4-Acetoxy-3-[1-(2-arylamino-1-hydroxy)ethyl]azetidin-2-ones: Intermediates for the Synthesis of Novel Carbapenems

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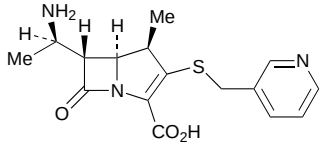
3-Vinyl- and 3-isopropenyl-azetidin-2-ones are transformed into the corresponding 4-acetoxy-3-[1-(2-arylamino-1-hydroxy)ethyl]azetidin-2-ones and 4-acetoxy-3-[1-(2-arylamino-1-hydroxy)propyl]azetidin-2-ones, intermediates for the synthesis of novel carbapenems.

Many carbapenems isolated and synthesised to date possess a 1-hydroxyethyl substituent at C-6, and the presence of this group consistently demonstrates potent antibacterial activity.[1] Mastalerz *et al.*[2] have reported improvements in activity against Gram negative bacteria, particularly against *Pseudomonas aeruginosa*, by replacing the hydroxy group of the hydroxyalkyl substituent at C-6 of carbapenems with an amino group. The 6-(1-aminoethyl)carbapenem **1** was demonstrated to be more active than the corresponding 6-(1-hydroxyethyl)carbapenem but was unstable in solution.[3] In this work the synthesis of hitherto unreported 4-acetoxy-3-[1-(2-arylamino-1-hydroxy)ethyl]azetidin-2-ones is described with a view to the introduction of such *β*-amino alcohol substituents at C-6 of carbapenems.



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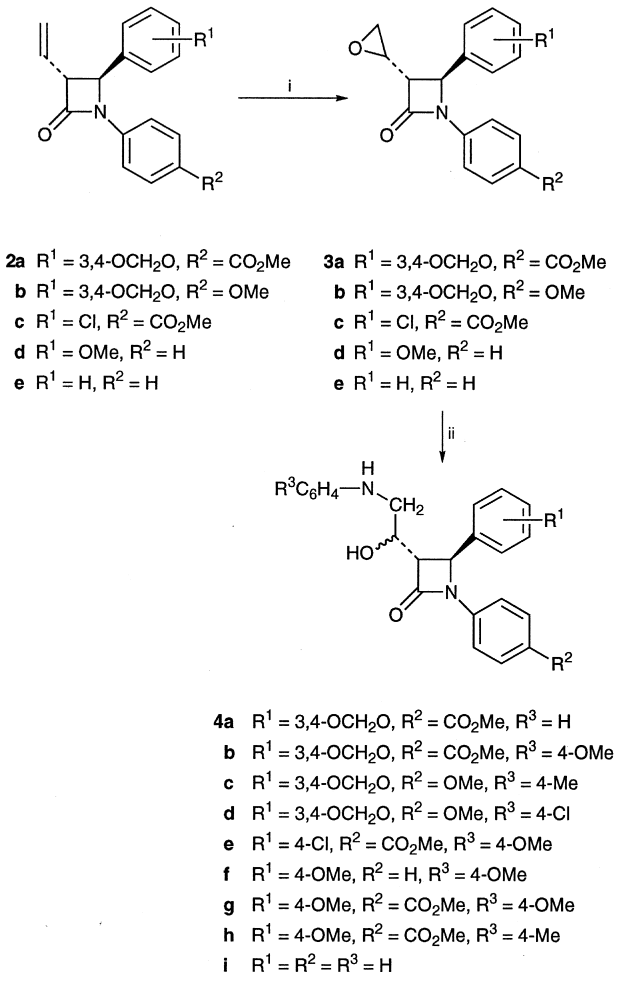
The aminolysis of epoxides provides a convenient route to *β*-amino alcohols and such reactions are well documented.[5,9] There are many methods available for the regioselective ring opening of epoxide with amines, *e.g.* using diethylaluminium amides[7] and aminolead compounds.[8] In this work, the cobalt(II) chloride catalysed aminolysis of 1,4-diaryl-3-(1,2-epoxyethyl)azetidin-2-ones **3a–e** with aniline, *p*-anisidine, *p*-toluidine and *p*-chloroaniline under mild conditions was first investigated. The diastereomeric epoxides **3a–e** required for this study were obtained by *m*-chloroperbenzoic acid (MCPBA) oxidation of *trans*-3-vinylazetidin-2-ones **2a–e**, which were prepared by stereoselective addition of crotonyl chloride to the appropriate Schiff bases. The epoxides **3a–e** were opened regioselectively on the least substituted carbon in all cases, giving rise to the corresponding *β*-amino alcohols **4a–i** in moderate yield as diastereomeric mixtures, Scheme 1.

As an alternative method for the regioselective aminolysis of *β*-lactam epoxides under mild conditions, the use of diethylaluminium amides[7] was investigated, Scheme 2. The diethylaluminium amide nucleophiles were prepared by reaction of triethylaluminium with the appropriate aryl amines. The amides were reacted with epoxides **3a–e** to generate after base catalysed hydrolysis the corresponding *β*-amino alcohols **4a**,**i**, **5a–c** as diastereomeric mixtures. Products **4a**,**i** were found to be identical with those produced using the cobalt(II) catalyst reaction; however in most cases the cobalt



Scheme 1 *Reagents and conditions:* i, MCPBA, CH_2Cl_2; ii, $R^3C_6H_4NH_2$, $CoCl_2$, MeCN

(II) catalysed reaction afforded superior yields and ease of preparation. Additional proof of the regioselectivity of this reaction was provided by the oxidation of the *β*-amino alcohol product **4i** to the corresponding *β*-aminoketone **7**, Scheme 2.

