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A MILD FOUR-CARBON HOMOLOGATION OF 4-FORMYL-AZETIDINONES [1]

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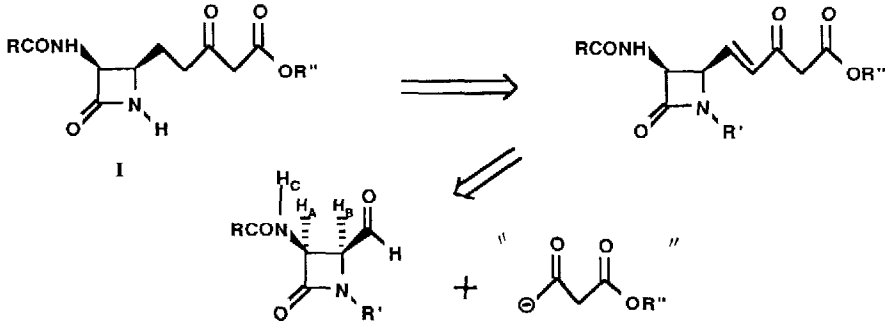
SUMMARY: A mild, four-carbon homologation of a 4-formyl-substituted azetidinone provides a route to compound **I**, a key intermediate in the total synthesis of the carbacephem antibiotics. The route features homologation with phosphorane **IV** and facile dioxenone opening in the final step of the sequence.

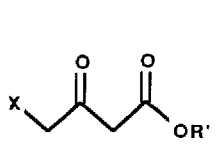
Beta-keto ester **I** (R"=*p*-nitrobenzyl) was a key intermediate in two recently reported syntheses of carbacephem antibiotics.[2] A route to **I** different from those previously reported is shown in Scheme I. Racemic azetidinone **II** can be obtained through a reliable, high-yielding sequence (*vide infra*), but its reactivity towards four-carbon homologating reagents, especially those which

Scheme I

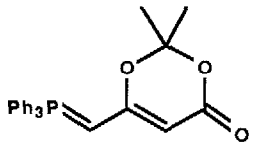


require strong base for activation, is not well-documented. Proton abstraction (H_A, H_B, H_C) and beta-lactam ring-opening may be competing pathways for reaction with a strongly basic reagent. Reported herein is a methodology for the successful homologation of **II** without epimerization of H_A or H_B. Hence completion of the sequence to afford the key intermediate **I** was achieved.

The following beta-keto ester equivalents were synthesized and tested in the coupling reaction with **I**:



IIIa, X=PPh_3, R'=Me
IIIb, X=$(EtO)_2P(O)$, R'=Me

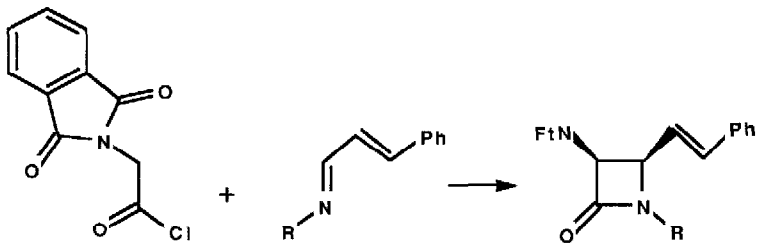


IV

A mixture of products resulting from both alpha and gamma coupling was observed in the reaction with **IIIa**.[3] The reaction of the dianion of **IIIb**[4] resulted in degradation of the azetidinone nucleus. The homologating reagent which gave the desired results was dioxenone **IV**.[5,6] A short, simple synthesis of **IV** is being reported.[6]

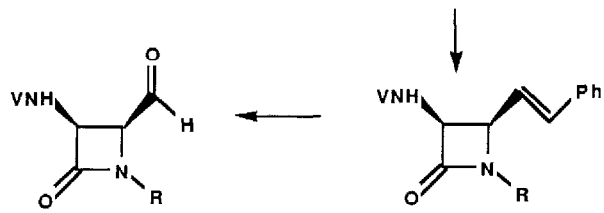
Scheme II describes the synthesis of the 4-formyl azetidinones required for homologation.[7]

