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A ROUTE TO PYRROLIZIDINES, INDOLIZIDINES AND QUINOLIZIDINES VIA INTRAMOLECULAR OXIME OLEFIN CYCLOADDITIONS [1]

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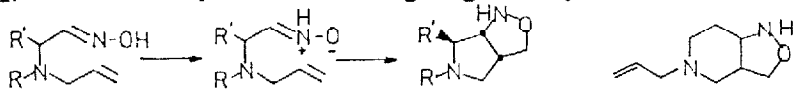
Abstract. A route to functionalized pyrrolizidines, indolizidines or quinolizidines is described. The reaction involves thermal cycloaddition of pyrrolidines or piperidines, possessing properly positioned aldoxime and alkene functions, and proceeds with stereospecific introduction of three stereo centers.

Intramolecular nitrone-olefin cycloadditions are of considerable utility in natural products synthesis.[2] Thermal dipolar cycloadditions of unsaturated oximes, which usually require the presence of Michael acceptor olefins in order to produce a nitrone intermediate, have been studied recently by Grigg and coworkers,[3] as well as by Padwa et al.[4] A few examples are known,[3b,5,6] that undergo an unassisted thermal cyclization, believed to involve a proton transfer from O to N to generate a 1,3-dipole as a reactive intermediate. For instance, we have recently[6] shown that selected oxime-olefins can undergo thermal cycloadditions leading to pyrrolidines fused to an isoxazolidine simply on heating to 80-110°C (see 1 3). These ring closures lead to stereospecific introduction of two or more stereochemical centers and presumably proceed via a tautomeric proton shift to an intermediate nitrone species 2, which is capable of undergoing the cycloaddition.



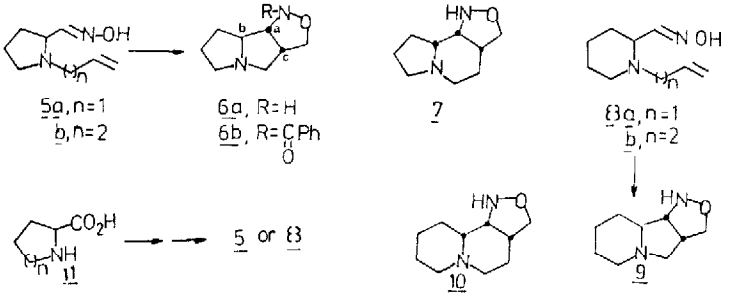
1 2 3 4

Unfortunately, the thermal ring closure while effective for formation of pyrrolidines 3, could not be applied to the synthesis of piperidines 4.

We were interested to determine if these ring closures could be used for the synthesis of functionalized fused rings such as pyrrolizidines, indolizidines and quinolizidines, since these ring systems occur widely in a number of alkaloids.[7] However, when we attempted the cycloaddition of the unsaturated pyrrolidine oxime 5 by heating in refluxing toluene or xylene (up to 140°C), virtually no ring closure was observed. Addition of metal salts[4] did not aid the cycloaddition. We now found that if 5 is heated in toluene in a sealed tube at 180°C, smooth conversion to the pyrrolizidine 6 takes place

in 60% yield.[8]

We were able to extend this reaction at 180°C in a sealed tube to the fusion of a 6-membered ring on to a 5-membered ring, e.g. 5 -> 7, and analogous reactions could be carried out with 8 and fuse unto it either a 5- or a 6-membered ring. In this manner we isolated indolizidine 9 in 76% yield by heating 8a, and quinolizidine 10 in 69% yield starting from 8b. Regioisomeric ring fused products were also synthesized (see below).



The required unsaturated pyrrolidine oximes 5 were readily prepared from proline 11 by conversion of the carboxy function to an aldoxime and introduction of unsaturation on nitrogen. This versatile method allows attachment of various unsaturated side chains that can serve for generation of functionalized 5- or 6- membered (and possibly even larger) rings.

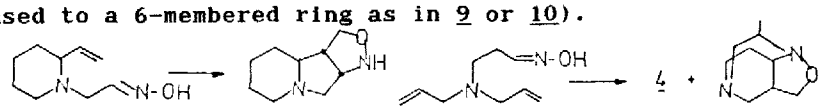
An alternate entry into unsaturated piperidine oximes 12 suitable for ring closure to indolizidines, would be the introduction of a two carbon aldoxime synthon on N, namely by reaction of 2-vinylpiperidine with an α-bromo-O-silyl aldoxime[9] or with ethyl bromoacetate. Application of this method led to formation of the oxime olefin 12 regioisomeric with 8. Here again heating at 180°C in a sealed tube was necessary to effect thermal ring closure of 12 to the indolizidine 13, which proceeded in 70% yield.

Under the above mentioned conditions, we also accomplished the previously unsuccessful ring closure of 14 to 4. In this reaction an additional product was isolated to which structure 15 (an ene reaction product of 4) was assigned.

It should be noted that the oxime-olefin cycloaddition described above is more suitable than the analogous nitrile oxide-olefin cycloaddition[10] for the synthesis of the functionalized pyrrolizidines and related fused rings, because conversion of 5a (with NaOCl) to a nitrile oxide led to ring closure in less than 10% yield.