The aminolysis of 3-(1,2-epoxyethyl)azetidin-2-ones was now applied to 4-acetoxy-1-(4-methoxyphenyl)azetidin-2-ones affording products which could be considered as precursors for carbapenems having the *β*-amino alcohol type substituent at C-6. The 4-acetoxy-3-vinylazetidin-2-ones **11a**,**b** were obtained from the 4-formyl-3-vinylazetidin-2-ones **9a**,**b**. The 4-formyl-3-vinylazetidin-2-ones **9a**,**b** were prepared by reaction of crotonic acid and 3,3-dimethylacrylic acid with *N*,*N*′-di-*p*-anisylethylenediimine (**8**) using Mukaiyama's reagent (2-chloro-*N*-methylpyridinium iodide)[15] as the carboxylic acid

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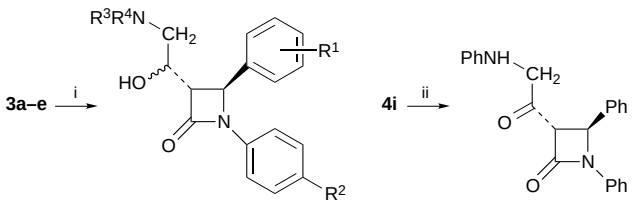
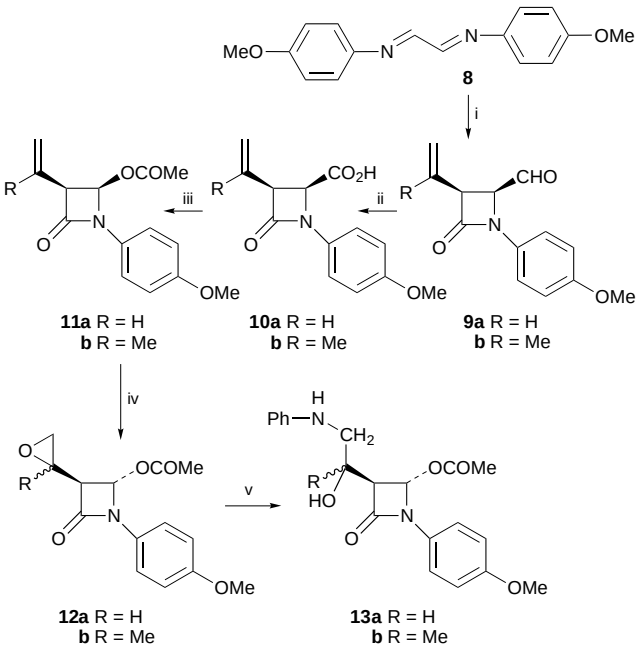


4a R^1 = 3,4-OCH_2O, R^2 = CO_2Me, R^3 = Ph, R^4 = H
i R^1 = R^2 = R^4 = H, R^3 = Ph
5a R^1 = 3,4-OCH_2O, R^2 = CO_2Me, R^3 = R^4 = Ph
b R^1 = 4-OMe, R^2 = H, R^3 = R^4 = Ph
c R^1 = Cl, R^2 = CO_2Me, R^3 = R^4 = Ph

Scheme 2 *Reagents and conditions:* i, $R^3R^4NAlEt_2$, CH_2Cl_2; ii, pyridinium chlorochromate



Scheme 3 *Reagents and conditions:* i, MeCR=$CHCO_2H$, Mukaiyama's reagent, Et_3N, CH_2Cl_2; ii, Jones' reagent, Me_2CO; iii, $Pb(OAc)_4$, DMF; iv, MCPBA, CH_2Cl_2; v, $PhNH_2$, $CoCl_2$, MeCN

activating agent followed by acid hydrolysis of the resulting 4-imino β-lactam intermediate. This method offers an alternative direct synthetic route to the 4-formyl compounds as the previously reported procedures involved reaction of the acid chloride with the diimine.[16] Decarboxylation–acetoxylation of the carboxylic acids **10a**,**b** was carried out with lead tetraacetate to afford the 4-acetoxy β-lactams **11a**,**b**.[17] Epoxidation of **11a**,**b** with MCPBA was carried out to afford the corresponding epoxides **12a**,**b** respectively as diastereomeric mixtures. The *trans* 4-acetoxy-3-(1,2-epoxyethyl)azetidin-2-ones **12a**,**b** were treated with aniline and cobalt(II) chloride and afforded the corresponding β-amino alcohol product **13a**,**b** Scheme 3.

A procedure for the synthesis of β-lactams containing a β-amino alcohol type substituent at C-3 is described, by aminolysis of 3-(1,2-epoxyethyl)azetidin-2-ones and 3-[2-(1,2-epoxypropyl)]azetidin-2-ones, under mild conditions and without destruction of the β-lactam ring. The products **13a**,**b** represent synthetic precursors for analogues of thienamycin and carpetimycin type carbapenem antibiotics having a β-amino alcohol function rather than a 1-hydroxyethyl or 2-hydroxypropyl C-6 substituent. Work is in progress on the elaboration of these intermediates to novel carbapenems containing a β-amino alcohol substituent at C-6.

On preliminary evaluation, the 3-[1-(2-amino-1-hydroxy)-ethyl]azetidin-2-ones **4a**,**f** and **5a** displayed antibacterial activity against *Escherischia coli* (**18**), *Staphylococcus aureus* (Oxford), *Klebsiella pneumoniae* 1588 and *Bacillus subtilis* (Oxford) at a concentration of 1 mg ml^{-1}, using a radial growth assay procedure.

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Techniques used: ^1H and ^{13}C NMR, IR, mass spectrometry, TLC

Schemes: 3

References: 20

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