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AN EFFICIENT CARBAPENEM SYNTHESIS *VIA* AN INTRAMOLECULAR WITTIG REACTION OF NEW TRIALKOXYPHOSPHORANE-THIOLESTERS

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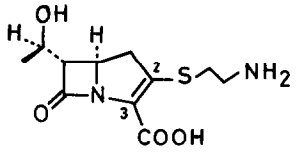
Summary: New trialkoxyphosphorane-thiolesters 10, obtained by reaction of oxalimides 9 with trialkyl phosphite, were efficiently cyclized by an intramolecular Wittig reaction to give carbapenems 11.

Several methods for the synthesis of carbapenem antibiotics, as represented by thienamycin 1 and olivanic acids, have been developed.[1] Of the methods for construction of the bicyclic ring system, the route developed by a Merck research group involves a carbene insertion reaction for ring closure between C-3 and the N atom.[2] Due to efficiency of both cyclization and subsequent introduction of a sulfur substituent at the C-2 position, this process has been widely used in recent syntheses of carbapenems. Another approach to the carbapenem ring system involves an intramolecular Wittig reaction of the triphenylphosphorane-thiolester 2 to the carbapenem 3 which can directly form the C-2 — C-3 double bond appending a C-2 sulfur substituent. A Beecham group utilized this cyclization reaction to synthesize various sulfur-containing carbapenems.[3] However, the Wittig cyclization was effected only with suitably activated thiolesters derived from mercaptans with an electron-withdrawing nature. If non-activated alkyl thiolesters cyclize in this manner, the Wittig cyclization method is still attractive for shortening the synthetic path to carbapenems.

In this paper we report an efficient carbapenem cyclization reaction based on an intramolecular Wittig reaction of new trialkoxyphosphorane-thiolesters which can also be applied to non-activated thiolesters.

We felt, during a study of the previously described penem synthesis *via* reductive cyclization of oxalimides with trialkyl phosphite,[4] that trialkoxyphosphoranes are more reactive than the corresponding triphenylphosphoranes in



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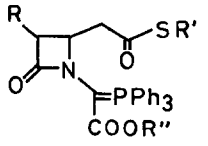

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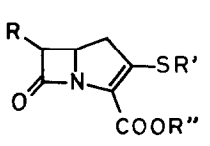
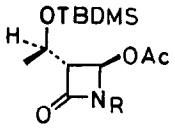
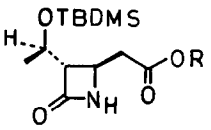


3

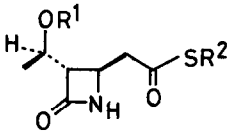
an intramolecular Wittig cyclization and hence this modification might be potentially applied in carbapenem synthesis. The penicillin-derived chiral 4-acetoxy-2-azetidinone 4[5] was used as a starting material for preparation of thiolester intermediates. N-Silylation of 4 (Me_3SiCl, Et_3N, THF, rt, 2 h) gave the azetidinone 5 (~100%), which was treated with 1-benzyloxy-1-(trimethylsilyloxy)ethylene (1.3 equiv) in the presence of trimethylsilyl trifluoromethanesulfonate[6] (TfOTMS, 0.1 equiv) in methylene chloride (rt, overnight) to afford, after N-desilylation [pyridinium *p*-toluenesulfonate (PPTS, trace), THF-H_2O, rt, 30 min], a 91% yield of the *trans* ester 6, mp 91-92.5°C. Debenzylation of the ester 6 was easily accomplished by hydrogenolysis (10% Pd/C, MeOH) to give the acid 7, mp 162°C (decomp.), in a quantitative yield. The acid 7 was transformed into various thiolesters 8a,b,f,i, in yields ranging from 85 to 92%, by treatment with appropriate mercaptans[7] and N,N'-dicyclohexylcarbodiimide in benzene in the presence of a catalytic amount of 4-(N,N-dimethylamino)pyridine (DMAP). The phenyl thiolester 8*l*, mp 94-95°C, was directly obtained from 5 in 83% yield by similar C-C bond formation reaction[6] with 1-phenylthio-1-(trimethylsilyloxy)ethylene using TfOTMS catalyst. The hydroxy protecting group in some of the thiolesters thus obtained was changed, for the convenience of its deblocking at the final step of the synthesis, from the *tert*-butyldimethylsilyl (TBDMS) group to the *p*-nitrobenzyloxycarbonyl (PNZ) group as follows. The silyl ethers 8b,f,*l* were treated with boron trifluoride



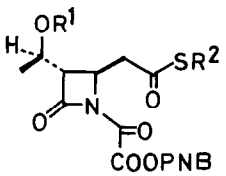
4: R=H
5: R=TMS



6: R=CH_2Ph
7: R=H



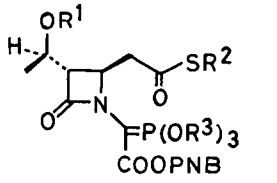
8a-d,f-i,*l*-n



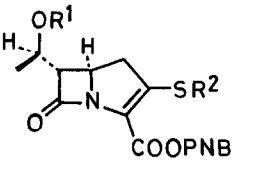
9a-f,h-*l*,n

	R^1	R^2	R^3 (for 10)
a	TBDMS	i-Pr	Et
b	TBDMS	NH-PNZ	Et
c	H		-
d	PNZ		Et
e	TMS		Et
f	TBDMS	H, N-PNZ	Et
g	H		-
h	PNZ		Et
i	TBDMS	H, N, N-PNZ, Me	Et
j	H		-
k	TMS		Et
l	TBDMS	Ph	Et, i-Pr
m	H		-
n	PNZ		i-Pr

