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Synthesis of 1,3-Diazetidin-2-ones (Aza-β-lactams) as Rationally Designed Transpeptidase and β-Lactamase Inhibitors

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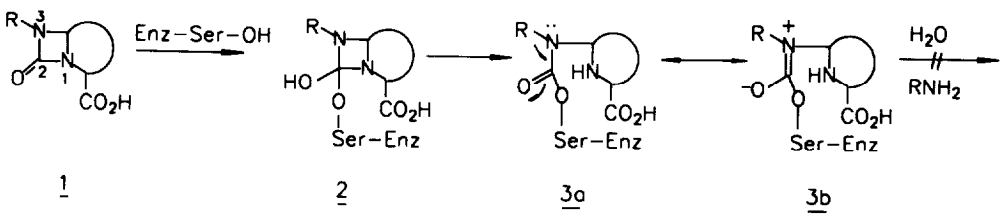
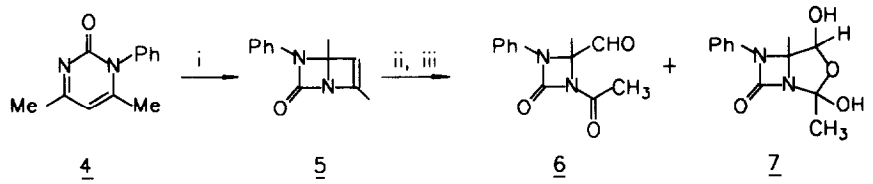
Abstract: Pyrimidinone **4** is converted to diazetidinone carboxaldehyde **6**. Selective chemical transformations on tricarbonyl substrate **6** with different reagents are performed. Synthon **6** is employed as a versatile template for elaboration to bicyclic diazetidinones **7**, **12** and **15**. A novel class of aza-β-lactam compounds are synthesised as potential transpeptidase and β-lactamase inhibitors.

The emergence of resistant bacterial strains in recent years has created an increased awareness about finding new and potent antimicrobial agents. β-Lactam antibiotics have been in widespread use as chemotherapeutic agents to treat diverse bacterial infections for close to five decades now. Despite the fact that there are about 150 β-lactam antibiotics in the market today, the threat that microbes are able to neutralise them is of growing concern to medicinal chemists and clinicians.[1]

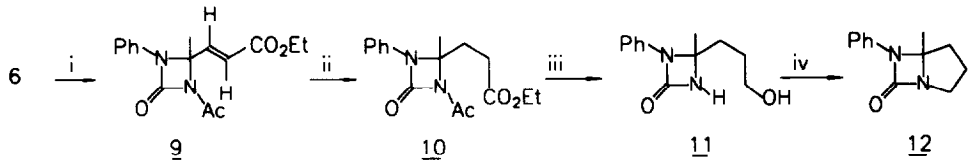
Majority of research leads for the discovery of new antibiotics have focused on the biologically active β-lactam ring.[2] Efforts at exploiting the activity of a bioisosteric core other than an azetidinone ring have been fewer.[3] Some time ago we got interested in exploring the potential of 1,3-diazetidin-2-ones (aza-β-lactams) as a novel class of antibacterial agents and β-lactamase inhibitors.[4] We reasoned that attack of active site serine peptidase on aza-β-lactam nucleus **1** will form tetrahedral intermediate **2**, which should collapse to carbamoyl enzyme intermediate **3**. Amide resonance in urethane **3** should impart it greater hydrolytic stability than the corresponding penicilloyl enzyme intermediate, and hence subsequent hydrolysis of **3** should be retarded. Transient trapping of transpeptidase or β-lactamase enzyme as a meta-stable species will result in mechanism based inactivation (suicide substrates) of the enzyme.[5] To understand the biochemistry delineated in Scheme 1, we carried out detailed AM1 calculations and were encouraged to find that our rationale was indeed borne out. Diazetidinones have a



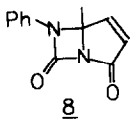
Scheme 1: *Enz-Ser-OH = Transpeptidase or β-Lactamase*

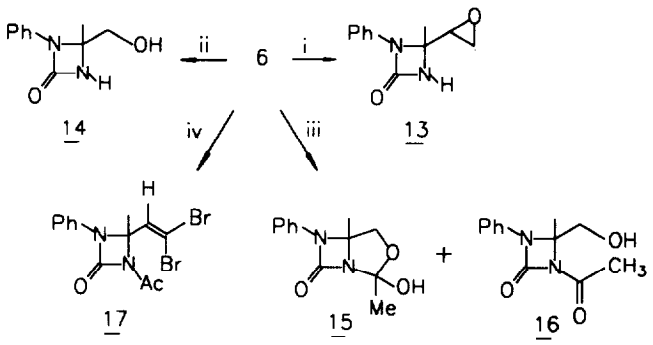


Scheme 2: *i) hν, λ > 300 nm, PhH; ii) O_3, CH_2Cl_2, -78°C; iii) Me_2S or Et_3N*



Scheme 3: *i) $Ph_3P{=}CHCO_2Et$ or $(EtO)_2P(O)CH_2CO_2Et$, NaH; ii) H_2, Pd/C; iii) $LiAlH_4$, Et_2O; iv) Ph_3P, $EtO_2C{-}N{=}N{-}CO_2Et$*





