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ALKYLPHOSPHONOUS ACID DIESTERS, NOVEL REAGENTS FOR THE OXALIMIDE CYCLIZATION TO PENEMS

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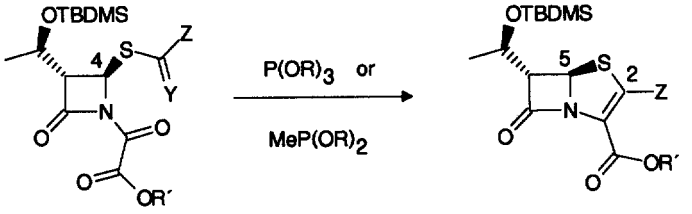
Abstract: *Alkylphosphonous acid diesters $MeP(OR)_2$ 3a-h were shown to be highly effective and mild reducing reagents in the oxalimide cyclization of azetidinone-1-oxalyl-4-di- or tri-thiocarbonates or 4-thioesters 1a-t forming penems 2a-t at lower temperature, shorter reaction times, and higher yields compared to classical phosphites $P(OMe)_3$ and $P(OEt)_3$.*

Penems, due to their outstanding antibacterial properties in vivo and in vitro, have been the subject of intense synthetic studies[1].

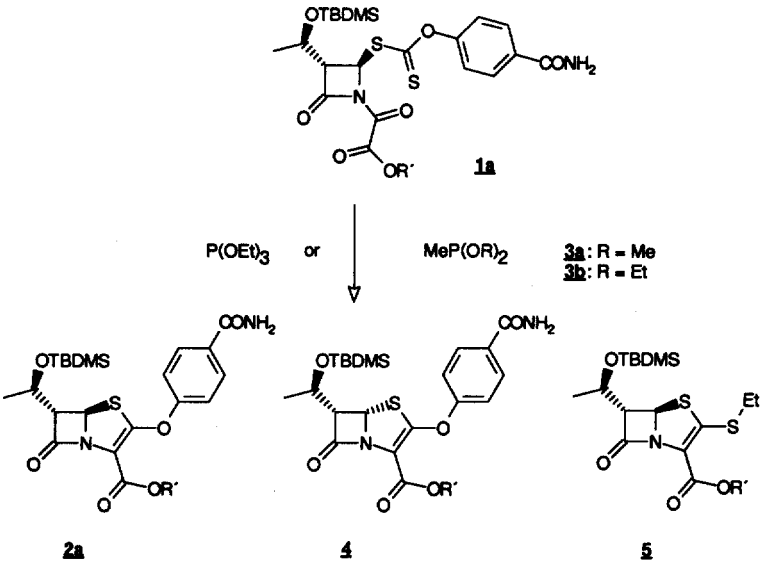
We examined a short and efficient synthesis of 2-aryloxy penems[2] 2 (Z = OAryl) applying the "oxalimide route", which includes the intramolecular closure of the C2-/C-3 bond by reaction of appropriate azetidinone-1-oxalyl-4-di-(Y=S)-thiocarbonates 1 with trialkyl phosphites $P(OMe)_3$ or $P(OEt)_3$[3].



1 2

However, initial attempts to cyclize 1a[4] (table 1) with excess $P(OEt)_3$ in toluene (110°C) afforded predominantly 2-ethylthiopenem 5 and only 5-20% of the desired 2-aryloxypenem 2a, contaminated with 20% of undesired cis isomer 4. At elevated temperatures (xylenes, 140°C) decomposition products prevailed. Further attempts to cyclize 1a using $P(OEt)_3$ (2 eqs.) in refluxing $CHCl_3$ instead of toluene led to an increased (40%) yield of 2a.

Therefore, we looked for more potent phosphorous(III)-compounds capable of inducing higher cyclization yields. The yield of 2a was dramatically increased using the dimethyl 3a[5a] and diethylester 3b[5b] of methylphosphonous acid[6] instead of trialkyl phosphites. Reaction times were shorter and, most important, reaction temperatures could be decreased considerably. Slow product formation was observed even at 0°C. This way, the troublesome C-5-epimerization to 4 and the formation of by-products could be minimized.



In a typical procedure 500 mg (0.77 mmol) 1a were dissolved under argon atmosphere in 345 ml $CHCl_3$ and 0.59 ml (5.5 mmol) $MeP(OMe)_2$ 3a, dissolved in 40 ml $CHCl_3$, were added within 30 minutes at 50 °C[7]. After aqueous work up, flash chromatography (toluene/ethyl acetate) of the crude product yielded 83% of crystalline 1b[8].

