“Synthesis of a bicyclic oxo-γ-lactam from a simple caprolactam derivative”

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Abstract

Synthesis of the 6-azabicyclo[3.2.1]octane ring system, via Dieckmann cyclization, is described. Ring closure involves reaction of a caprolactam enolate with a C6 ester, the reactive axial conformation of which is promoted by the presence of an N-butyloxycarbonyl group on the lactam nitrogen. The results will enable the synthesis of new bridged caprolactams for testing as antibacterials and nucleophilic enzyme inhibitors.
The β-lactams remain the most important antibacterials; they work by reaction with a nucleophile serine residue in penicillin binding proteins (PBP), which catalyse essential transpeptidase reactions during bacterial cell-wall peptidoglycan biosynthesis. A common mechanism of resistance to the β-lactam antibacterials, involves β-lactamases, which catalyse β-lactam hydrolysis. All clinically used PBP inhibitors are β-lactams and until recently this has been the case for β-lactamase inhibitors. Following on from synthetic γ-lactam analogues of the β-lactams and the discovery of the natural product lacticin, the cyclic urea avibactam has recently been introduced as a broad spectrum serine β-lactamase inhibitor. However, while the β-lactam based inhibitors react irreversibly with the nucleophile serine of the PBP and β-lactamases, avibactam reacts reversibly with its target serine β-lactamases. The discovery of avibactam has stimulated interest in non β-lactam inhibitors of the serine β-lactamases and PBPs. We have been interested in bridged lactams as inhibitors of nucleophilic serine / threonine / cysteine enzymes; however, for ring sizes > 6 there are only limited reports on their synthesis. Here we describe the synthesis of the 6-azabicyclo[3.2.1]octane bridged ring system, starting from a readily available caprolactam precursor (Fig. 1).

![Diagram of lactam antibacterials, inhibitors, and analogues](image)

**Fig. 1** Examples of β-lactam antibacterials, β-lactam inhibitors and non-β-lactam analogues: a) penicillins, b) carbapenems, c) an inactive γ-lactam analogue, d) an active γ-lactam analogue, e) avibactam and f) the target of the current work (1) which has a 6-azabicyclo[3.2.1]octane core ring system.

The 6-azabicyclo[3.2.1]octane ring system is present in a wide range of biologically active compounds and is isomeric with the tropane nucleus present in alkaloids, including cocaine and atropine. Preparation of respective 6-azabicyclo[3.2.1]octane derivatives and related
compounds is restricted to the intramolecular ring closure of \(\gamma\)-lactam derivatives,\(^5\) amide formation in substituted cyclohexanes\(^6\), and Diels-Alder reaction of appropriately unsaturated \(\gamma\)-lactams with acrylic acid.\(^7\) There is only one reported route to a 7,8-dioxo-6-azabicyclo[3.2.1]octane derivative of (I), which employs semipinacol rearrangement of a \(\beta\)-lactam precursor.\(^8\) We envisaged bicycle 1 could be succinctly prepared via cyclization of a simple caprolactam via Dieckmann cyclization. We anticipated that then Dieckmann cyclization may only proceed efficiently, when the ester group adopts an axial position (Fig. 2a/b/c).

![Diagram](image)

**Fig. 2** Proposed Dieckmann cyclisation to give the 6-azabicyclo[3.2.1]octane ring system. a) The two energetically favoured ‘pseudo chair’ conformations of an \(N\)-substituted caprolactam methylester. b) Synthesis of 1 via Dieckmann cyclization. c) Only the axially positioned ester group can react via the desired Dieckmann cyclization. d) View from a crystal structure of 3 showing that the –COOMe group adopts an axial conformation, as observed for both polymorphs. In solution an equilibrium between the ‘axial’ and ‘equatorial’ conformers (70 % : 30 %) is observed.\(^{12}\)
Caprolactams can adopt (pseudo) chair, boat or transition (twist boat) forms. In the ‘chair’ form, two energetically favoured conformations are manifested (\(\text{1,}^\text{N}C_4\) and \(\text{4,}^\text{C}_1\)) assuming an planar amide. Similar to cyclohexane chair conformations, caprolactams feature axial and equatorial positions of ring hydrogens and respective substituents. The axial substituents are higher in energy than equatorial ones (as shown for \(C-2/C-6\) substituted caprolactams). In a previous study, we investigated the influence of a second substituent on the conformation of the \(C-6\) caprolactam methylester (2) (Fig. 3). Importantly for the current purpose, we observed by crystallography that introduction of the bulky tert-butyloxy carbonyl (Boc) group at the caprolactam nitrogen causes the \(C-6\) ester to adopt the normally energetically disfavored axial conformation. Note the short distance of 2.53 Å (polymorph I) and 2.66 Å (polymorph II, Tabs. S1 and S2, Scheme S1, ESI), respectively, between the \(C-6\) ester carbonyl and the axial \(C-2\) hydrogen as observed by X-ray crystallography (Fig. 2d). Indeed, treatment of 3 with LiHDMS (lithium bis(trimethylsilyl)amide) produced the desired bicyclic lactam in its protected form (1a) in low (8 %) yield (Fig. 3). Although it is likely that the cyclisation yield can be optimised, initial attempts to improve the yield by use of other bases (DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene, and potassium tert-butoxide) and varying temperature (including use of LiHMDS at room temperature), and, somewhat surprisingly, concentration (Tab. S3, ESI) were unsuccessful.

