Transformation of 4-acetoxy-3-vinylazetidin-2-ones to 3-(1-hydroxyethyl)azetidin-2-ones and 3-ethylideneazetidin-2-ones: intermediates for carbapenem antibiotics

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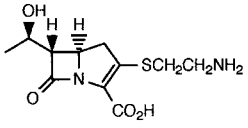
Anthony D. Neary, Catherine M. Burke, Aisling C. O'Leary and Mary J. Meegan*

Department of Pharmaceutical Chemistry, School of Pharmacy, Trinity College Dublin, Dublin 2, Ireland

4-Acetoxy-3-vinylazetidin-2-one and 4-formyl-3-vinylazetidin-2-one are transformed to the carbapenem intermediates 4-acetoxy-3-(1-hydroxyethyl)azetidin-2-one and 4-acetoxy-3-ethylideneazetidin-2-one respectively, and the synthesis of a 6-vinylcarbapenem is reported.

Keywords: 4-acetoxy-3-vinylazetidin-2-one; 4-formyl-3-vinylazetidin-2-one, carbanenem intermediates

3-(1-Hydroxyethyl)azetidin-2-ones which are suitably substituted at the C-4 and N-1 positions are potential synthetic precursors for thienamycin **1** and related carbapenem antibiotics.[2] The 6-(1-hydroxyethyl) substituent is the most common C-6 substituent on clinically important carbapenems such as imipenem and meropenem[3] **2**. In the present work, the conversion of 3-vinyl and 3-isopropenylazetidin-2-ones to 3-hydroxyethyl or 3-[2-(2-hydroxypropyl)]azetidin-2-ones is investigated by a number of routes. We have previously reported the transformation of 3-vinylazetidin-2-ones to 3-(2-hydroxyethylidene)azetidin-2-ones, 3-[1-(2-arylamino-1-hydroxy)ethyl]azetidin-2-ones and 3-(2-alkoxy-1-hydroxy)ethyl]azetidin-2-ones.[5,7] β-Lactams with thienamycin type side chain have previously been prepared from α-vinyl β-lactams by an oxymercuration-reduction procedure,[8,9] while reductive opening of 3-(1,2-epoxyethyl) azetidin-2-ones was carried out in the presence of NaI and *n*Bu_3SnH to afford the 3-(1-hydroxyethyl)azetidin-2-one.[11]



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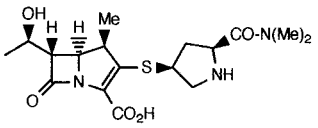

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The objective of the present work was an investigation of the direct preparation of bromohydrins from 3-vinyl and 3-isopropenylazetidin-2-ones and their subsequent transformation to 3-(1-hydroxyethyl) and 3-[2-(2-hydroxypropyl)] azetidin-2-ones. In order to investigate the feasibility of this reaction, the direct preparation of bromohydrins from 3-vinyl and 3-isopropenylazetidin-2-ones **3** and **4** was first examined. Treatment of the vinyl compound **3** with NBS in DMSO afforded two products in equal amounts, (Scheme 1). Product **5** was obtained as a diastereomeric mixture where H-4 was clearly observed as two doublets δ 4.97, 5.07 J ~ 1.0Hz, each 0.5H. The more polar product **6** was also obtained as a diastereomeric mixture; H-4 was again observed as two doublets in the region δ 4.94–5.14, *trans* coupled to H-3. When the 3-isopropenylazetidin-2-one **4** was treated with NBS in DMSO a single product **7** was obtained in 42% yield as a 50/50 diastereomeric mixture. Reaction of **7** with *n*-Bu_3SnH and AIBN afforded the reduction product **8** having the 2-hydroxypropyl substituent at C-3 of the β-lactam ring as found in carpetimycins and related carbapenems. Reduction of **5** with *n*-Bu_3SnH and AIBN gave the diastereomeric product **9** with the 1-hydroxyethyl substituent at C-3, i.e. the thienamycin type C-3 substituent, in 76% yield, ($J_{3,4trans}$, 2.7Hz).

