity of carbonyl compounds towards phosphites[16], and the propensity of these reagents to interact with diazo compounds to form phosphazines (thus precluding an alternative access to carbenes)[17] concur in severely restricting the reaction scope. In fact, our preliminary experiments with simple 1,2-dicarbonyl compounds (benzyl glyoxylate[18], ethyl pyruvate[16], diethyl oxomalonate[19]) failed to give any of the expected phosphoranes or alkene dimers. Perhaps, oxoamides 2 are ideal substrates; for certain, ß-lactam chemistry did not fail to amaze its disciples once more.



Reagents : (i) O_3, then Me_2S ; (ii) O_3, then $P(OMe)_3$; (iii) $P(OMe)_3$; (iv) $P(OEt)_3$; (v) $P(NMe_2)_3$; (vi) PPh_3 ; (vii) $P(OPh)_3$; (viii) H_2O ; (ix) thermolysis

($R' = CH_2CCl_3$, $R'' = CH_2OCONH_2$, $R''' = CO_2CH_2CCl_3$ for specifically described compounds)

References and Notes

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2. C. Battistini, C. Scarafile, M. Foglio, and G. Franceschi, preceeding paper.
3. A. Afonso, F. Hon, J. Weinstein, and A.K. Ganguly, J. Am. Chem. Soc., 104, 6138 (1982).
4. This trapping could give a fused oxirane species C (see Scheme), whose deoxygenation would lead to the observed penem along a process analogous to the Schering oxalimide cyclization reaction[3]. We ruled out this pathway by considering that oxiranes, different from thiiranes, undergo phosphorous-carbon attack; attainment of the four-membered cyclic transition state D would thence require a rotation on the C-C bond that is forbidden by the pentatomic cycle.
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7. All new compounds were characterized by IR, NMR and mass spectroscopy. Salient data: 2: νmax(film) 1815, 1755, 1710cm^{-1}; δ($CDCl_3$) 3.81 and 5.95(each 1H, dd and d, J = 3.8, 6.5Hz, β-lact.); 3: νmax($CHCl_3$) 1755, 1695, 1650cm^{-1}; δ($CDCl_3$) 3.43 and 5.62(each 1H, br, β-lact.), 3.92(9H, d, J = 12Hz, $P(OCH_3)_3$); MS(FD) m/z 732$[M^{\cdot}]^+$; 4: mp 177°dec.; νmax(KBr) 1775, 1730, 1705cm^{-1}; δ($CDCl_3$) 3.97 and 5.67(each 1H, dd and d, J = 2.0, 8.0Hz, β-lact.), 5.12(2H, ABq, J = 10Hz, 2-CH_2); 5: νmax(film) 1755, 1695, 1655cm^{-1}); δ($CDCl_3$) 3.47 and 5.7(each 1H, br, β-lact.), 4.12(6H, m, $P(OCH_2CH_3)_3$); 6: νmax(film) 1765, 1695, 1630cm^{-1}; δ($CDCl_3$) 3.22 and 5.80(each 1H, br, β-lact.), 7.57(15H, br s, PPh_3); MS(FD) m/z 870$[M^{\cdot}]^+$; 7: νmax($CHCl_3$) 1760, 1700, 1635cm^{-1}; MS(FD) m/z 771$[M^{\cdot}]^+$; 8: νmax($CHCl_3$) 1760, 1695, 1650cm^{-1}; δ($CDCl_3$) 3.33 and 5.57(each 1H, br, β-lact.), 7.27(15H, br s, $P(OPh)_3$); MS(FD) m/z 918$[M^{\cdot}]^+$; 10: νmax(film) 1775-1745, 1645cm^{-1}; δ($CDCl_3$) 3.10 and 6.12(each 1H, br, β-lact.), 4.21(6H, m, $P(OCH_2CH_3)_3$); MS(FD) m/z 644$[M^{\cdot}]^+$, 587$[M-{}^{\cdot}C_4H_9]^+$; 11: νmax($CHCl_3$), 1775 sh, 1760, 1700 sh cm^{-1}; δ($CDCl_3$) 3.58 and 5.58(each 1H, dd and d, J = 2.2, 7.5Hz, β-lact.), 4.10(2H, ABq, J = 18Hz, NCH_2CO); MS(FD) m/z 610$[M^{\cdot}]^+$, 476$[M-{}^{\cdot}SCOCH_2OCONH_2]^+$; 12: νmax($CHCl_3$) 1775 sh, 1755, 1700cm^{-1}; δ($CDCl_3$) [1:1 diast. mixture] 3.76(1H, m, H-3), 4.4-5.16(1H, obscured, P·CH), 5.6 and 5.77(1H, d, J = 2.4Hz, H-4), 7.14-7.34(10H, m, $P(OPh)_2$); MS(FD) m/z 842$[M^{\cdot}]^+$; 13: νmax($CHCl_3$) 1775, 1755cm^{-1}; δ($CDCl_3$)[major isomer] 3.2 and 6.64(each 1H, br, β-lact.), 5.00(1H, d, J = 24Hz, P·CH) 4.06-4.30(4H, m, $P(OCH_2CH_3)_2$).
8. As indicated in the supplier's catalog (Strem Chemicals) : $P(OMe)_3$, $P(OEt)_3$; PBu_3, $P(NMe_2)_3$, air sensitive; ETPB, $P(OPh)_3$, PPh_3, air stable.
9. Remarkably, trichloroethyl triphenylphosphoranylideneacetates were considered too unreactive to be conveniently cyclized to penems. I.Ernest, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackman, H.R. Pfaendler, and R.B. Woodward, J. Am. Chem. Soc., 100, 8214 (1978).
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11. We were therefore surprised in comparing the conditions reported by Sankyo chemists for the preparation of p-nitrobenzyl (5R, 6S)-6-[(1R)-tert-butyldimethylsilyloxyethyl]-2-[2-(p-nitrobenzyloxycarbonylamino)ethylthio] penem-3-carboxylate from its triethoxyphosphoranylidene (125°, 3h; ref. 6 above) and triphenylphosphoranylidene precursor (125~130°, 15 h; T. Hayashi, A. Yoshida, N. Takeda, S. Oida, S. Sugawara, and E. Ohki, Chem. Pharm. Bull., 29, 3158 (1981)).
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14. Hydrolysis to 11 was also operative; thus after a few days standing (open vessel) compound 8 was recovered as a 1:1:1 mixture of 11 and each diastereoisomer 12.
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18. From this reaction we isolated dimethyl(p-nitrobenzyloxycarbonylmethyl)phosphate (~10%) as the main phosphorous-containing product; νmax($CHCl_3$) 1760, 1270, 1110, 1040cm^{-1}; δ($CDCl_3$) 3.80(6H, d, J = 11.5Hz), 4.65 (2H, d, J = 11.5Hz), 5.20(2H, s), 7.3(5H, s); MS(FD) m/z 274 $[M^{\cdot}]^+$.
19. No reaction ensued after heating (125°) with alkyl phosphites.

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