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FUSED β-LACTAMS VIA INTRAMOLECULAR DIPOLAR CYCLOADDITION

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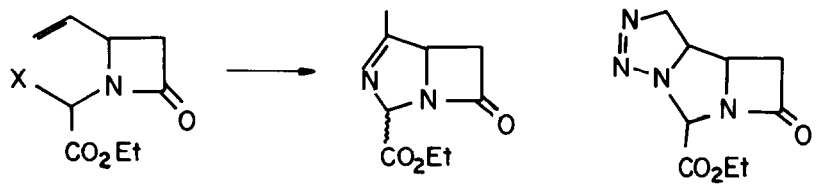
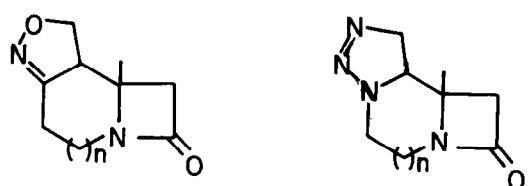
Abstract: Two routes were examined that permit conversion of 4-vinyl-2-azetidinones 7 via intramolecular nitrile oxide-olefin or azide-olefin cycloaddition into tricyclic β-lactams. Stereoselectivity in these cycloadditions as well as further chemoselective transformation of the products were shown to be dependent on the size of the newly formed ring.

The antimicrobial activity found in many new β-lactams has maintained a continuous interest in synthetic approaches to modified or fused 2-azetidinones.[2] Recently, Pearson[2a-c] as well as other workers[3] have successfully used the dipolar cycloaddition of unsaturated azido β-lactams as an entry into β-lactams fused to a heterocyclic ring. An example is provided by the conversion of 1 (X=OH) via its sulfonate into an azide 1 ($X=N_3$) and thermolysis to give 3 as a mixture of two stereoisomers. The logical intermediate 2 is usually not isolated.



1 3 2

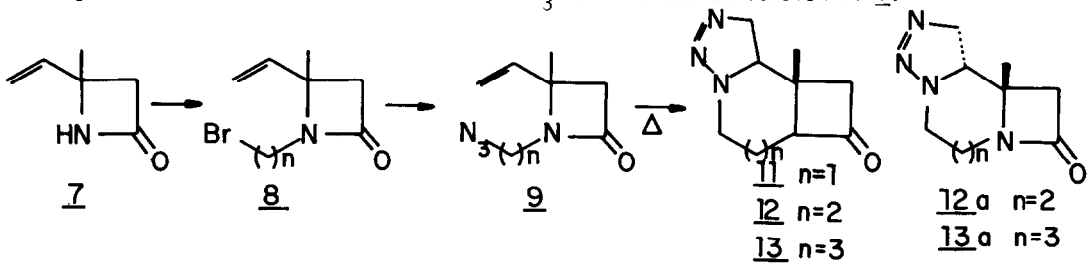
In connection with our interest in intramolecular nitrile oxide-olefin cycloadditions (INOC) and intramolecular azide-olefin cycloadditions (IAOC), we wish to report stereoselective entries into novel systems of type 5 or 6 in which the β-lactam ring is fused to a 6-, 7- or 8-membered ring (carbocyclic or heterocyclic) and contains additional functionality in the form of a third ring. Little is known about the stereochemical effect of substituents and the influence of ring size during intramolecular dipolar cycloadditions and this work also provides some interesting observations on this aspect.



5 6

Vinyl β-lactam 7 is readily available by reaction of isoprene with chlorosulfonyl isocyanate.[4] In order to introduce the required bifunctionality shown in 9 and 10, we successfully employed dibromoalkanes in the monoalkylation of 7 using KOH and $Bu_4N^+ Br^-$, adopted from

a method recently described.[5] The remaining halide in 8 was converted either into a nitro[6] or an azido function. For the latter transformation we utilized a new polymeric reagent[7] which gave much cleaner reaction than the NaN_3 used in the conversion of 1.



7 8 9 11 n=1 12 n=2 13 n=3 12a n=2 13a n=3

For instance, 8, n=2 or 3, when heated with NaN_3 in MeOH-H_2O was transformed into a mixture of 8, azide 9 and cyclized products. By contrast, shaking of 8 with polymeric azide reagent[7] at room temperature led to quantitative conversion of 8 to 9 (n=2,3,4). Azido olefin 9 (n=2) ring closed on heating in benzene (14 hr) to the tricyclic β-lactam obtained exclusively as the cis isomer 11. Stereochemical proof is provided by NOE experiments[8], ^1H and ^{13}C spectral data (see Table).

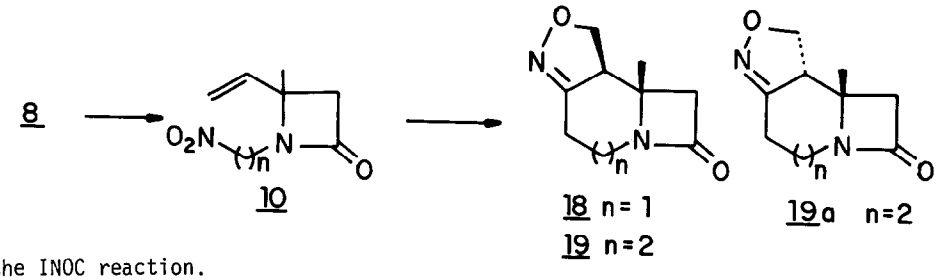
In the formation of the 7-membered ring 12, both cis and trans isomers 12 and 12a were formed, with a great preference for 12 (ratio of 12:12a = 9:1). As the ring size increases one observes a reduced selectivity as shown by formation of 13 and 13a in a ratio of 6:4, as well as a reluctance to undergo the IAOC reaction.[9] In the cis isomers the γ-effect on the Me group is evident by an upfield shift in the ^{13}C-NMR (e.g. Me in cis 13 absorbs at 15.2 ppm, while in trans 13a it is found at 20.7 ppm).