Moreover, 3a-b also proved to be superior or at least comparable to $P(OMe)_3$ or $P(OEt)_3$ in the synthesis of various penems with different alkoxy, alkylthio, aryl or alkyl substituents at C-2 (Table 1).

In the case of Y = S, cyclization reaction conditions are compatible with several carboxyl protecting groups R' such as PNB[9], allyl or TMSE[9] without significant changes in yields and by-products. But in the case of less reactive monothiocarbonates, like 1d and 1p, the allyl protecting group should be avoided. 1d is reacted predominantly to 6 and 7 resulting from cyclopropanation or reduction respectively. Similarly the allyl protected monothioacetate 1p delivers only cyclopropanation products, while the corresponding TMSE-protected compound 1q leads to a good yield of the desired penem 2q.

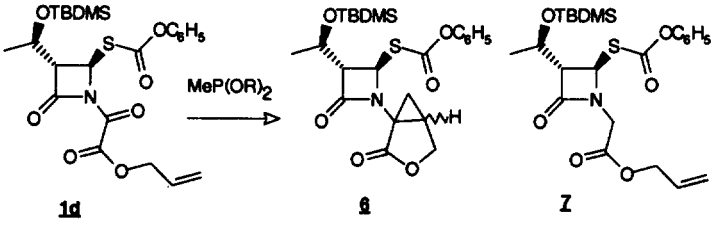
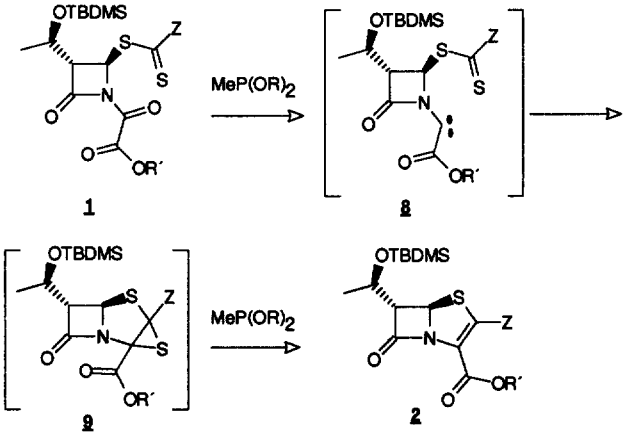


Table 1: Oxalimide cyclization forming different penems[9]

Azetidinone	Y	Z	R'	Penem	Yield with $MeP(OR)_2$	$P(OR)_3$
1a	S	4-$OC_6H_4CONH_2$	PNB	2a	83 %	40 %
1b	S	4-$OC_6H_4CONH_2$	TMSE	2b	57 %	36 %
1c	S	4-$OC_6H_4CONH_2$	Allyl	2c	62 %	28 %
1d	O	OC_6H_5	Allyl	2d	0 %	
1e	S	OMe	PNB	2e	38 %	25 %
1f	S	OMe	TMSE	2f	55 %	48 %
1g	S	OMe	Allyl	2g	48 %	22 %
1h	S	O-c.C_5H_9	PNB	2h	80 %	11 %
1i	S	SMe	PNB	2i	67 %	51 %
1k	S	SMe	TMSE	2k	61 %	23 %
1l	S	SMe	Allyl	2l	75 %	
1m	S	C_6H_5	TMSE	2m	20 %	24 %
1n	O	4-$C_6H_4CO_2$allyl	TMSE	2n	55 %	
1o	O	4-pyridyl	TMSE	2o	25 %	
1p	O	Me	Allyl	2p	0 %	
1q	O	Me	TMSE	2q	65 %	
1r	O	2-furanyl	TMSE	2r	55 %	
1s	O	2-tetrahydrofuranyl	TMSE	2s	37 %	
1t	O	3-c.butanoyl	TMSE	2t	72 %	

Regarding the reaction mechanism, it is reasonable to assume that 3a-b behave similarly to the trialkyl phosphites in the oxalimide cyclization process[3]. Thus 3a-b may participate in the mechanism of the oxalimide reaction by initial formation of a reactive carbene intermediate 8, which in the case of Y=S adds to the thiocarbonyl double bond forming an intermediate episulfide 9, which is then desulfurized by the P(III)-reagent. Thus, the superior reactivity of 3a-b can be attributed to enhanced carbene formation (cyclopropanation reactions with allyl protected azetidinones can already be observed at temperatures where $P(OR)_3$ doesn't work at all) and eventual acceleration of desulfurization.



