UNSATURATED β-LACTAMS

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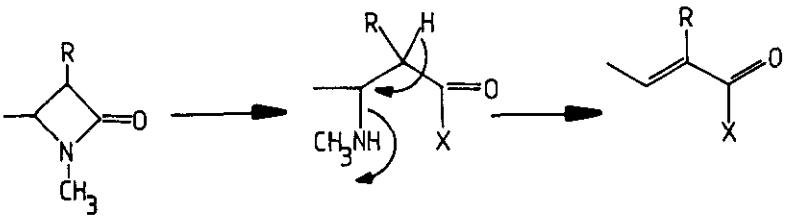
Abstract —— Lithium enolates of β-lactams are shown to exclusively yield 1,2-addition products to propargylic aldehyde. Products of subsequent Peterson elimination and propargylic rearrangements are described.

In recent years β-lactams have become easily available starting materials and especially the CSI-cycloadditions to various olefins are providing a wealth of β-lactams in industrial scales.[1] Reason enough to consider them as starting material or building block for synthetic projects[2], particularly as these moieties - as given in Scheme 1 - formally are representing the masked synthetic equivalent of an α,β-unsaturated carbonyl group.

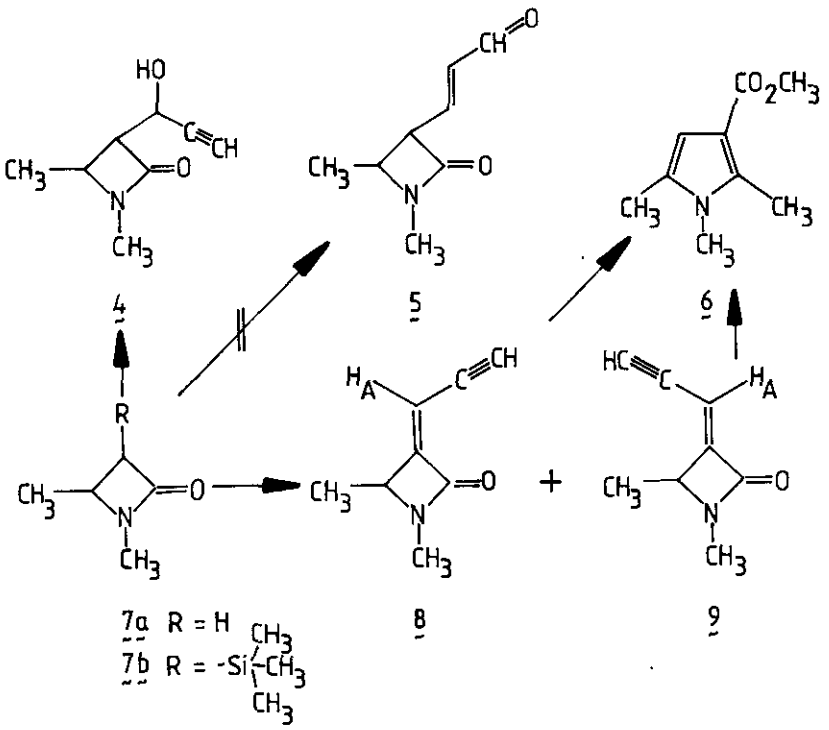


1 2 3

In order to attach to this molecule a second α,β-unsaturated aldehyde unit, thus making available a compound containing twice this functional group in different forms of protection, we did investigate the reaction of β-lactam lithium enolates with propargylic aldehyde.

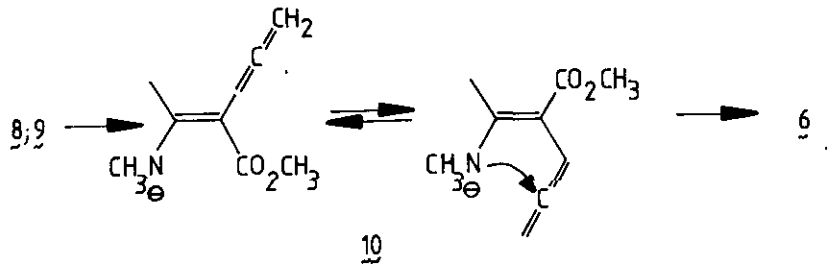
To make sure for monoaddition the silylated β-lactam 7b was deprotonated with LDA and propargylic aldehyde was added at slow rate and low temperature to yield a 1 : 1 mixture of the exocyclic vinylacetylenes 8 and 9 which was separated by flash chromatography.

These substances showing UV absorption at 252 and 242 nm represent the products of 1,2-addition to the aldehyde with subsequent Peterson elimination and proved to be quite stable crystalline compounds with none of the corresponding 1,4-addition product (e.g. 5) visible in the reaction mixture.