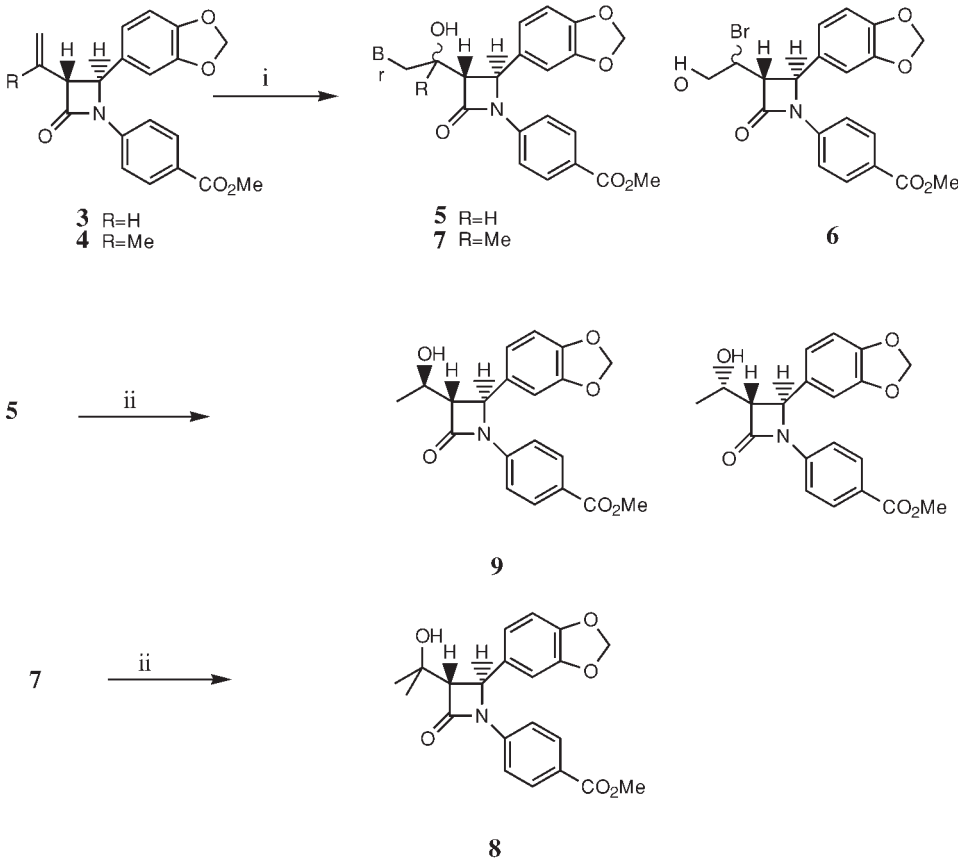
3-(1-Hydroxyethyl)substituted azetidin-2-ones suitably derivatized at the C-4 and N-1 positions are potential precursors for thienamycin, the most potent member of the naturally occurring carbapenems.[2] We now investigate the conversion of the 4-acetoxy-3-vinylazetidin-2-one and 4-acetoxy-3-isopropylazetidin-2-one to the corresponding bromohydrins. (Scheme 3). The predominantly *trans* α-vinyl β-lactams **16, 17** were obtained from the 4-formyl compounds **29, 30** by oxidation followed by decarboxylation and acetoxylation.[7] The 4-acetoxyazetidin-2-one **16** was treated with NBS and DMSO/H_2O to afford the expected bromohydrin **18** together with the isomeric product **20**, both as diastereomeric mixtures. Bromohydrin **19** was similarly obtained from **17**. Compound **18** was now treated with *n*-Bu_3SnH to afford the *trans* β-lactam product which is a precursor for thienamycin as a diastereomeric mixture **21a**, **21b**. The H-3 occurs as two distinct signals at δ 3.24 and δ 3.29 in ratio of 0.4 : 0.6 with coupling constants $J_{3,5}$ = 4.3Hz (0.6H), J = 6.9Hz (0.4H) (H-3). The major isomer is assigned the relative configuration **21a**.[8,9] Compound **22** is a useful precursor for the carpetimycin group of carbapenem antibiotics is afforded by reduction of the bromohydrin **19**.

