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INTRAMOLECULAR OXIME OLEFIN CYCLOADDITIONS. STEREOSPECIFIC FORMATION OF FUNCTIONALIZED PYRROLIDINES.[1]

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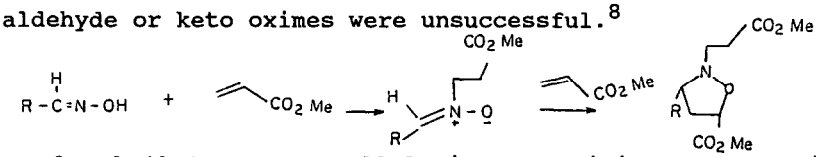
Abstract. Allylamines possessing a properly positioned aldoxime or ketoxime chain undergo thermally induced dipolar cycloaddition to bicylic isoxazolidines, with stereospecific introduction of three stereo centers. This provides an entry into stereospecifically functionalized pyrrolidines.

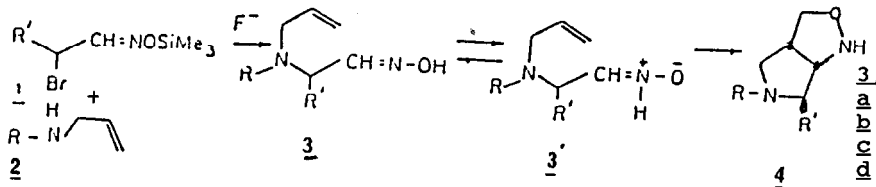
Intramolecular nitrile oxide olefin cycloadditions (INOC) have been of considerable synthetic and mechanistic interest[2], especially since the resulting isoxazoline ring can serve as a precursor to hydroxy ketones[3] or to other functional groups.[4] The related nitrone olefin cycloadditions lead to saturated isoxazolidines[5] hence to the introduction of an additional stereochemical center. Both types of cycloaddition reaction have been used increasingly in stereoselective syntheses.[6] However, nitrones react more sluggishly with alkenes than do nitrile oxides and the products contain a substituent on nitrogen which may not be desirable.

In recent elegant work, Grigg et al[7] were able to form N-substituted isoxazolidines both in inter as well as in intramolecular additions of oximes to olefins. This was achieved by converting the oximes in situ into nitrones by means of olefins bearing electron withdrawing substituents (see eq.1). Though 2-oximes of 1,2,3-tricarbonyl systems have been shown to undergo an unassisted proton transfer from O to N to generate a 1,3-dipole as a reactive intermediate, attempts to extend this cycloaddition process to simple aldehyde or keto oximes were unsuccessful.[8]



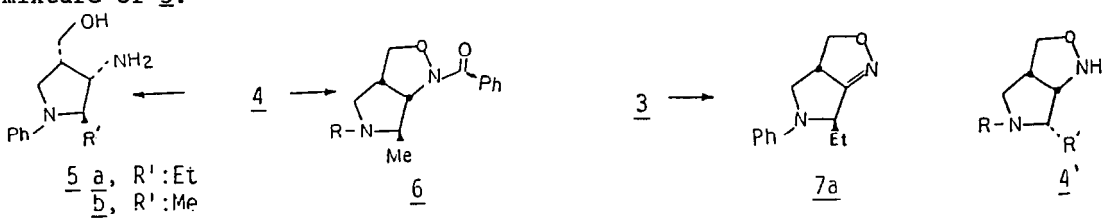
eq 1

We now found that 3a, an allylamine containing an aldoxime chain, undergoes smooth intramolecular cycloaddition to the pyrrolidino isoxazolidine 4a simply on heating at 80-110°C or even upon standing for long periods of time at room temperature. This ring closure proceeded stereospecifically to generate three adjacent stereochemical centers that provide an entry into functionalized pyrrolidines, for instance amino alcohols that do not bear a substituent on the amine function. Apparently these reactions proceed via a thermal equilibration of the oxime to its nitrone tautomer 3', which undergoes subsequent intramolecular dipolar cycloaddition.



3,4	R	R′
a	Ph	Et
b	Ph	Me
c	c-hex	Et
d	c-hex	Me
e	allyl	Et
f	allyl	Me

In order to establish the generality of this reaction and its applicability to the synthesis of pyrrolidine derivatives, we have investigated a number of closely related systems. Introduction of the required aldoxime chain into the allylamine 2a-c to give 3a-f was accomplished in 70-80% yield, by reaction with α-bromo-O-silylaldoximes 1 [9] in the presence of fluoride ions at 0-20°C. Heating of the resulting N-allylamino aldoximes 3a-f at 110°C in toluene under argon for 6-10 hr led via intramolecular cycloaddition to pyrrolidines 4a-f obtained as oils in 65-100% yield. Only one stereoisomer was isolated in high yield in all cases studied. Reductive ring opening of 4a and 4b with $LiAlH_4$ led in 75% and 82% yield respectively to pyrrolidines 5a and 5b, possessing stereospecifically positioned substituted 1,3-amino alcohol functionality. Oxidation of 3a with NaOCl-Et_3N led to isoxazoline 7a in 60 % yield, via a nitrile oxide intermediate. The advantage of oxime-olefin cycloadducts 4 over nitrile oxide-olefin adducts 7 in the stereoselective introduction of amino alcohol functionality was demonstrated by the fact that LAH reduction of 4a gave 5a as a single isomer, while reduction of 7a led to an isomeric mixture of 5.

