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New Applications of the Mitsunobu Reaction in the Synthesis Of C-2 N-Methyl Carbapenems

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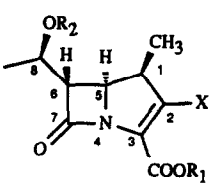
Key Words : *Mitsunobu reaction ; carbapenem ; amination ; amide formation ;amino heterocycle alkylation.*

Abstract : *N-acyl amides and N-acylamino heterocycles can be reacted regioselectively with C-2 hydroxymethyl carbapenems under Mitsunobu conditions:synthesis of amides, exocyclic alkylation of amino heterocycles and transformation into 2-aminomethyl carbapenems are reported.*

The discovery of the carbapenem antibiotics has resulted in intense interest in the synthesis of novel carbapenems. Research effort has been devoted mainly to the functionalisation of the C-2-SR side chain (Structure 1) and only a limited number of studies on C-2-carbon linked substituents have been published.[1-5]



1 X=SR R_1,R_2=H
2 X=CH_2-A-R A=O,N,S R_1,R_2=H
3 X=CH_2OH R_1,R_2=H or protecting group

A major structural feature in cephalosporins is the presence of a heteroatom at the C-3' position and this prompted us to synthesise carbapenems carrying heteroatom linked substituents at their equivalent C-2' position (Structure 2). Such an approach has proved to be successful in the penem series.[6-7]

In an attempt to maximize the variation of the C-2' substituent, our synthetic strategy was based on the functionalisation of the key 2-hydroxymethyl carbapenem 3. The chemical reactivity of the carbapenem nucleus requires that synthetic operations be performed under neutral and very mild conditions; thus we investigated the potential of the Mitsunobu reaction which should be suitable for such transformations.

We wish to report here the transformation of 3 into aminomethyl derivatives 2 (A=N) by new applications of the Mitsunobu reaction.

This reaction which operates under mild and essentially neutral conditions is an important synthetic tool in the alkylation of acidic groups (carboxylic acids, phenols and imides) with alcohols.[8] It has also been used for the introduction of nitrogen groups ; azide salts, cyclic imides or sulfonamides are suitable nucleophiles.[9] Linear diacyl amines have received little attention[10-11] and give a mixture of O and N-alkylated products. During the course of this work, tosylcarbamates and imidodicarbonates have been used as amine synthons and it has been found that yields correlate with acidity in DMSO.[12]

In an attempt to transform the C-2' alcohol function into amides, we investigated the reaction of 3 with allyloxycarbonyl protected amides 5 ; when the carbapenem 3a, formed in situ by cyclisation of the phosphorane 4a at 110°C in toluene, was treated with 5a[13] in the presence of PPh_3 and DEAD, only N-substituted amide 6a was obtained[14] ; subsequent treatment with Pd $(PPh_3)_4$ afforded the final deprotected carbapenem 7a.[15] The regioselectivity of the amide formation was illustrated by the reaction of C-8 deprotected carbapenem 3b with 5a which gave the expected compound in about the same yield. Additional examples of transformations of primary alcohol 3b into amides 6 are listed in Table 1 (the yield was calculated on 2 steps and was not optimised).