![Synthetic pathway to bicycle 1a.](image)

Caprolactam 3 features two C-H acidic position (C-2 and C-6) and a competing deprotonation may be one reason for the low yield of the bicyclic lactam 1a in the cyclisation step. To investigate the proposal of competing C-6 deprotonation, Boc-protected ethylester 5 was prepared. Thus, caprolactam methylester 2 was saponified to yield free acid 4, which was esterified with EtOH and, subsequently, treated with Boc anhydride. When 5 was subjected the Dieckmann cyclization, a higher yield of 1a (15 %) was achieved (Fig. 3), likely due to reduced C-6 deprotonation relative to 3 due to the higher steric demand of the ethyl ester.
$^1$H and $^{13}$C NMR (Fig. S1, ESI) as well as COSY analyses (Fig. S2, ESI) support the assigned structure of 1a. Of note, the $^1$H spectrum exhibits a 'doublet of doublets of doublets' (ddd) coupling for H2 and H6. The third coupling likely results from $^4J_{HH}$ long-range ‘W’ coupling\textsuperscript{14,15} of H2 with H6 over the keto bridge. For the bicyclic lactam 1a, H2 and H6 couple with $^4J$ values of 4.89 and $^4J$=4.88 Hz respectively; the analogous value for cyclobutanone is 4.8 Hz.\textsuperscript{16} By contrast the $^3J$-couplings are rather low, both for the coupling of H2 with H3/H3’ ($^3J$=2.50/1.95 Hz) and of H2 with H6 ($^3J$=1.88/1.33 Hz) (Fig. 4; Fig. S3, ESI).

Fig. 4 Close up view from the $^1$H NMR (125 MHz) spectrum of 1a; the H2 signal with the respective ddd coupling pattern and the respective $^3J_{HH}$ and $^4J_{HH}$ values is shown.

Bicycle 1a crystallized from ethyl acetate and cyclohexane as its corresponding hydrate 1b (Fig. 5a), a phenomenon which was already observed with a related compound.\textsuperscript{9} The plate like twinned crystals are in spacegroup $P$-1 with molecules featuring (R,R) and (S,S) stereochemistry. As expected, the five-membered ring of 1b adopts an envelope conformation, while the caprolactam adopts the rarer boat conformation (Fig. 5b). A comprehensive comparison of bond lengths and angles with related compounds can be found in the Supplementary Material (Tab. S4, ESI). The molecules of 1b arrange in hydrogen bonded ribbons running in the direction of the crystallographic $a$ axis. In the ribbons two diols face each other making an $R^2_2$($8$) motif and these dimers then bond into C6 chains via the ring carbonyl groups (Fig. 5c; Tab. S5, ESI). The ribbons stack up on each other with only weak C-H⋯O(-H) hydrogen bonds in the direction of the crystallographic $b$ axis. The tert-butyl groups point outward from the sheet assembled via these interactions and stacking errors of these sheets cause the crystals to be twinned.
Conclusions

Overall, we have described the concise synthesis of a bridged caprolactam ring system, *via* Dieckmann cyclization. This route builds upon work that has defined the transformations of readily accessible caprolactam derivatives. Closure to give the 6-azabicyclo[3.2.1]octane ring system involves the reaction of a caprolactam enolate with an C-6 ester in an axial conformation. The presence of the reactive axial conformation is promoted by an N-butyloxy carbonyl group on the caprolactam nitrogen. The yield is increased on with use of an ethyl, rather than a methyl, ester, likely due to diminished C-6 deprotonation with the ethyl ester. Future work can focus on a deeper understanding of the mechanism and minimising side reactions. The results will enable the synthesis of 6-azabicyclo[3.2.1]octane ring derivatives for testing as antibacterials and nucleophilic enzyme inhibitors.
Experimental