The facile transformation of 3-vinylazetidin-2-ones to the corresponding ethylidene compounds was investigated as a method of providing synthetic precursors for asparenamycins[20] and other α-alkylidenecarbapenems.[19] Specific procedures for the synthesis of α-alkylidene-β-lactams include addition of chlorosulfonyl isocyanate to functionalised alkenes and condensation of lithium enolates of 3-(*N*,*N*-dialkylamino)esters and imines.[23] We report that the hydride reducing agent sodium borohydride can promote the isomerisation of the 3-vinyl group in compounds such as **29** to afford the 3-ethylidene product with ease.

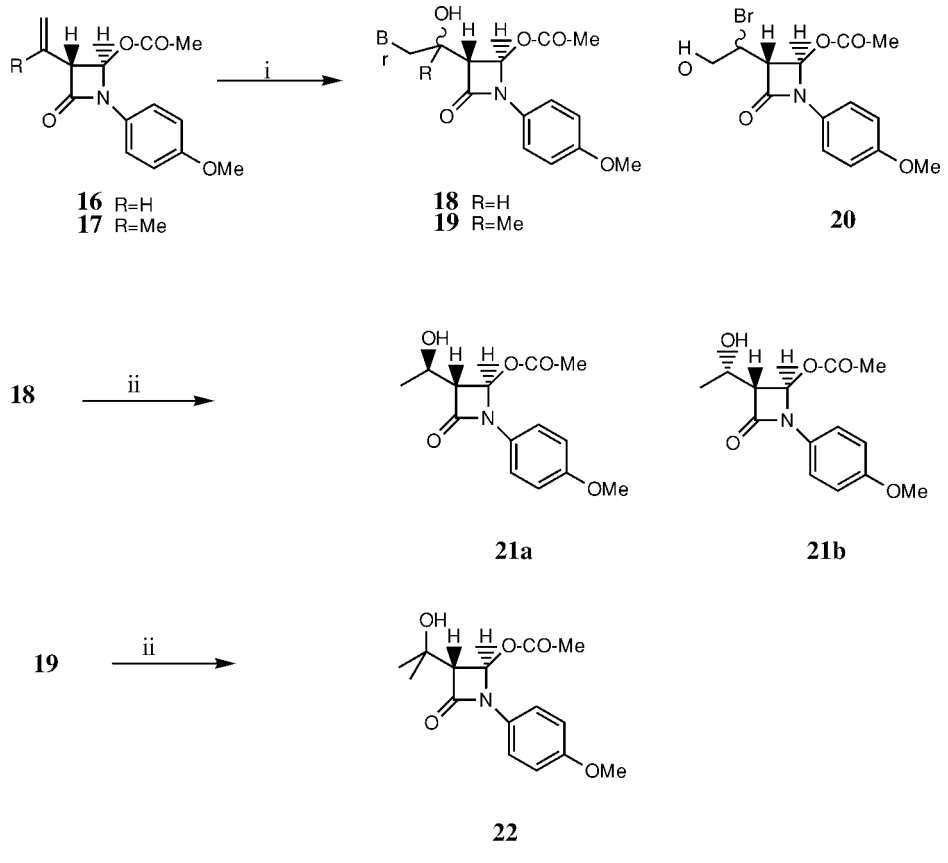
The 4-formyl-3-vinylazetdin-2-one **29** was treated with sodium borohydride to afford the expected alcohol **31** as the trans product together with the 3-ethylidenealcohol **32** as the major product, (Scheme 5). Oxidation of **32** to the intermediate acid **34** followed by decarboxylation/acetoxylation afforded the carbapenem intermediate **35**. The aldehyde **36** was also obtained by oxidation of the alcohol **32**. The 4-acetoxy compounds **35** and **37** could be directly obtained from the 3-vinyl compounds **16** and **17** respectively by treatment with borane–methyl sulfide complex.