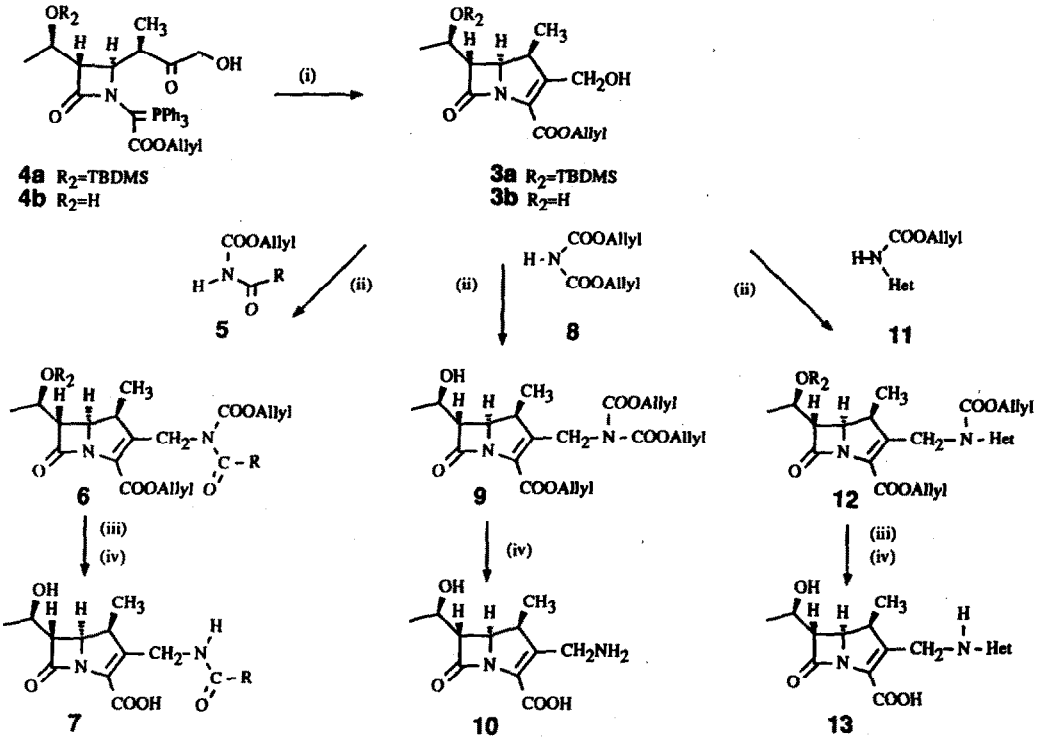
Since it was important in the course of our program to have an easy access to 2-aminomethyl carbapenem 10,[16] the reaction with diallyl imidodicarbonate 8 was investigated. When 8[17] was reacted with the carbapenem alcohol 3b, the expected product 9 was obtained in 40 % yield. Palladium catalysed removal of the allyl protection provided the key aminomethyl intermediate 10, which was used for further functionalisation. Toluene as solvent is preferable since in THF, which is commonly used in the Mitsunobu conditions, 9 was obtained in a low yield.

Extension of the work to N-acylamino heterocyclic systems 11 has been investigated. It is a general observation that alkylation of amino substituted π deficient heteroaromatic systems normally occurs at the ring nitrogen except in strongly basic medium where alkylation at the exocyclic nitrogen is observed.[18]

We have synthesised N-allyloxycarbonylamino derivatives of pyrimidine, thiazole and imidazole (11a,b,c) by acylation of the amino heterocyclic derivative and investigated their reactions in the Mitsunobu conditions. Coupling with 2-hydroxymethyl carbapenems 3a-b gave only the exocyclic N-alkylated product 12 in 40-63 % yield, which was subsequently deprotected to give 13.

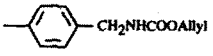
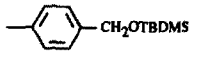
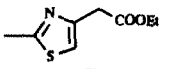
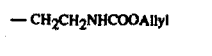
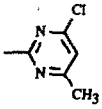
In summary we have demonstrated that N-acylamides and N-acylamino heterocycles are useful nucleophiles in the Mitsunobu reaction, and have shown that this reaction can be an efficient tool for the transformation of primary alcohols into amides and for the exocyclic alkylation of amino heterocycles. We also report a simple and regioselective synthesis of the versatile 2-aminomethyl carbapenem 10 from 2-hydroxymethylcarbapenem 3b.

This methodology which was successfully applied to a chemically very sensitive entity represents an improvement over standard syntheses. In particular the amination reaction should find new synthetic applications in the chemistry of highly functionalised and chemically sensitive molecules.



(i):toluene,110°,1h (ii):toluene,DEAD(1.5 eq),PPh_3(1.5 eq),20°,30 min
(iii):R_2=TBDMS, $(nBu)_4NF$,THF/AcOH (iv):THF,$Pd(PPh_3)_4$,dimedone

TABLE 1

Entry	Nucleophile R	Carbapenem 3 R_2	Product [1] Entry	Yield(%) [2]	Entry	Nucleophile Het	Carbapenem 3 R_2	Product [1] Entry	Yield(%) [2]
5a		TBDMS	6a	50	8	–	H	9	45
5b		H	6b	22	11a		TBDMS	12a	68
5c		H	6c	32	11b		H	12b	40
5d		H	6d	45	11c		H	12c	50

1: All products gave satisfactory ^1H NMR and MS data
2: The yields were calculated on isolated product for the transformation of 4 into 6 , 9 or 12

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13. N-acyl amides were prepared according to CA 55 : 22309.
14. The Mitsunobu reactions were typically performed as follows : a solution of 4 in toluene was heated at 110°C for 1 h ; after cooling the N-acyl derivative (1eq), PPh_3 (1.5eq) and DEAD (1.5eq) were added. The reaction mixture was stirred at 20°C for 30 min and then worked-up classically.
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