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Preparation of 3-Benzoylpenems and Penem Amides by Wittig Methodology.

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ABSTRACT: Condensation of phenyl glyoxal with azetidin-2-ones (1a-c) gave the hemi-aminals (2a-c). Subsequent conversions produced the 4-(formylthio)phosphoranes (4a-c) which gave on heating the 3-benzoylpenems (5a-c), formed by intramolecular Wittig cyclisation. Thermal isomerisation of *trans*-6-substituted-3-benzoylpenems allowed the preparation of the *cis*-6-substituted-3-benzoylpenems (7a-c). Using similar methodology the penem amides (7d-e) were synthesised.

The pathways involved in protein secretion in bacteria are rapidly becoming of widespread interest as new targets for antimicrobial chemotherapy[1]. In bacteria, the release of preproteins from the outer surface of the plasma membrane involves removal of the signal sequence or cleavable membrane anchor. In *Escherichia coli* there is an enzyme, leader peptidase (LP), which fulfills this function for most proteins[2]. The discovery that LP is a serine protease led to the screening of a wide range of beta-lactams as potential inhibitors of LP. This resulted in the identification of penem esters and amides as LP inhibitors[3].

In order to investigate the scope for variation of the C-3 substituent in penem LP inhibitors the previously undescribed 3-benzoylpenems were selected as synthetic targets. It was decided to investigate the modification of the widely used Woodward methodology for preparing penem esters (Scheme 1).

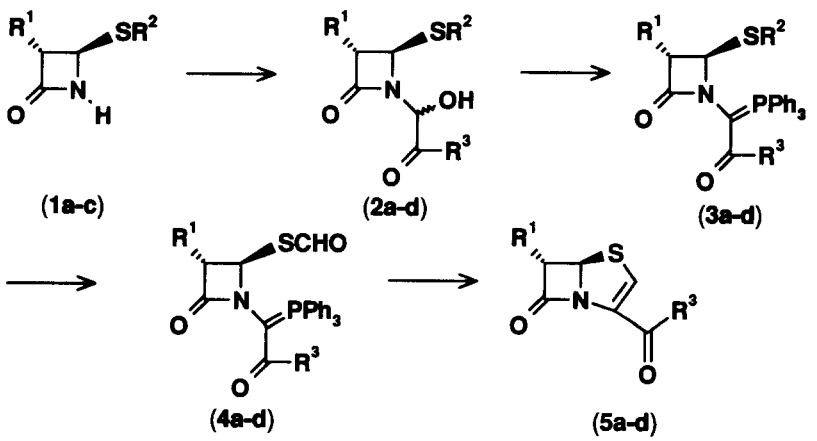
Reaction of azetidinone[4] (**1a**) with phenylglyoxal monohydrate (2 equivalents) in toluene, with azeotropic removal of water, gave the required condensation products (**2a**). This crude material was then converted by standard methodology[5] to the phosphorane (**3a**) (overall yield 82%). Ozonolysis in the presence of trifluoroacetic acid produced the crude formylthio phosphorane (**4a**), which on heating to 105°C in toluene (1h) cyclised to the required penem (**5a**), albeit in low yield (8%). This 3-benzoylpenem (**5a**) was found to be unstable under thermal, acidic and basic conditions.

In the hope of increasing stability, the preparation of 6-substituted derivatives was investigated. The readily available 3-ethyl-4-(triphenylmethylthio)azetidin-2-one[6] (**1b**) was converted to the phosphorane (**3b**) (overall yield 56%). Oxidative cleavage [silver nitrate, 4-(*N*,*N*-dimethylamino)pyridine, acetonitrile] and formylation of the resulting silver thiolate [acetic formic anhydride, 4-(*N*,*N*-dimethylamino)pyridine, sodium iodide] gave the crude formylthio phosphorane (**4b**), which on heating at 105°C in toluene (2h) gave the required penem (**5b**), containing 15% of the *cis*-isomer. The pure *trans*-penem (**5b**) could then be obtained by a single recrystallisation in 24% yield. The isolated *trans*-penem (**5b**) was stable in toluene at 100°C for 1h, but increasing the temperature to 110°C for 1h resulted in a 3:2 mixture of the *trans*- and *cis*-isomers with considerable degradation. These studies showed the narrow temperature range over which cyclisation could occur without degradation and with low thermal isomerisation.

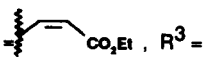
Previous studies[3] on penem esters and amides had shown that 6-substitution with a 1-hydroxyethyl group gave good LP activity when the absolute stereochemistry at the three chiral centres was 5*S*, 6*S*, 8*R*. This form of substitution has also been shown to increase the stability of penems. The commercially available (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]azetidin-2-one provides two of the required chiral centres. It was hoped that conversion to the *trans*-3-benzoylpenem (**5c**) followed by thermal isomerisation and subseqent deprotection would allow rapid preparation of the required (5*S*, 6*S*, 8*R*)-6-(1-hydroxyethyl)-3-benzoylpenem (**7c**).

Treatment of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]azetidin-2-one with the anion of ethyl *cis*-ß-mercaptoacrylate[4] gave the *trans*-substituted azetidinone (**1c**) in 58% yield. Conversion to the phosphorane (**3c**) (56%) as described above, followed by successive ozonolysis in the presence of

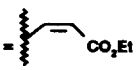
Scheme 1

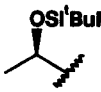
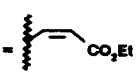
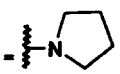


R^1, R^2 in (1); R^1, R^2, R^3 in (2,3); R^1, R^3 in (4,5)

a[i] : R^1 = H, R^2 =  , R^3 = Ph

b[i] : R^1 = Et, R^2 = CPh_3, R^3 = Ph

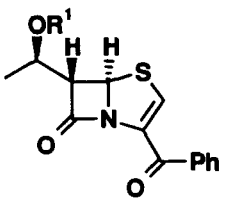
c : R^1 =  , R^2 =  , R^3 = Ph

d : R^1 =  , R^2 =  , R^3 = 

i. Racemic, one diastereomer shown for convenience.