TBDMS: *tert*-butyldimethylsilyl
PNZ: *p*-nitrobenzyloxycarbonyl
TMS: trimethylsilyl
PNB: *p*-nitrobenzyl



10a,b,d-f,h,i,k,*l*,n



11a-f,h-*l*,n

etherate (1-2 equiv) in acetonitrile[8] at 0°C for 15-30 min followed by neutralizatiom with phosphate buffer to give the alcohols 8c,g,m, respectively, in quantitative yields. These alcohols 8c,g,m were again protected with the PNZ group [PNZCl (3-5.5 equiv), DMAP, CH_2Cl_2] to give the thiolesters 8d,h,n, in 67, 61, 45% yield, respectively. The trialkoxyphosphorane-thiolesters 10, precursors to carbapenems, were prepared in an analogous way as described previously.[4] The above-mentioned thiolesters 8 were treated with *p*-nitrobenzyloxyoxalyl chloride (2-5 equiv) and base (Et_3N or diisopropylethylamine) in methylene chloride at 0°C followed by aqueous work-up and purification by rapid silica gel chromatography to give the corresponding oxalimides 9 in good yields. Formation of the trialkoxyphosphoranes 10 *via* a carbene intermediate[4,9] were easily effected by heating the oxalimides 9 with a five molar excess of triethyl or triisopropyl phosphite[10] in benzene or toluene at 80-90°C for 1-3 h. The yields of the phosphoranes 10 were excellent judged by TLC and NMR spectra. Since the trialkoxyphosphorane group was previously found to be susceptible to hydrolysis,[4] the products 10 were usually not purified. The reaction mixture itself or the crude product obtained by brief removal of solvent and volatile substances (trialkyl phosphite and trialkyl phosphate) *in vacuo* from the reaction mixture was directly subjected to cyclization reaction by heating in toluene or xylene at 95-120°C under a nitrogen atmosphere in the presence of a trace amount of hydroquinone. Results of cyclization reaction of the trialkoxyphosphoranes 10 to the carbapenem esters 11 are summarized in Table I. Cyclization resulted in a moderate to high yield depending on the nature of the thiolester and hydroxy protecting group. The activated phenyl thiolester 10*i* cyclized with more ease in a higher yield than other non-activated thiolesters. The PNZ protecting group for the hydroxy group seems to decrease the cyclization reactivity compared with the TBDMS protecting group. Superiority of this trialkoxyphosphorane cyclization to the usual triphenylphosphorane cy-

Table I. Cyclization Reaction of Trialkoxyphosphoranes 10 to Carbapenem Esters 11

Compd.	R^1	R^2	R^3	Reaction conditions			Yield[a] of 11 (%)
				Solvent	Temp(°C)	Time(h)	
10a	TBDMS	i-Pr	Et	xylene	120	70	51
10b	TBDMS		Et	toluene	95	18	68
10d	PNZ		Et	toluene	100	44	40
10e	TMS		Et	toluene	100	24	48
10f	TBDMS		Et	toluene	95	70	83
				xylene	120	18	61
10h	PNZ		Et	toluene	100	80	57
10i	TBDMS		Et	toluene	95	24	75
10k	TMS		Et	toluene	105	50	63
10*l*	TBDMS		Et	toluene	100	18	88
			i-Pr	toluene	100	18	77
10n	PNZ		i-Pr	toluene	105	48	67

a) Isolated yield based on oxalimides 9. All compounds were fully characterized from IR, NMR and elementary analysis.

clization is evident, for instance, in preparation of thienamycin precursor 11d which has been reported to be obtained only in a poor yield by the latter method.[11] When the hydroxy group was not protected, as in the oxalimides 9c and 9j which were obtained in high yields by treatment of 9b and 9i with boron trifluoride etherate in acetonitrile,[8] respectively, cyclization with trialkyl phosphite did not occur. Therefore the hydroxy group in 9c and 9j was again silylated [N,O-bis(trimethylsilyl)trifluoroacetamide, THF, DMAP (trace)] to give the trimethylsilyl oxalimides 9e and 9k, respectively, in over 90% yields after purification by rapid silica gel chromatography. Cyclization of these compounds *via* triethoxyphosphoranes 10e and 10k in a similar manner (Table I) afforded the carbapenems 11e, mp 105-106°C, and 11k, mp 95-96°C, which were easily desilylated by treatment with a catalytic amount of PPTS in THF-H_2O to a thienamycin precursor 11c,[2c] mp 171-171.5°C, and an RS-533[12] precursor 11j, mp 150°C (decomp.), respectively, in good yields (>80%).

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