Tetrahedron Letters,Vol.30,No.24,pp 3219-3222,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

# SYNTHESIS OF NOVEL 3-FORMAMIDO-3-ACYLAMINO-MONOBACTAMS

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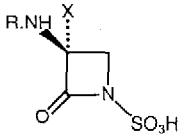
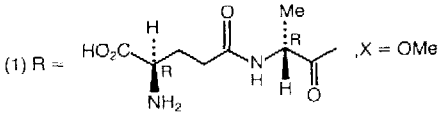
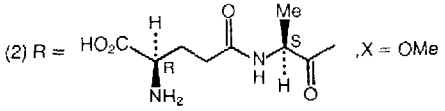
Summary: The syntheses and biological activities of potassium (3RS)-3-[(2R)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-2-phenylacetamido]-3-formamido-2-oxoazetidine-1-sulphonate and potassium (3RS)-3-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-formamido-2-oxoazetidine-1-sulphonate are described.

Isolation of monocyclic β-lactams such as sulfazecin (1) and isosulfazecin (2) from bacterial sources has resulted in the synthesis of a large number of derivatives of 3-aminomonobactamic acid (3).[1,2,3] During the course of our investigations on C6 substituted penicillins and C7 substituted cephalosporins we found that α-formamido substituents conferred β-lactamase stability, whilst the compounds retained their antibacterial activities.[4,5] It was therefore of interest to investigate the chemistry and biology of 3-formamido substituted monobactams.[6]



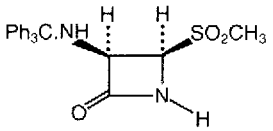




(3) R = X = H

Reductive elimination of an alkylsulphonyl moiety has been used in the removal of the thiazolidine ring of penicillins,[7] and it was therefore envisaged that the readily available 4-methylsulphonylazetidinone(4)[8] was a potential source of the required 4-unsubstituted azetidinone(5).[9] A wide variety of reducing agents were investigated but $NaBH_4$ in aqueous THF (0° - 20°C, 1.5h) was preferable, providing (5), $[\alpha]_D^{22}$ = -155° (c = 1.00, $CHCl_3$), in yields greater than 80%. De-tritylation of (5) (p-toluenesulphonic acid monohydrate, EtOAc) followed by condensation of the free amine (6) with p-nitrobenzaldehyde gave the Schiff base (9). Attempts to functionalise (9) at C3 via methylthiolation of the Schiff base anion[10,11]

(MeS.$SO_2$.Me, KOH, EtOAc-propan-1-ol, 0°C), were complicated by competing β-lactam-N methylthiolation.[12] However, silylation of (5) ($Bu^tMe_2SiCl$, $Et_3N$, DMF, 0°C) yielded N-protected azetidinone (7) (77%), which was detritylated to the crystalline amine (8) (60%). Condensation of the latter with p-nitrobenzaldehyde afforded the crystalline Schiff base (10) which was successfully converted to the methylthio compound (11) (60%) by treatment with DBU in the presence of methyl methanethiolsulphonate ($CH_2Cl_2$, 20°C). Employing other bases in the methylthiolation resulted in either β-lactam cleavage or dimer (12) formation. As anticipated, compound (11) was racemic, resulting from the lack of a C4 substituent to exert steric control over the methylthio insertion; this is in contrast to the exclusive α-face insertion generally observed in fused bicyclic β-lactam systems.[10]

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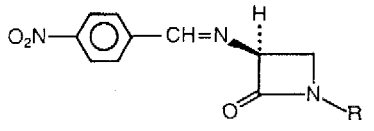
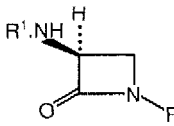
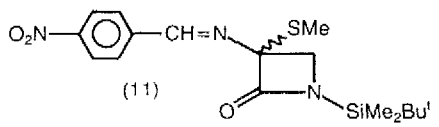



(9) R = H
(10) R = -$SiMe_2Bu^t$




(5) $R^1$ = $Ph_3C$-, $R^2$ = H
(6) $R^1$ = $R^2$ = H
(7) $R^1$ = $Ph_3C$-, $R^2$ = -$SiMe_2Bu^t$
(8) $R^1$ = H, $R^2$ = -$SiMe_2Bu^t$

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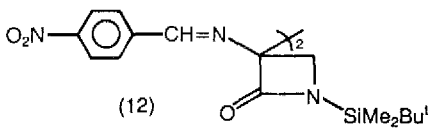