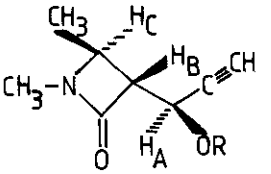


Even if the reaction mixture was quenched at low temperature 8 and 9 turned out to be the only reaction products which proves the Peterson elimination to be very efficient in this case even at low temperature. Configuration assignment of 8 and 9 relys mainly on the chemical shift of proton H_A which is recorded at 5.95 δ for the less polar (9) and at 5.50 δ for the more polar stereoisomer (8), reflecting the influence of the carbonyl group on the in-plane proton for configuration 9.

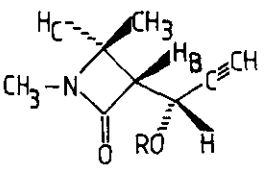
As may be expected both compounds do react very quickly with sodium methoxide in methanol to give a very stable and well-known pyrrole derivate 6[3] which by comparison was confirmed to be identical with an authentic sample prepared independantly. In both cases this product is accompanied by an unstable oily yellow material as a by-product which was not purified. The formation of the pyrrole from both stereoisomers may be explained by nucleophilic ring-opening and base catalyzed isomerisation to yield 10 as the common intermediate, which as an anion of a vinylogue urethan will quickly equilibrate.



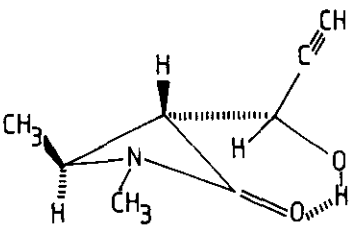
To avoid formation of the pyrrole but keep the option for functionalizing the triple bond the anion on the β-lactam 7a was directly treated with propargylic aldehyde at low temperature to again secure exclusively the product of 1,2-addition (4) in excellent yield which as expected turns out to be a mixture of stereoisomers.



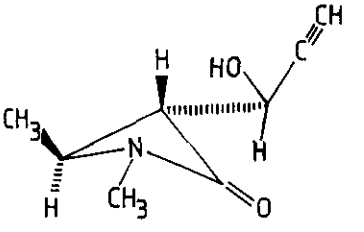
11 R = H
12 R = $COCH_3$



13 R = H
14 R = $COCH_3$



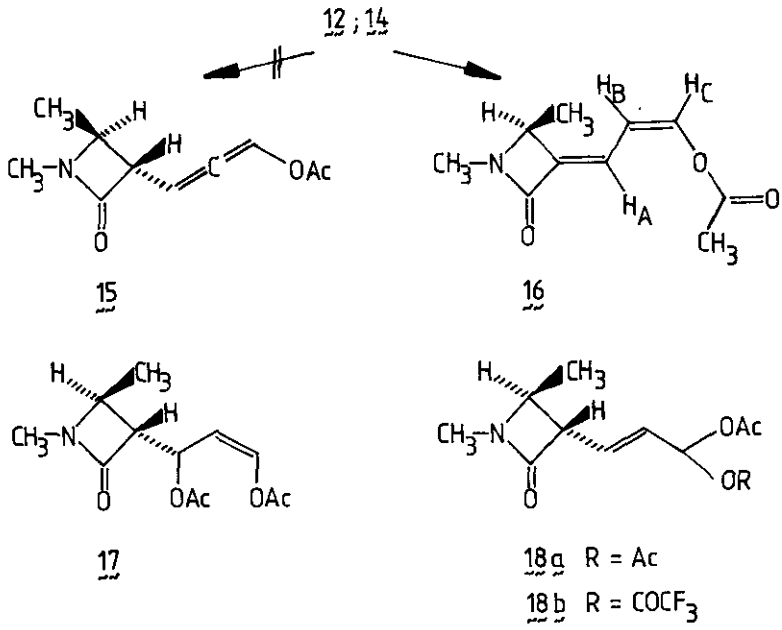
11'



13'

Spectral data prove them to be the alcohols 11 and 13. A small (2 Hz) splitting of all lines of the quartet for H_B indicates the trans-configuration of the substituents on the β-lactam for both compounds[4] and as one of the carbinols nicely crystallized and shows a strong hydrogen bond in the infrared spectrum we assign configuration 11 (see 11') to this epimer. In agreement with this assignment H_B is appearing as a narrow multiplet in 11 while the corresponding signal in 13 shows a 6.5 Hz coupling with H_A (see 13').

To convert 11, 13 into an equivalent of the α,β-unsaturated aldehyde 5 we investigated silver catalyzed propargylic rearrangemnt of the acetates 12 and 14. When these stereoisomers are refluxed in an acetic acid - acetic acid anhydride mixture in the presence of silver acetate a quite polar, very stable crystalline compound can be isolated as the final product of the rearrangement which by NMR and infrared data very quickly can be shown not to be an allenic one (e.g. 15).