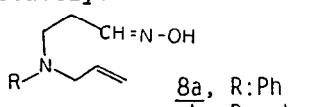


5 a, R′:Et
5 b, R′:Me

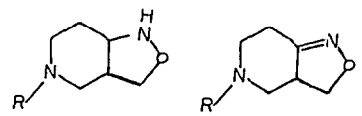
The basic structure of the products was apparent from H- and C-correlated NMR and mass spectra.[10] It is interesting to note that both the ^1H- and ^{13}C-NMR spectra of these bicyclic pyrrolidines 4 showed broad absorptions indicative of a relatively high energy barrier (probably in the order of 12-15 kcal) between conformers in this ring system. N-Benzoylation of the isoxazolidine nitrogen in 4d gave 6, mp 112-113°C which exhibited clean sharp NMR spectra. Amino alcohols 5a and 5b, formed by ring opening of 4a and 4b also showed sharp NMR spectra. This suggests that the energy barrier is due to the alpha heteroatam effect[11] which restricts rotation between the O and N atoms in the isoxazolidine ring.

Unfortunately the spectral data did not permit a stereochemical assignment to the cycloadducts 4 although only one isomer was obtained during the cyclization. However, cooling of 4e to -45°C resolved the NMR spectrum into sharper peaks which allowed a stereochemical cis-trans assignment to this adduct. When 4d was ring opened by LAH to the amino alcohol 5d, the NMR ($J_{2,3}$ 0.5 Hz) again clearly indicated a trans stereochemistry of these protons. Indeed MM2 calculations[12] confirm the stereochemical assignment showing a 3.8 kcal difference in energy between the cis-cis (4') and the cis-trans (4) isomers in favor of the latter.

It is interesting to note that, in contrast to the ease of cyclization of 4 to the pyrrolidine 5, the homologs 8 failed to undergo ring closure to piperidine derivatives 9 even at 130°C. This may be due to the longer chain which raises the overall entropy of the reaction, coupled with a low equilibrium concentration of the nitrone tautomer. On the other hand conversion of 8a and 8b to nitrile oxides by means of chloramine-T[13] did lead to INOC cyclization and formation of 10a and 10b in 61% and 51% yield respectively.



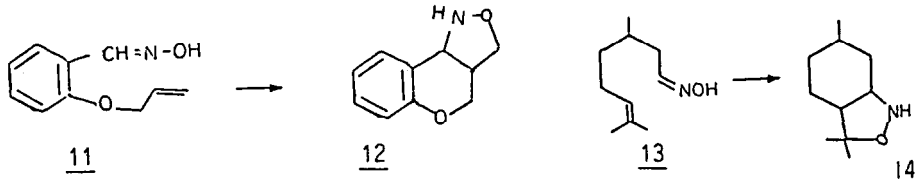
8a, R:Ph
b, R:c-hex



9

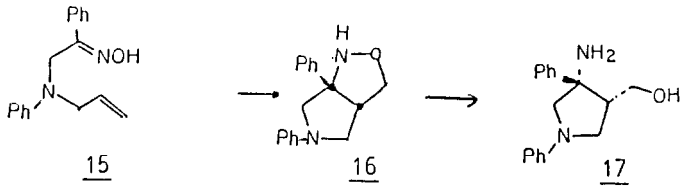
10 a, R:Ph
b, R:c-hex

It was possible to effect intramolecular oxime-olefin cyclization at 110°C, leading in low yield (ca.20%) to 6-membered rings, i.e. o-allyloxy benzaldoxime 11 12 and citronellal oxime 13 14. In fact Oppolzer[14] had previously reported the intramolecular oxime olefin cycloaddition of 11 to 12 in 20% yield by heating at 130°C. Attempts to improve proton transfer from O to N in the oxime and thus promote ring closure by means of Lewis acid or amine catalysis was successful only in the case of 13 which in the presence of $ZnCl_2$ gave 14 in improved yield (60% vs 22% on heating alone).



11 12 13 14

Furthermore, we suceeded to extend the scope of these oxime-olefin cycloadditions to the ketoxime system 15. The latter was prepared by amination of α-bromoacetophenone with the allylamine 2a. Heating of 15 at 110°C for 8 hr led to intramolecular cycloaddition with formation of the fused pyrrolidine 16 in 88% yield. Again only one stereoisomer was formed and LAH reduction led stereospecifically to amino alcohol 17. Extensions of



15 16 17

the scope and synthetic potential of these cyclizations are being investigated.