Scheme 4: *i) $Me_2S{=}CH_2$ or $Me_2S(O){=}CH_2$; ii) $LiAlH_4$, Et_2O; iii) $NaBH_4$, MeOH; iv) Ph_3P, CBr_4*

highly electrophilic carbonyl group, should react with active site serine hydroxyl to form species **2** which will lead to stable carbamoyl intermediate **3** by cleavage of C_2-N_1 bond, have pyramidality at N-atom (N_1) comparable to active β-lactams, and hence are bioisosteric with β-lactams.[4] In order to evaluate their biological activity and assess their potential as serine peptidase inhibitors, we targeted bicyclic aza-β-lactams fused to 5/6-member rings. We were somewhat surprised to find that there is practically no prior art on the synthesis or reactions of diazetidinones **1**. We report herein preliminary results on the reactivity of diazetidinone carbonyl group and synthesis of some mono- and bicyclic aza-β-lactams.†

Photolysis of pyrimidinone **4** afforded a ~1:1 photostationary mixture of 3-phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo[2.2.0]hex-5-ene **5** and starting material (SM) from which pure **5** was obtained in 42% yield after silica gel chromatography (SGC).[6] Ozonolysis and reductive work-up (Me_2S) provided an easily separable >4:1 mixture of aldehyde **6** and acetal **7** (Scheme 2). The isolated yield of acetal **7** can be significantly improved (**6**:**7**~1:1) when the ozonide is treated with Et_3N[7] instead of Me_2S. Out of four possible diastereomers of **7**, three were purified, isolated (SGC) and characterised by their acetal C-H signals at δ 5.85, 5.43 and 5.00.[8] Examination of the crude residue indicated formation of these three stereoisomers in varying ratios depending on work-up conditions of Me_2S or Et_3N.

Subsequent studies started from aldehyde **6** as the key synthon. The objective was two-fold: 1) to assess the reactivity of tricarbonyl **6** towards selective chemical transformations and functional group manipulations, and 2) to synthesise bicyclic aza-β-lactams represented by general structure **1**. Although the target molecules in this study are devoid of the crucial carboxyl group at C_3 of penicillins (C_4 in cephalosporins), the idea was to develop synthetic routes on model substrates which may be eventually applied towards more complex aza-β-lactams which contain functional groups at defined positions for non-covalent interactions between enzyme and substrate. Attempted cyclisation of 1,4-dicarbonyl **6** to γ-lactam **8** was unsuccessful using a variety of bases (LDA, LiHMDS, pyrrolidine). Although the SM was consumed, no olefinic signals were observed in the crude residue.

Treatment of aldehyde **6** with stabilised phosphorane or phosphonate anion afforded the expected *trans*-ester **9** which was uneventfully hydrogenated to **10**. Reduction of **10** with $LiAlH_4$ at 0 °C for 1 h afforded alcohol **11** in which the acetyl group was surprisingly cleaved during chemical reduction, although the diazetidinone ring was intact. Cyclisation of amide alcohol **11** under Mitsunobu conditions (TPP, DEAD)[9] afforded bicyclic aza-β-lactam **12** in excellent yield (Scheme 3). Model substrate 1,6-diazabicyclo[3.2.0]heptan-7-one **12** is an analog of carbapenam antibiotics.

The observation that the acetyl group is behaving like a protecting group which can be conveniently unmasked under nucleophilic conditions at a suitable stage was investigated further. Epoxidation of aldehyde **6** rapidly occurred with Corey-Chaykovsky epoxidation reagents ($Me_2S{=}CH_2$ or $Me_2S(O){=}CH_2$)[10] and provided epoxide **13** with concomitant acetyl group "deprotection". Cognisant of our earlier result that LAH cleaves the acetyl group, the isolation of deprotected alcohol **14** was not surprising. However, exposure to less reactive $NaBH_4$ afforded an easily separable >9:1 mixture of γ-lactol **15** and amido alcohol **16**. The AB CH_2O pattern of two distinct geminally coupled doublets (J=12Hz) is better separated in cyclic **15** (δ=4.30,3.75) than in acyclic **16** (δ=4.20,3.95). In an attempt to further gauge our ability in performing selective reactions on **6**, we subjected it to Wittig conditions ($Ph_3P{=}CH_2$ and $Ph_3P{=}CHOMe$), but were unable to isolate any characterisable material. It is likely that the strongly nucleophilic unstabilised Wittig reagent attacks tricarbonyl **6** indiscriminately and

destroys the least reactive diazetidinone ring in the process. The use of milder Corey's conditions (Ph_3P, CBr_4)[11] afforded dibromoalkene **17** without any complication (Scheme 4).

Thus, we have explored the chemistry of a novel non-natural β-lactam core structure which is produced by rational design.[12] The IR carbonyl stretching frequencies of bicyclic aza-β-lactams **7**, **15** and **12** appear in the expected decreasing order at 1810, 1800 and 1775 cm^{-1}. These values are in excellent agreement with amide carbonyl stretch for active β-lactam antibiotics (1770-1800 cm^{-1}).[13] Efforts are currently under way to obtain crystallographic analysis of these bicyclic aza-β-lactams to determine values of structural parameters important for biological activity, such as extent of pyramidalisation at N_1, sum of bond angles at N_1, and C_2-N_1 bond distance. Screening assays on these model compounds will be reported separately.

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† All new compounds were characterised by combination of FT-IR, ^1H (200MHz) and ^{13}C (50MHz) NMR, microanalysis, mass, and 2D COSY NMR data.
Aza-carbapenam 12: PMR δ 7.40-7.05 (m,5H), 3.65-3.45 (m,1H), 2.85-2.70 (m,1H), 2.50-2.35 (m, 1H), 2.15-2.00 (m, 2H), 1.78 (s, 3H), 1.75-1.60 (m, 1H). CMR δ 158.12, 137.61, 129.40 (X2), 123.04, 115.76 (X2), 84.17, 46.41, 32.18, 26.94, 22.86.

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