Materials and Methods

Melting points were determined using a microscope heating stage PHMK Rapido (VEB Dresden Analytik). IR spectra were measured using a Bruker Tensor 27 ATR-FT-IR with the ATR method. NMR spectra were recorded using a Bruker Avance DRX 500 spectrometer at 500.13 MHz (1H-NMR) and 125.77 MHz (13C-NMR), respectively. Chemical shifts δ are reported in parts per million relative to the internal reference TMS. Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet) and m (multiplet). Mass spectra were measured on a Varian 320 MS. Elemental analyses were performed on a Heraeus CHN-Rapid Analyzer. All reactions involving moisture sensitive reagents were carried out under a nitrogen atmosphere. Cooling was performed in ice-water baths (0 °C) or dry ice-acetone baths (-78 °C). Anhydrous solvents were used as supplied. Thin layer chromatography (TLC) was performed on Merck DC-Kieselgel 60 F 254 0.2 mm precoated plates with fluorescence indicator. Visualization of spots was achieved using UV light (254 nm) and by developing in a basic solution of KMnO4 followed by heating. The syntheses of the starting caprolactam 2, the Boc-protected lactam 3 and the free acid 4 have been described previously.12 Synthetic procedures for compounds 5 and 6 are given in the Supplementary Material.

tert-Butyl 7,8-dioxo-6-azabicyclo[3.2.1]octane-6-carboxylate (1a). To a stirred solution of the appropriate Boc-protected lactam (3 or 6, resp.) (1 eq.) in dry THF (15 ml) at -78 °C was added a 1M solution of lithium hexamethyldisilazide (LiHDMS) in ethylbenzene/THF (1.1 eq.). The reaction mixture was then stirred at -78 °C for 3 h. Subsequently, the reaction was quenched with sat. aqueous ammonium chloride solution (30 ml) at -78 °C and extracted with ethyl acetate (3x). The combined organic phases were dried (Na2SO4), then filtered. Evaporation of the solvent yielded a dark, oily residue which was separated by flash column chromatography (SiO2; n-hexane/ethyl acetate = 1:1 → ethyl acetate) to yield 8 % (43 mg, 0.18 mmol) (methyl ester) or 15 % (22 mg, 0.092 mmol) (ethyl ester), respectively, of a white solid. Mp. 93-94 °C. Rf = 0.30 (SiO2; n-hexane/ethyl acetate = 1:1). 13C NMR (100 MHz, CDCl3): δ = 207.3 (CO), 168.9 (CONH), 148.4 (NCOO'Bu), 84.1 (CH3), 64.9 (COCHCO), 55.0 (NCHCO), 33.2 (CH2), 32.7 (CH2), 28.0 (CH3), 17.1 (CH2). 1H NMR (400 MHz, CDCl3): δ = 4.39 (m, 1H, NHCH), 2.99 (m, 1H, COCHCO), 2.44-2.31 (m, 2H, CH2), 2.05-1.96 (m, 1H, CH2), 1.95-1.88 (m, 1H, CH2), 1.84-1.75 (m, 2H, CH2), 1.54 (s, 9H, C(CH3)3). IR: 3391, 2992, 2932, 2874, 1769, 1789, 1752, 1713, 1448, 1393, 1365, 1326, 1305, 1249, 1220, 1154, 1089, 1068, 1052, 1014, 993, 975, 953, 888, 865, 712. m/z = 238.11 [M-H+] +, calc. 238.12.

X-ray crystallography

Bicycle 1a was crystallized from ethyl acetate and cyclohexane using the vapor diffusion approach resulting in hydrate 1b. Crystals suitable for single crystal X-ray diffraction studies of polymorph II of compound 3 were obtained by crystallization from ethyl acetate/n-hexane (1:2) and have a melting point of 69-71 °C; this is about 20 K higher than observed for polymorph I. Single crystal X-ray diffraction was performed at 173K with a Bruker D8 Venture diffractometer using a Cu-Kα source. Structure solution was carried out with shelxt and structure refinement with shelxl was finished using ShelXle software. The twin matrix for 1b was acquired from twinnomat in Platon.20 For crystal data and refinement parameters see ESI. CCDC numbers 1528320 (1b) and 1522636 (3).
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