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References

1. Cycloadditions 38. For paper 37 see Hassner A., Murthy K.S.K., Padwa A., Bullock W.H., Stull P.D. J.Org.Chem. 53, 0000 (1988).
2. Confalone, P.N., Pizzolato, G., Confalone, D.L., Uskokovic, M.R. J.Am.Chem.Soc. (1980) 102, 1954; Kozikowski, A.P. Acc.Chem.Res. (1984) 17, 410 and references cited.
3. Curran, D.P. J.Am.Chem.Soc. (1982) 104, 4024; Kozikowski, A.P., Chen, Y.Y. J.Org.Chem. (1981) 46, 5248; Hassner, A., Murthy, K.S.K. Tetrahedron Lett. (1986) 27, 1407.
4. Jaeger, V., Schwab, W. Tetrahedron Lett. (1978) 3129.
5. Padwa, A. in "1,3-Dipolar Cycloaddition Chemistry", Padwa, A. Ed. Wiley-Interscience, New York, Vol 2, (1984); Tufariello, J. Acc.Chem.Res. (1979) 12, 396.
6. Kametani, T., Huang, S.D., Nakayama, A., Hondu, T. J.Org.Chem. (1982) 47, 2328; Tufariello, J. in "1,3-Dipolar Cycloaddition Chemistry", Padwa, A. Ed. Wiley-Interscience, New York, Vol 2, (1984);
7. Grigg, R., Jordan, M., Tangthongkum, A., Einstein, F.W.B., Jones,T. J.Chem.Soc. Perkin Trans I (1984) 47; Armstrong, P., Grigg, R., Warnock,W.J. J.Chem.Soc. Chem.Commun. (1987) 1327: Grigg, R. Chem.Soc.Rev. (1987) 16, 89.
8. Grigg, R., Thianpantangul, S. J.Chem.Soc. Perkin Trans. I (1984) 653.
9. Murthy, K.S.K., Hassner, A. Tetrahedron Lett. (1987), 28, 97.
10. Typical yields and spectra: 4a, yield 100%, ^{1}H-NMR($CDCl_3$,) 7.23 (2H, dd, J=9, 7.5 Hz), 6.73 (1H, t, J=7.5 Hz), 6.62 (2H, dd, J=9, 1 Hz), 3.84 (1H, d br, J=7.5 Hz), 3.75 (1H, dd, J=10, 3 Hz), 3.51-367 (1H, br), 3.46 (1H, t br, J=10 Hz), 3.25-3.37 (2H, m), 1.71 (1H, ddq, J=15, 10, 7.5 Hz), 1.38 (1H, ddq, J=15, 10, 7.5 Hz), 0.96 (3H, t, J=7.5 Hz); ^{13}C-NMR 10.29 (q), 21.61 (t), 46.36 (d), 51.67 (t), 62.78 (d), 69.86 (d), 78.77 (t), 113.02 (o-C), 117.01 p-C), 129.17 (m-C), 146.41; MS EI (% rel. abund.) $C_{13}H_{18}N_2O$ 218 (74.7, M^+), 189 (59.9), 172 (16.3), 171 (20.4), 159 (100), 145 (18), 132 (39.5).
5a, yield 82%, ^{1}H-NMR 7.22 (2H, dd, J=9, 7.5 Hz), 6.67 (1H, t, J=&.5 Hz), 6.54 (2H, dd, J=(, 1 Hz), 4.01 (1H, dd, J=11.5, 4.5 Hz, H-6), 3.87 (1H, dd, J=11.5, 6.5 Hz, H-6'), 3.47 (1H, d, J=5Hz, H-3), 3.39 (1H, t, J=9.5 Hz, H-5), 3.37 (1H, dd, J=10.5, 3 Hz, H-2), 3.31 (1H, t, J=9.5 Hz, H-5'), 2.59 (1H, tddd, J=9.5, 6.5, 5, 4.5 Hz, H-4), 2.40 (3H, s br, NH_2,OH), 1.76 (1H, dqd, J=14, 7.5, 3 Hz, H-7), 1.28 (1H, ddq, J=14, 10.5, 7.5, H-7'), 0.99 (3H, dd, J= 7.5, 7.5 Hz, Me); ^{13}C-NMR 10.97 (q), 24.3 (t), 40.99 (d), 46.81 (t), 56.66 (d), 61.11 (t), 71.22 (d), 111.6, 115.7, 129.2, 146.9. MS EI $C_{13}H_{20}N_2O$ 220 (34.8, M^+), 191 (100), 146 (35.6), 144 (21.7), 132 (22.2), 117 (2.0).
Satisfactory elemental analyses or HRMS were obtained for key new compounds.
11. Riddell, F.G., Turner, E.S., Boyd, A., Tetrahedron (1979) 35, 259.
12. Details of these calculations will be reported in the full paper. We wish to thank Prof. A. Padwa for carrying out the MM2 calculations.
13. Hassner, A., Rai, L.S. Synthesis (1988), 0000
14. Oppolzer, W., Keller, K. Tetrahedron Lett. (1970) 1117.

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