The UV absorption at 287 nm in connection with chemical shifts and coupling constants of three olefinic protons indicates structure 16 for this final product. Interestingly, all resonances but the one of the methyl group on the β-lactam ring are doubled in the NMR spectrum recorded in $CDCl_3$, which may be explained by hindered rotation in the donor acceptor substituted π-system. The formation of this material could be explained by an allene-butadiene rearrangement following the well documented[5] formation on an allene acetate. Two less polar intermediates however, that can be isolated after running the reaction for 4 h at 50°C and which can be shown to give rise to 16 under reflux in the acid acid anhydride mixture cast severe doubt on this assumption, NMR data of these substances (see Experimental) prove them to be enol acetate 17 as the primary reaction product (acetic acid addition to the triple bond) which is in equilibrium with the corresponding acetal 18a. If the reaction is run in a TFA-TFA anhydride mixture this compound is shown to be the mixed acetal 18b-again showing all signals doubled, which in this case is due to the creation of a new centre of chirality at the acetal carbon atom. Without knowing whether 17 or 18a or both are generating the diene, we may assume that elimination from these products leads to 16. The isolation of 16 and the detection of 18a an an intermediate without running the reaction to completion proves the possibility to obtain derivates and hence synthetic equivalents of unsaturated aldehydes in the β-lactam series. As compounds of this type are expected to be very useful synthetic intermediates elaboration and optimisation of this transformation is in hand in our laboratory.

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EXPERIMENTAL

Deprotonation procedure. 565 mg diisopropylamine in 70 ml dry tetrahydrofuran was treated at room-temperature with 3.5 ml of a 1.6 molar solution of butyllithium in hexane and cooled to -78°C. At this temperature a solution of 505 mg 1,4-dimethyl-2-azetidinone in 15 ml dry tetrahydrofuran was added slowly. After completion of addition the mixture was left for 3 min at -78°C and then 0.7 ml trimethylchlorosilane was added. After quenching with saturated aqueous ammonium chloride solution, extraction with ether and after evaporation the silylated β-lactam 7b was obtained in quantitative yield. ^{1}H-NMR ($CDCl_3$): δ = 0.1 [s,9H], 1.32 [d,3H], 2.73 [s,3H].

When this solution was treated with 0.5 ml propargylic aldehyde dissolved in 5 ml dry tetrahydrofuran instead of trimethylchlorosilane, warmed slowly up to -50°C and then worked up as above a 95% yield of the two stereoisomeric carbinols 11 and 13 was obtained. After separation by flash chromatography they were isolated in a 1 : 1 ratio with the less polar one (11) crystallizing from ether.

11: mp 116°C. IR (KBr): 1730, 2100, 3240 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.35 [d,3H,J = 6Hz], 2.50 [d,1H,J = 1.8Hz], 2.80 [s,3H], 3.04 [m,1H], 3.82 [q,1H,J = 6Hz, J = 2.0Hz], 4.10 [d,1H,J = 6.5Hz], 4.84 [m,1H]. MS (20°C): M^+ 153 ME (3%), 149 (12), 138 (4), 108 (13), 96 (51), 81 (100).

Anal.Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14; Found: C, 62.62; H, 7.24; N, 9.11.

13: IR ($CHCl_3$): 1730, 2100, 3300, 3350 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.33 [d,3H,J = 6Hz], 2.48 [d,1H,J = 2Hz], 2.81 [s,3H], 3.07 [m,1H], 3.70 [q,d,1H,J = 6Hz, J = 2Hz], 4.15 [m,1H], 4.76 [d,d, 1H,J = 6.5Hz, J = 2Hz]. MS (20°C): M^+ 153 ME (4%), 149 (6), 108 (10), 96 (54), 81 (100).

When the silylated β-lactam was deprotonated and subsequently treated with propargylic aldehyde as above a mixture of the two stereoisomeric vinylacetylenes 8 and 9 was gained in 90% yield and separated by flash chromatography.

8: mp 93°C. UV (CH_3OH): λ_{max} 245, 253 nm. IR (KBr): 1680, 1760, 2080, 3300 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.35 [d,3H,J = 6.5Hz], 2.90 [s,3H], 3.31 [d,1H,J = 2.5Hz], 4.12 [q,d,1H,J = 6.5, J = 1Hz], 5.50 [dd,1H,J = 2.5Hz, J = 1Hz]. MS (20°C): M^+ 135 ME (55%), 120 (57), 79 (48), 78 (100), 57 (49). Anal.Calcd for C_8H_9NO: 135.06841; Found: 135.06836. Calcd: C, 71.08; H 6.71; N 10.36; Found: C, 71.08; H, 6.70; N, 10.39.