The stereochemical outcome of the cycloadditions deserves comment. Ring closure to pyrrolidines led mainly to the cis-anti isomer (see 6, 9), while formation of the 6-membered fused piperidine produced the cis-syn stereoisomer (see 7, 10 etc). The products formed were usually stereochemically pure by NMR and tlc. Structure proof for 5-13 comes from correlated H and C-NMR and mass spectra.[11]

The ring junction between the isoxazolidine and the newly formed 5- or 6-membered ring is always cis ($J_{a,c}$ =8.5 Hz, with nearly eclipsed H_a and H_c when fused to a 5-membered ring as in 6 or 7, and $J_{a,c}$ =8.5 Hz, with gauche H_a and H_c when fused to a 6-membered ring as in 9 or 10).



12 13 14 4 15

Concerning the N-bridged rings, a trans fusion is possible in the indolizidine 7 or 9 (axial electron pair on N). It is well established[12] that in such systems, the vicinal protons oriented anti to the axial electron pair on nitrogen absorb at about 1 ppm higher field than corresponding syn protons or protons adjacent to a nitrogen bearing an equatorial pair of electrons. This is indeed observable in compounds 7, 9 and 10. Thus in 7, H_b and the axial H-6 proton are both vicinal to the bridgehead N and absorb at higher field (2.34 and 2.01 ppm respectively) than the equatorial proton at C-6 (3.02 ppm). By contrast, the pairs of protons vicinal to N in pyrrolizidine 6b absorb close to each other (one pair at 3.07 and 3.15, the other at 3.13 and 2.67) and H_b at 3.54 ppm indicative of an equatorial electron pair on N. The 3 Hz coupling constant between H_a and H_b is consistent only with anti stereochemistry and a flattened center ring in 6b, since in a syn isomer the two hydrogens would be nearly eclipsed and give rise to a much larger coupling constant.

Furthermore, the indolizidino isoxazoline 7 or the quinolizidino coumpound 10 exhibited vicinal coupling constants $J_{a,b}$ of 3 and 2.8 Hz respectively indicative of a gauche dihedral angle and therefore of syn stereochemistry between these protons. By contrast, the 8.5 Hz coupling constant between H_a and H_b in 9 reflects anti stereochemistry. This interpretation is based on an almost full analysis of the proton spectrum of 9 and comparison to the NMR of analogues which will be published elsewhere.

In a typical procedure, oxime olefin 5a (50 mg) in 3 mL of toluene was heated in a sealed tube at 180°C for 10 hr. the mixture was poured unto a basic alumina column and chromatographed (elution with chloroform) to give 35 mg (70%) of 6a as a light yellow oil, ^{1}H-NMR (300 MHz, $CDCl_3$): broad. ^{13}C-NMR (75 MHz, $CDCl_3$, broad): 24.22, 29.1, 48.59 (C-H_c), 52.87 (C-5), 57.9 (C-6), 71.1 (C-H_b), 71.8 (C-H_a) 77.35 (C-7). mass spectra EI $C_8H_{14}N_2O$ MW 154: 155 (11.5%, MH^+), 154 (4.8%, M^+), 136 (24.8), 125 (10.4%), 124 (98.4%), 123 (100%, M-HNO), 108 (38.7%), 96 (78.8%), 81 (22.2%).

Reaction of 5a with benzoyl chloride in acetonitrile gave benzamide 5b, in 80% yield, ^{1}H-NMR ($CDCl_3$): 7.80 (m, 2H), 7.41 (m, 3H), 4.80 (dd, H_a, J= 8.5, 3 Hz), 3.94 (dd, H_{7a}, J= 8.5, 2 Hz), 3.85 (dd, H_{7b}, J= 8.5, 6 Hz), 3.54 (ddd, H_b, J= 8, 6, 3 Hz), 3.36 (dddd, H_c, J= 8.5, 7.5, 6, 2 Hz), 3.14 (dd, H_{6a}, J= 12, 7.5 Hz), 3.07 (dd, H_{6b}, J= 12, 6 Hz), 3.13 (ddd, H_{5a}, J= 10.5, 6,

2.5 Hz), 2.67 (dt, H_{6b}, J= 10.5, 7 Hz), 2.24 (m, 1H), 1.8-2.0 (m, 3H). ^{13}C-NMR ($CDCl_3$, at 75 MHz): 24.67 (t), 29.61 (t), 46.31 (d, C-H_c), 53.44 (t, C-5), 57.20 (t, C-6), 67.79 (d, C-H_b), 71.99 (d, C-H_a), 74.67 (t, C-7), 127.90, 129.28, 131.43, 132.98 (arom C), 169.45 (C=O). Mass spectra $C_{13}H_{18}N_2O_2$. MW 258 m/e (%): 259 (12%, MH^+), 257 (2%, M-1), 228 (26%), 173 (23%), 153 (9%), 151 (8.5%), 123 (84%, M-PhCONO), 108 (87%), 105 (100%), 83 (60.5%).

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