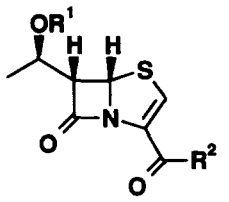
trifluoroacetic acid to the formylthio phosphorane (**4c**), and heating to 85°C in toluene for 4h gave the required *trans*-penem (**5c**) in 62% yield. The *cis*-isomer (**7a**) was present as a minor impurity (*cis*: *trans* ratio of 1:25) and was readily removed by a single recrystallisation. Thermal isomerisation in toluene (105°C, 3h) gave a 3:1 mixture of the *trans*- (**5c**) and *cis*- (**7a**) isomers which were readily separated by column chromatography (60 and 20% yields respectively). However, all attempts to remove the *t*-butyldimethylsilyl group from the *cis*-penem (**7a**) gave only decomposition. Deprotection of *trans*-penem (**5c**) gave *trans*-6-[(*R*)-1-hydroxyethyl] penem (**6a**), but thermal isomerisation was accompanied by considerable degradation and the *cis*- and *trans*-isomers could not be separated by column chromatography. However, protection of the hydroxyl group as a trimethylsilylether (**6b**) followed by thermal isomerisation (105°C, 3h) gave the separable *cis*- penem (**7b**) (11% overall yield) and recovered *trans* - penem (**6b**) (50% overall yield). Deprotection of the *cis*-penem (**7b**) (Bu_4NF/acetic acid/THF/5 min) gave the required 6-(hydroxyethyl)penem (**7c**) in 33% yield (see **Fig.1**).

Fig. 1



(6)

a: R^1 = H
b: R^1 = $SiMe_3$



(7)

a: R^1 = Si^tBuMe_2, R^2 = Ph
b: R^1 = $SiMe_3$, R^2 = Ph
c: R^1 = H, R^2 = Ph
d: R^1 = Si^tBuMe_2, R^2 = 
e: R^1 = H, R^2 = 

It was also of interest to see if this methodology could be extended to the preparation of 6-substituted penem amides. The required 1-(1,2-dioxoethyl)pyrrolidine was readily prepared in two steps from fumaryl chloride[7]. Conversion to the phosphorane (**3d**) (66%) as in the ketone series proceeded uneventfully. Ozonolysis in the presence of trifluoroacetic acid and cyclisation in toluene at 40°C (0.5h) gave only the required *trans*-penem amide (**5d**) (62%). Isomerisation was achieved by photolysis[3] (medium pressure UV, through pyrex) giving the *cis*-penem (**7d**) in 20% yield and recovered *trans*-penem (**5d**) in 60% yield. Deprotection (Bu_4NF/acetic acid/THF) proceeded readily to give the required *cis*-6-(1-hydroxyethyl)penem amide (**7e**).

3-Benzoylpenems (**5a, 7c**) and amide (**7e**) possessed micromolar I_{50} values in LP *in-vitro* assay[3]. No LP activity was found for any 3-benzoyl penems with 5*R*-stereochemistry, again confirming the requirement for 5*S* stereochemistry of penems for LP activity. Full details of these and further studies on the synthesis of 3-benzoylpenems, their aqueous stability and their LP activities will be published elsewhere.

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3. Allsop, E.A.; Brooks, B.; Bruton, G.; Coulton, S.; Edwards, P.D.; Hatton, I.K.; Kaura, A.C.; McLean, S.D.; Pearson, N.D.; Smale, T.C.; Southgate, R. Penem Inhibitors of Bacterial Signal Peptidase, *Biorg. Med. Chem. Letts.*, **1995**, 5, 443.
4. Prepared by the method of Pfaendler H.R. *et. al.* (*J. Amer. Chem. Soc.*, **1979**, 101, 6306) using ethyl propiolate.
5. General Procedure.The crude hemi-aminal was treated sequentially with 2,6-lutidine (2 equivalents) and thionyl chloride (2 equivalents) in THF (4ml / mmol of hemi-aminal) at -20°C for 1h. Addition of toluene (12ml / mmol of hemi-aminal), filtration and evaporation of the filtrate to dryness under reduced pressure gave the crude chloro-derivative. Subsequent treatment with triphenylphosphine (4 equivalents) and 2,6-lutidine (2 equivalents) in dioxane (1ml/mmol of hemi-aminal) at RT for 2h gave the required phosphorane.
6. 1-(*t*-Butyldimethylsilyl)-4-(triphenylmethylthio)azetidin-2-one, prepared by the method of Martel, A. *et.al.* (*Can. J. Chem.*, **1983**, 61, 613), was treated with lithium diisopropylamide at -75°C. After 1h, addition of excess iodoethane and warming to RT over 0.5 h gave the *trans*-3-ethyl product. Deprotection with potassium fluoride in methanol at 0°C for 2h gave the required trans-3-ethyl-4-(triphenylmethylthio)azetidin-2-one (87%).
7. Addition of fumaryl chloride to pyrrolidine (2.2 equivalents), triethylamine (excess) and catalytic 4-(*N,N*-dimethylamino)pyridine in dichloromethane at -30°C followed by warming to RT over 4h gave the diamide. Subsequent treatment with ozone at -30°C in dichloromethane for 1h followed by addition of dimethylsulfide (1 equivalent) gave the required 1-(1,2-dioxoethyl)pyrrolidine (40% overall yield).

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