9: mp 75°C. UV (CH_3OH): λ_{max} 251, 242 nm. IR (KBr): 1670, 1730, 1750, 2990, 3220 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.45 [d,3H,J = 6Hz], 2.90 [s,3H], 3.18 [d,1H,J = 2.5Hz], 4.15 [q,d,1H,J = 6Hz, J = 1.8Hz], 5.95 [dd,1H,J = 2.5Hz, J = 1.8Hz]. MS (20°C): M^+ 135 ME (100%), 120 (51), 79 (45), 78 (70). Anal.Calcd for C_8H_9NO: C,71.08; H, 6.71; N, 10.36; Found: C, 71.09; H, 6.72; N, 10.36.

Methyl-1,2,5-trimethylpyrrole-3-carboxylate (6): 135 mg (1 mmol) of either 8 or 9 was given to a solution of 80 mg sodium in 5 ml methanol and refluxed for 30 min. This solution was poured into a mixture of ice and saturated aqueous citric-acid and extracted with methylene chloride. After washing with saturated sodium bicarbonate solution and brine the solvent was evaporated under vacuum and the residue crystallized from ether. Yield 120 mg (72%). This substance proved to be identical (IR, NMR) with a sample prepared according to lit.[3].

Acetate 12: 306 mg (2 mmol) of carbinol 11 were left in a mixture of 10 ml acetic acid anhydride and 10 ml pyridine for 4 h at room temperature. After evaporation under vacuum the residue was several times dissolved in methylene chloride and methanol evaporated under vacuum and finally purified by flash chromatography. Yield 370 mg (90%).

IR ($CHCl_3$): 1750, 3300 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.42 [d,3H,J = 6Hz], 2.16 [s,3H], 2.52 [d, 1H,J = 2Hz], 2.81 [s,3H], 3.13 [m,1H], 3.74 [q,d,1H,J = 6Hz, J = 2Hz], 5.63 [dd,1H,J = 4.5Hz, J = 2Hz]. MS (20°C): M^+ 195 ME (3%), 153 (10), 138 (22), 135 (21), 123 (41), 96 (100), 78 (90). Anal.Calcd for $C_{10}H_{13}NO_3$: 195.88954; Found: 195.88971.

Enolacetate (16): 400 mg of acetate 12 were dissolved in a mixture of 20 ml acetic acid and 5 ml acetic acid anhydride. After addition of 200 mg silver acetate the mixture was refluxed for 5 h, evaporated under vacuum and the residue dissolved in methylene chloride. This solution was washed with brine, dried over magnesium sulfate and evaporated. The remaining yellow oil crystallized from aceton to yield 240 mg (60%) of the enolacetate 16 with mp 97°C.

UV (CH_3OH): λ_{max} 286 nm. IR (KBr): 1570, 1630, 1710 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.49 [d,3H,J = 6.5Hz], 1.98 and 2.17 [s,3H], 2.63 and 2.87 [s,3H], 5.05 and 5.35 [q,1H,J = 7Hz], 6.20 and 6.28 [tr,1H,J = 5.5Hz], 7.23 and 7.30 [m,1H], 6.39 and 6.45 [dd,1H,J = 5.5Hz, J = 2Hz]. MS (20°C): M^+ 195 ME (3%), 153 (10), 152 (100), 139 (20), 100 (6), 58 (28). Anal.Calcd for $C_{10}H_{13}O_3N$: 195.88954; Found: 195.88952. Calcd: C, 61.54; H, 6.71; N, 7.17; Found: C, 61.51; H, 6.72; N, 7.20.

When this reaction was run at 50°C for 4 h and worked up as given above two isomeric compounds were separated by flash chromatography which according to their ^{1}H-NMR and infrared spectra are 17 and 18a.

17: IR (CCl_4): 1670, 1760 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.26 [d,3H,J = 6Hz], 1.98 [s,3H], 2.13 [s,3H], 2.70 [s,3H], 2.85 [d,1H,J = 6.5Hz], 3.40 [q,d,1H,J = 6Hz, J = 2Hz], 4.80 [dd,1H,J = 6.5Hz, J = 8Hz], 5.88 [dd,1H,J = 6.5Hz, J = 8Hz], 7.13 [d,1H,J = 6.5Hz].

18: IR (CCl_4): 1670, 1760 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.35 [d,3H,J = 6Hz], 2.03 [s,3H], 2.75 [s,3H], 3.13 [d broad,1H,J = 6Hz], 3.35 [q,d,1H,J = 6Hz, J = 2Hz], 5.67 [dd,1H,J = 16Hz, J = 5.5Hz], 6.05 [dd,1H,J = 16Hz, J = 6Hz], 6.95 [d,1H,J = 5.5Hz].

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