Scheme II



V a, R=PMP, 95%
V b, R=DMB, 74%

VI a, R=PMP, 80%
VI b, R=DMB, 43%



VIII a, R=PMP, 73%
VIII b, R=DMB, 86%

VII a, R=PMP, 74%
VII b, R=DMB, 79%

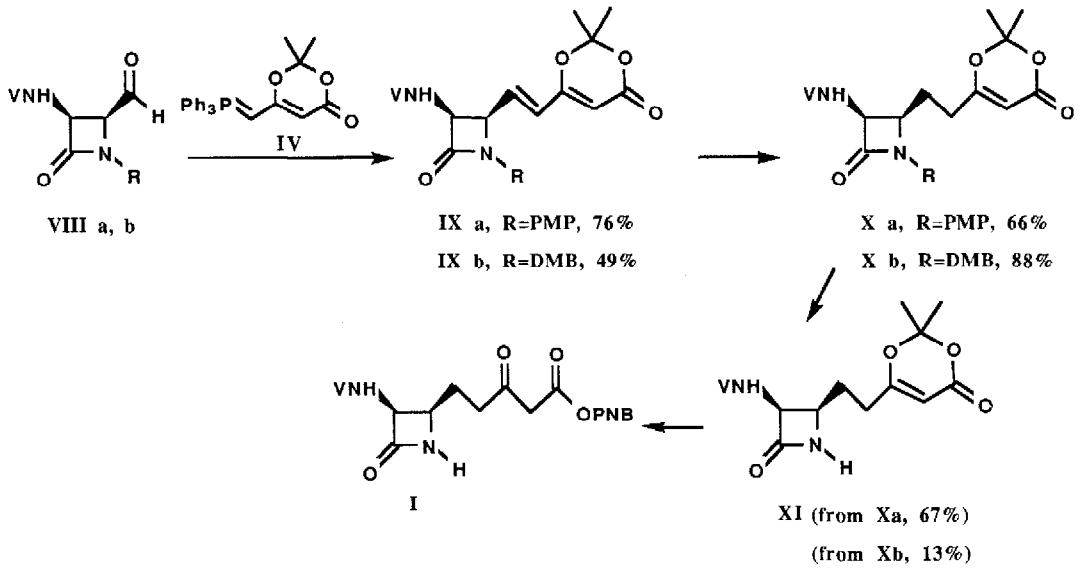
V=phenoxyacetyl

Both N-phenyl (PMP=*para*-methoxyphenyl) and N-benzyl (DMB=dimethoxybenzyl) protected azetidinones were tested in the sequence. Imines **Va** and **Vb** are crystalline solids formed upon condensation of cinnamaldehyde and the appropriate amine (**Va**: 95% yield; **Vb**: 74% yield). Staudinger-type [2+2] cycloaddition of imine with the acid chloride of N-phthaloylglycine (triethylamine, 0° C)[8] gave azetidinones **VI** (**VIa**, 80%; **VIb**, 43%). Removal of the phthaloyl

group[9] from **IV** and reprotection of the 3-amino functionality with phenoxyacetyl chloride under Schotten-Baumann conditions afforded crystalline intermediates **VIIa** (74%) and **VIIb** (79%). The 4-cinnamyl side-chain was converted via ozonolysis to the requisite 4-formyl group (R=PMP, 73 %; R=DMB, 86%).

Scheme III details the conversion of the key 4-formyl azetidinones **VIII** to form the penultimate intermediate **I**. In the critical homologation reaction, the solids **VIII** and **IV** were combined in

Scheme III



acetonitrile, stirred at ambient temperature for 16h, the solvent was removed under reduced pressure and the product **IX** was crystallized from the resulting residue (R= PMP, 76%; R=DMB, 49%). Compounds **IXa** and **b** were hydrogenated (for **IXa**, 5% Pd/C, EtOAc, 18 h, 66%; for **IXb**, 10% Pd/C, 5 d, EtOAc, 88%). The N-protecting group was oxidatively removed using ceric ammonium nitrate[10] in the case of **Xa** (67%) and buffered potassium persulfate[11] in the case of **Xb** (13%). At this point both sequences had converged upon the common intermediate **XI**. Samples of both oxidation reaction products were identical to each other in all respects.

By simply combining **XI** with an equivalent of p-nitrobenzyl alcohol in toluene, warming to 110° C, cooling and filtering, the crystalline racemic product **I** was obtained in 57% yield. The material thus obtained was analytically pure and identical in all respects (except for optical activity) with authentic samples of **I** which had been generated by the previously reported route.[2b] The synthesis detailed in this paper could be made asymmetric by employing a chiral auxillary in the cycloaddition step (as in footnotes 2a,b), or by incorporating a resolution into the conversion of **VI** to **VII**.

The use of phosphorane **IV** provides an efficient means of incorporating the beta-keto ester functionality into base-sensitive azetidinones such as **VIII**. We have thus demonstrated that this

methodology provides a workable alternative for the construction of precursors to the carbacephem antibiotics.

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