The synthetic potential of the 3-vinylazetidin-2-ones was demonstrated by conversion of **16** to a 6-vinylcarbapenem

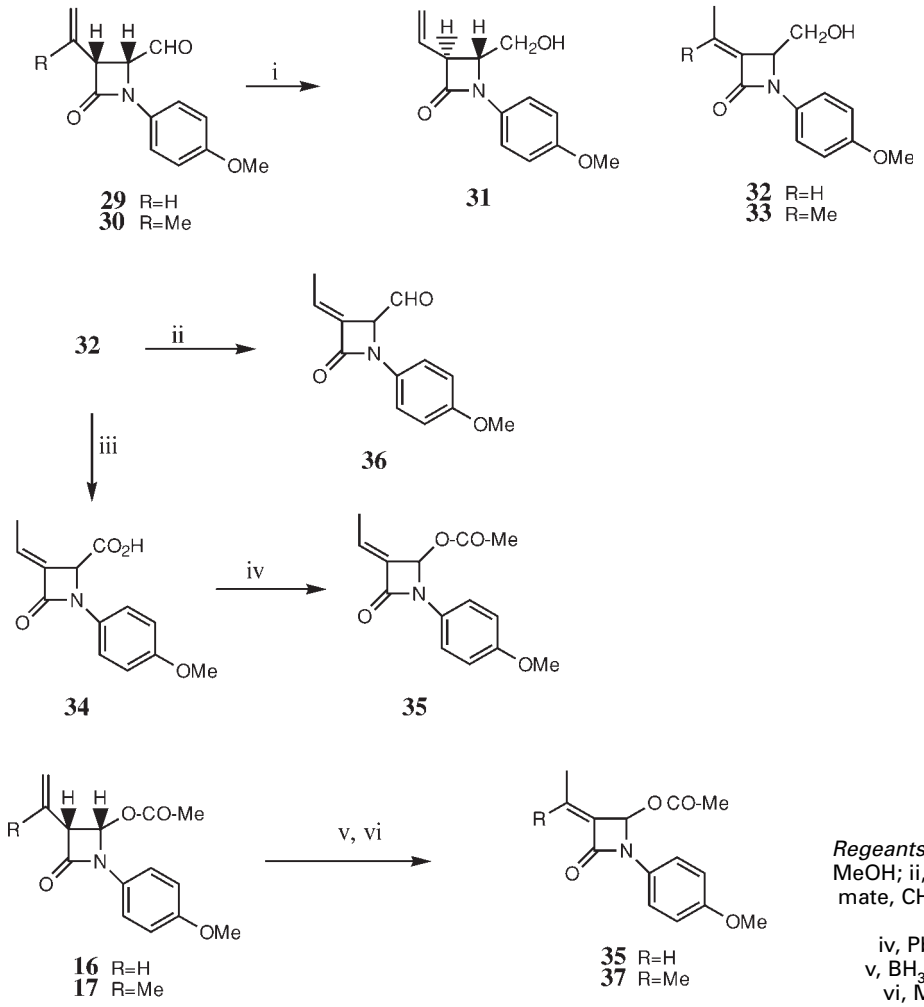
* To receive any correspondence. E-mail mmeegan@tcd.ie