Whereas thermolysis or photolysis[11] of triazolines 11-13 resulted in a mixture of aziridine, imine and polymeric material, a smooth chemoselective transformation of these triazolines was achieved by treatment with silica gel. Interestingly, the fused 6-membered ring 11 gave exclusively imine 14, while the fused 7-membered ring 12 and 12a led to a 7:3 mixture of imine 15 and aziridine 16. The fused eight membered ring triazoline 13 (separated by chromatography on alumina) was converted on silica gel to aziridine 17 only.[10] 13a furnished an isomeric aziridine, hence the triazoline decomposition is stereospecific. Furthermore, we observed a dependence on ring size in the ease of decomposition of the fused triazolines, the order being 11>12>13.

14 n=1 15 n=2 16 n=2 17 n=3

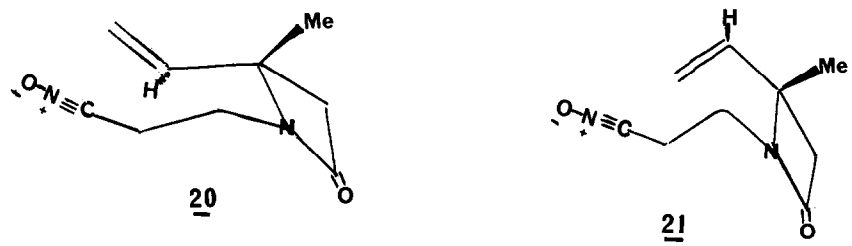
The conversion of nitro olefin 10, n=3 into a nitrile oxide, which underwent spontaneously the INOC reaction, was carried out by means of phenylisocyanate-triethylamine. In analogy to 11, exclusive formation of the cis isomer of the tricyclic isoxazoline β-lactam 18 was observed. It is interesting to note that the INOC reaction starting with 10, n=4 produced preferentially the trans isomer 19a (19:19a = 40:60). The stereochemical assignment is again based on NOE,

^{1}H and ^{13}C-NMR data. Attempts to effect the INOC cyclization on 10, n=2 and n=5 did not lead to the expected 5- and 8-membered ring annellation products. In 10, n=2, reverse Michael addition apparently occurred, whereas in 10, n=5, dimerization of the nitrile oxide takes preference. Apparently, ring closure to the 8-membered rings is more favorable for the IAOC than



for the INOC reaction.

We attribute the cis stereoselectivity during ring closure to the fused 6-membered ring system 18, as well as 11, to a preference for a chair like transition state, 20, over a boat like transition state 21. Models indicate that 20 also provides better orbital overlap of the dipolar component and olefin than does 21. As the size of the newly formed ring increases from six to seven to eight the greater conformational flexibility permits the formation of trans isomers.



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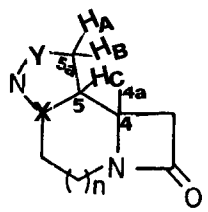
8. Irradiation of the angular methyl group gave rise to a 5% enhancement for the signal attributed to one of the methylene hydrogens in the triazoline ring. Additional evidence for the ^{1}H NMR chemical shift assignment comes from the correlation of ^{13}C-off resonance data by the graphical method.
9. Formation of 13 and 13a requires refluxing in toluene.
10. In an NOE experiment one of the aziridine methylene hydrogen signal showed 6% enhancement upon irradiation of the angular methyl group.
11. For a review of triazoline decomposition by thermolysis and photolysis see P. Scheiner in "Selective Organic Transformations" Vol. 1, p. 327-362, B.S. Thyagarajan Ed. John Wiley and Sons,1970.

TABLE

Important ^{1}H and ^{13}C NMR data[a]:



11–13, 18, 19

	11	12	12a	13	13a	18	19	19a
H_A(dd)	4.36	4.30	4.66	4.48	4.58	4.35	4.35	4.34
J_{AB} J_{AC}	16.0,11.0	16.5,12.5	17.0,12.5	17.5,13.0	17.5,12.5	11.5,9.5	11.0,9.0	10.0,9.0
H_B(dd)	3.77	3.95	c	4.02	3.95	4.21	4.14	4.19
J_{BA} J_{BC}	16.0,12.5	16.5,10.0		17.5,9.5	17.5,9.0	9.5,7.5	9.0,6.0	9,3.5
H_C(dd)	3.19	3.57	c	3.29	3.27	3.38 [b]	3.53	3.38
J_{AC} J_{BC}	12.5,11.0	12.5,10.0		13.0,9.5	12.5,9.0	11.5,7.5,1	11.0,6.0	10,3.5
CH_3(4a,s)	1.35	1.32	1.38	1.23	1.39	1.34	1.39	1.48
C-4a(q)	17.1	17.8	24.0	15.2	20.7	17.3	18.2	24.5
C-5(d)	64.2	66.4	65.5	65.6	61.3	57.2	61.0	57.5
C-5a(dd)	65.1	67.0	70.9	70.4	72.0	68.7	70.5	72.0

a. Measured on a Brucker AM300, 300 MHz NMR spectrometer, with $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are in δ ppm, coupling constants J are in Hz. d = doublet, q = quartet, b. ddd. c. difficult to assign by NMR of mixture 12 and 12a.

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