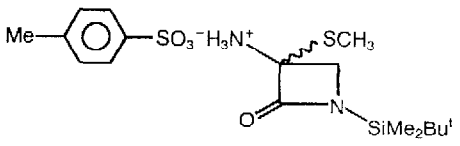

(12)

Acid catalysed hydrolysis of the Schiff base (11) (p-toluenesulphonic acid monohydrate) afforded the crystalline salt (13) (98%), which was progressed directly to the N-benzyloxycarbonyl derivative (14) (96%) ($PhCH_2$.O.COCl, $Et_3N$, propylene oxide, $CH_2Cl_2$) without isolation of the intermediate free base. De-silylation of (14) ($Bu^n{}_4NF$, AcOH, THF) provided the methylthio-azetidinone (15) which was elaborated to the formamido derivative (16) via the reported sulphoxide displacement procedure.[13] Thus sequential oxidation of the sulphide (15) (AcOOH, dioxan, 0°C), displacement with ammonia in THF and formylation ($CH_3CO_2$.CHO, pyridine, dioxan) furnished the formamido azetidinone (16) in 79% overall yield.

Sulphonation[14] of (16) ($SO_3$-pyridine, dioxan, 20°C, 2h) and extractive isolation of the tetra-n-butylammonium salt (17) followed by catalytic hydrogenation provided the nucleus (18) (94% from 16).

In common with bicyclic systems[4,15], restricted rotation about the C-N bond of the formamide group resulted in two rotameric forms being

discernible in the $^1H$ n.m.r. spectra of these monocyclic compounds [the major, Z, rotamer possessing $^3J \sim 1$ Hz for NH-CHO and the minor, E, rotamer $^3J \sim 11$ Hz for NH-CHO].



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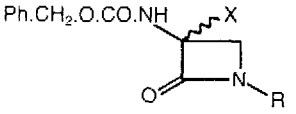
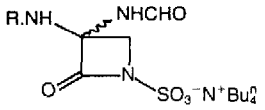
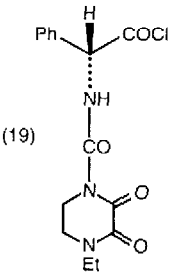


(14) X = -SMe, R = -$SiMe_2Bu^t$
(15) X = -SMe, R = H
(16) X = -NHCHO, R = H

Acylation of (18) with the chiral acid chloride (19)[16] in the presence of propylene oxide followed by precipitation ($F_9C_4.SO_3^-K^+$, acetone -$Et_2O$) and purification on Diaion HP20SS resin provided (20) (58%) as an inseparable mixture of diastereomers (1:1 by $^1H$ n.m.r.). Similarly, reaction with the protected aminothiazolyl acid chloride (21)[17] afforded the chloroacetyl protected monobactam (22) (66%), which, when treated with sodium N-methyldithiocarbamate[17] ($H_2O$, 5° to 20°C, 1.5h), furnished the racemic aminothiazolyl compound (23) (54%).



(17) R = $Ph.CH_2.O.CO$-
(18) R = H



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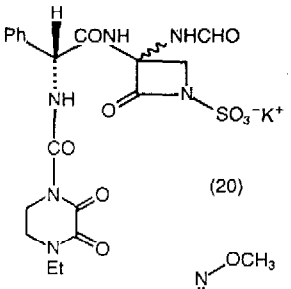

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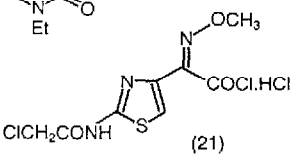

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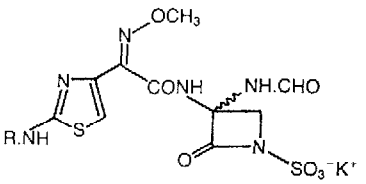

(22) R = $ClCH_2CO$-
(23) R = H

Compound (20) possessed moderate antibacterial activity and in a standard microtitre minimum inhibitory concentration test (μg/ml) gave the following results: E.coli JT4, 25; E.coli NCTC 10418, 12.5; S.marcescens US32, 12.5; K.aerogenes A, 3.2; E.cloacae N1, 12.5; and P.morganii, 6.4. In comparison the aminothiazolyl derivative (23) was much less active, the corresponding figures being >128, 128, >128, 64, >128, and >128.

Acknowledgements

We wish to thank R. Dixon and S.J. Knott for the biological evaluation of these compounds.

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(Received in UK 2 May 1989)