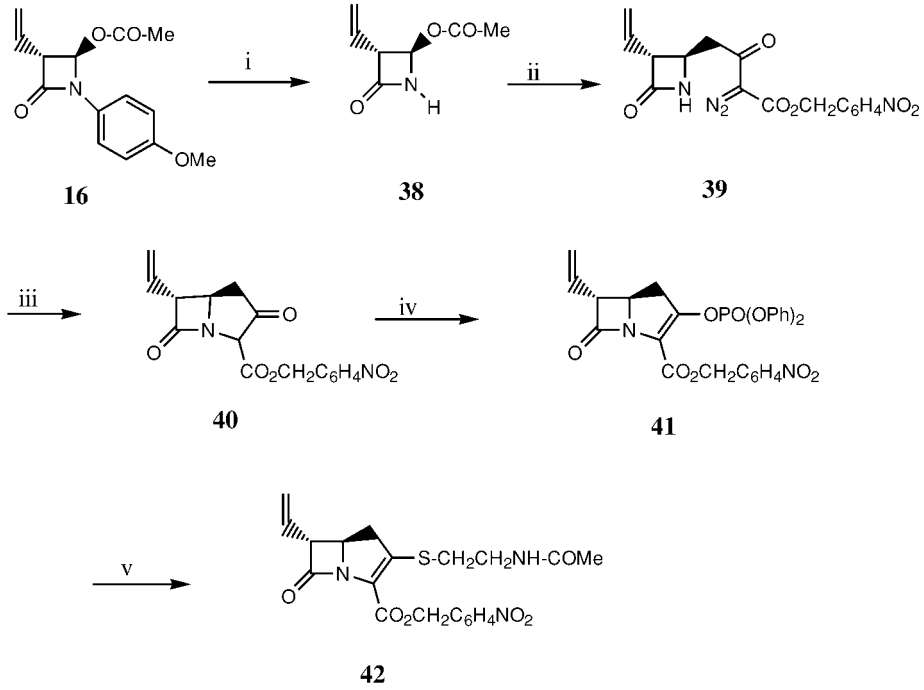
Scheme 1 *Regeants and conditions:* i, NBS, DMSO, H_2O; ii, nBu$_3$SnH, C_6H_6, AIBN, reflux



Scheme 3 *Regeants and conditions:* i, NBS, DMSO, H_2O; ii, nBu$_3$SnH, C_6H_6, AIBN, reflux



Scheme 5
Regeants and conditions: $NaBH_4$, MeOH; ii, Pyridinium chlorochromate, CH_2Cl_2; iii, Jones reagent, acetone;
iv, $Pb(OAc)_4$, DMF, 60°C;
v, $BH_3.Me_2S$, diglyme, 0°C;
vi, $Me_3NO.2H_2O$, reflux



Scheme 6 *Regeants and conditions:* i, $(NH_4)_2Ce(NO_3)$, H_2O, CH_3CN; ii, $CH_2C(OSiMe_2{}^tBu)CH_2CO_2CH_2C_6H_4NO_2$, $ZnCl_2$, iii, Rh_2OAc_4, C_6H_5Me; iv, $(OPh)_2POCl$, Hunig's base, CH_3CN; v, $HSCH_2CH_2NHCOCH_3$, CH_3CN, Hunig's base

product. 4-Acetoxy-3-vinylzetidin-2-ones can be utilized for carbapenem synthesis by means of a carbene insertion process (Scheme 6). Deprotection of **16** with ceric ammonium nitrate followed by treatment of **38** with the appropriate silylenol ether affords the α-diazo-β-ketoester **39**. Stereospecific formation of the trans product was accomplished by treatment of the α-diazo-β-ketoester **39** with a catalytic amount of rhodium(II) acetate to afford the bicyclic ketone **40**.[25] The C-2 oxo substituent was now converted into the enol phosphate **41** which facilitates attack by N-acetylcysteamine to afford the protected carbapenem product **42**. *Trans* stereochemistry was confirmed by the $J_{5,6}$ coupling constant of 2 Hz.

The procedures presented may be useful in the preparation of functionalised 3-ethylideneazetidin-2-ones and transformations of 3-vinylazetidin-2-ones.

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Techniques used: ^{1}H, ^{13}C NMR, EIMS, IR.

Schemes: 6

References: 29

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