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SYNTHESIS OF CARBAPENEMS WITH CARBON SUBSTITUENTS

AT C-3 USING A WITTIG APPROACH

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Summary: Reaction of ketone 2 with phosphorane 4 produced a mixture of endocyclic and exocyclic carbapenem esters 5 and 6. Hydrogenolysis of these gave carbapenems 7 and 8 or carbapenams 9 and 10.

Carbapenems are an important new class of antibiotics of which thienamycin (1) is the most well-known example¹. They distinguish themselves from the classical β -lactams such as penicillins and cephalosporins by their broad-spectrum antibacterial activity, covering a wide range of both gram-positive and gram-negative bacteria. One of the main obstacles on their way to useful therapeutic agents is their instability towards renal dehydropeptidase leading to low urinary recovery². In an attempt to identify carbapenems with greater metabolic stability we have synthesized carbapenems with fluorine instead of hydroxyl in the 8-position³. In this communication we report our synthetic efforts towards syntheses of carbapenems that in addition are devoid of sulphur in the side chain at C-3. Published syntheses of C-3 carbon substituted carbapenems⁴ have always relied on variations on the method originally developed by Woodward and coworkers⁵.

We were intrigued by the possibility of using bicyclic ketone 2 as precursor for this class of carbapenems. This compound (i.e. 2a) was developed by Merck chemists as intermediate for the syntheses of sulphur substituted carbapenems⁶; in our laboratories we have used 2b and 2c for the same purpose³. The ketone moiety in 2 is exceptionally reactive for its kind: We found that most nucleophiles react instantaneously with 2b,c giving rise to ring-opened products of type 3 (Scheme 1)⁷. We were therefore gratified to find that stabilized phosphoranes 4 reacted with 2b,c to produce an inseparable mixture of 3-substituted carbapenem esters 5 (endo) and 6 (exo; E and Z)^{8,9} (Scheme 2, for conditions and yields see Table 1).

Table 1: Reaction of bicyclic ketone **2** with phosphoranes **4***

Entry	R	Z ¹¹	Conditions	Yield**	Product Ratio ¹⁰			Suffix
					5	6-E	6-Z	
1	CH ₃	CN	CH ₂ Cl ₂ , RT, 20 hrs.	68 %	51	36	13	k
2	CH ₃	CO ₂ Et	CH ₂ Cl ₂ , RT, 2 hrs.	94 %	83	12	5	l
3	H	CN	CH ₂ Cl ₂ , RT, 2.5 hrs.	82 %	56	34	9	m
4	H	CO ₂ Et	CH ₂ Cl ₂ , RT, 0.75 hrs.	83 %	93	5	2	n
5	H	COCH ₃	CH ₂ Cl ₂ , reflux 5 hrs.	43 %	38	62	--	o

* 1.5 eq of phosphorane, c = 0.05 - 0.07 mol/l

** Yields of purified products (column chromatography: silica, CH₂Cl₂).

With phosphoranes **4p** and **4q** the reaction proceeded very smoothly at room temperature. Reaction between **2b** and **4r** was more sluggish and took 5 hrs. at CH₂Cl₂ reflux temperature. Reactions with more basic phosphoranes such as Ph₃P=CHCl¹² and Ph₃P=CHSCH₃¹³ did not lead to products and bicyclic ketone **2** was recovered in good yield; presumably hydrogen exchange occurred.

Unfortunately, hydrogenolytic removal of the p-nitrobenzyl protective ester caused serious problems. Only with the cyanomethyl substituted carbapenem esters (5,6k and 5,6m) were we able to obtain carbapenem potassium salts 7 and 8 as inseparable mixtures in moderate yields, when short hydrogenation times were used (Table 2).

Table 2: Hydrogenolysis of carbapenem p-nitrobenzyl esters (5,6)*

Entry	R	Z	Time	Yield	Product Ratio					Suffix
					<u>7</u>	<u>8E</u>	<u>8Z</u>	<u>9</u>	<u>10</u>	
1	CH ₃	CN	1 hr.	43 %	35	53	12	traces		k
2	CH ₃	CO ₂ Et	1.25 hr.	73 %	--	--	--	21	79	l
3	H	CN	5 min.	45 %	15	55	30	traces		m
4	H	CN	1 hr.	60 %		traces		94	6	m
5	H	CO ₂ Et	15 min.	22 %		traces		65	32	n

* Conditions: 100 mg of the mixture of 5 and 6 and 100 mg of 10 % Pd/C in a mixture of 8 ml of EtOAc and 8 ml of phosphate buffer pH 7 (c = 0.15 M) were hydrogenated at 1 bar H₂ over the period indicated in the table. After filtration the aqueous layer was concentrated and purified over a C-18 column.

However, the already unfavorable endocyclic/exocyclic ratio shifted even further towards the - presumably antibacterially inactive - exocyclic product. Attempted equilibration of the product of entry 3 (Table 2) in D₂O at room temperature over 3 hrs. had the adverse effect and led to a further increase in 8m. Short hydrogenolysis of ethoxycarbonylmethyl substituted carbapenem esters (5,6l and 5,6n) only gave a mixture of carbapenamams 9 and 10¹⁴. Carbapenamams were also produced upon prolonged hydrogenation of the 3-cyanomethyl carbapenem esters 5,6m.

None of the product mixtures of Table 2 showed interesting antibacterial activity.

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