Interestingly the use of cyclic ester derivatives of methylphosphonous acid, e.g. the cyclic ester of ethyleneglycol, only led to decomposition of the starting material. Further enhancement of the reducing power by using dimethylphosphinous acid monobutylester also led to a decreased yield, only traces of the desired cyclization product 2a could be observed.

Acknowledgement: The authors wish to thank Dr. Kleiner (Hauptlabor) for supplying 3a-b[5].

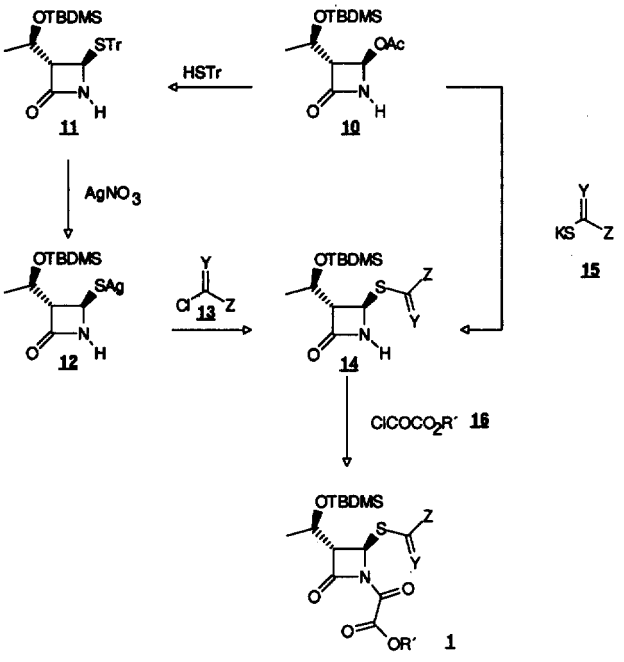
References and Notes:

1. For a review see S. W. McCombie and A. K. Ganguly, Med. Res. Rev.8, 393 (1988).

2. M. B. Cooke, K. W. Moore. B. C. Ross and S. E. Turner, in 'Recent Advances in the Chemistry of β-Lactam Antibiotics', The Royal Society of Chemistry, Special Publication No. 52, 1985, 100-115.

3. A. Afonso, F. Hon, J. Weinstein, A. K. Ganguly and A. T. Mc Phail, J. Am. Chem. Soc. 104, 6138 (1982).

4. The required precursors 1 were prepared via intermediate 14 starting with readily available 10 a) by displacement of -OAc with -STr[9], followed by detritylation of 11 with $AgNO_3$ and acylation of 12 with 13 to 14, or b) by direct displacement with 15. Final N-acylation with $ClCOCO_2R'$ 16 afforded 1[9].



5. a) L. Maier, Helv. Chim. Acta 46, 2667 (1958), b) F.W. Hoffmann and T. R. Moore, J. Am. Chem. Soc., 80, 1150 (1958).

6. K.-H. Budt, W. Dürckheimer, G. Fischer, R. Hörlein, R. Kirrstetter and R. Lattrell, EP Appl. EP399.228 (25.04.90).

7. Formation of 2a can be accomplished already at 0°C, but this is accompanied by some alkylation product 5. This unwanted side reaction can be suppressed by working at 50°C.

8. δ ($CDCl_3$): 8.17, 7.55 (4H, AA'BB', J = 8.7Hz); 7.83, 7.21 (4H, AA'BB',J = 8.8Hz); 5.65 (1H, d, J = 1.4 Hz); 5.38, 5.21 (2H, AB, J = 13.8 Hz); 4.41-4.24 (1H, m); 3.76 (1H, dd, J = 1.4 Hz, 4.8 Hz); 1.25 (3H, d, J = 6.2Hz); 0.82 (9H,s); 0.09 (3H, s); 0.05 (3H, s):

9. Abbreviations: PNB = 4-nitrobenzyl, TMSE = 2-trimethylsilylethyl, TBDMS = tert.-butyldimethylsilyl, Tr = triphenylmethyl.

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