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UNSYMMETRICAL DIENE-NITRONE CYCLOADDITIONS. A SYNTHESIS OF THE QUINOLIZIDINE NUCLEUS.

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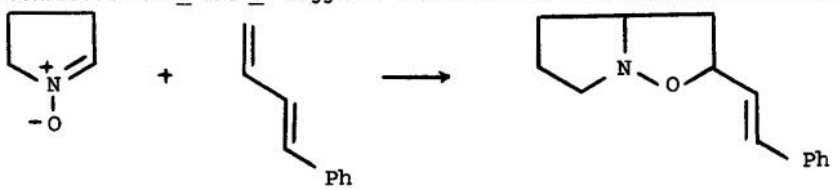
The widespread presence of the quinolizidine nucleus in nature is exemplified by its incorporation in the lupin, sparteine, matrine, Ormosia, Lythraceae, Nuphar, and pyridoquinolizine alkaloids[1]. We have previously recorded an entry into the lupin class (i.e. lupinine and epilupinine) using a nitrone-incorporating annelation procedure[2]. It is noteworthy that a 4-substituted quinolizidine moiety is present in certain of the alkaloids (decinine[3], deoxynupharidine[4]) of the Lythraceae and Nuphar classes. Thus, we report herein a new nitrone-based entry into the quinolizidine system, incorporating provisions for the 4-substituent present in these alkaloids. Our synthesis utilizes a highly regioselective and site-selective nitrone-diene cycloaddition. Although the regioselectivity of intermolecular nitrone-alkene cycloadditions has been the subject of considerable discussion[5], the corresponding additions to unsymmetrical conjugated dienes have received little attention. For our exploratory study, we chose to investigate the additions of 1-pyrroline-1-oxide(1) and 3,4,5,6-tetrahydropyridine-1-oxide (2), readily available from the corresponding hydroxylamines using a mercuric oxide oxidation procedure[2], to trans-1-phenyl-1,3-butadiene (3)[6].

In principle, the cycloadditions could proceed at either olefinic center. Indeed, a consideration of regiochemical and stereochemical factors, in addition to site-selectivity, suggests the possible formation of eight isomeric monoadducts. In spite of the paucity of literature examples regarding such diene additions, certain predictions have been made using a perturbation-based molecular orbital approach. Thus, a frontier orbital treatment[7,8] suggests that 1-substituted-1,3-butadienes with conjugating substituents (e.g. phenyl) should undergo cycloaddition to the less substituted double bond, a prediction reinforced by a consideration of steric factors[5]. Moreover, these theoretical treatments predict that the cycloadditions should proceed with definable regiochemistry[7] to afford, for example, isoxazolidine 4 from nitrone 1, and adduct 5 from nitrone 2.

In accord with the predictions based in frontier orbital considerations, the cyclization of nitrone 1 with trans-1-phenyl-1,3-butadiene (3)[6] gave 5-substituted isoxazolidine 4, presumably as a mixture of diastereomers, in 61% yield. That the adduct is 4 and not its regioisomer (i.e. 6) can be ascertained from its pmr spectrum which exhibits a quartet at δ 4.67 ppm (1H, J = 7 Hz). Adduct 6 would be expected to show a two-proton multiplet in this region of the spectrum. The related cycloaddition of diene 3 with the six-membered ring nitrone 2 gave the expected isoxazolidine 5 (94% Yield) which exhibits a one-proton multiplet at δ 4.68 ppm in its pmr spectrum ($CDCl_3$, TMS). The appearance of the pmr spectra of both isoxazolidines 5 and 4 suggests that both are diastereomeric mixtures but that both possess



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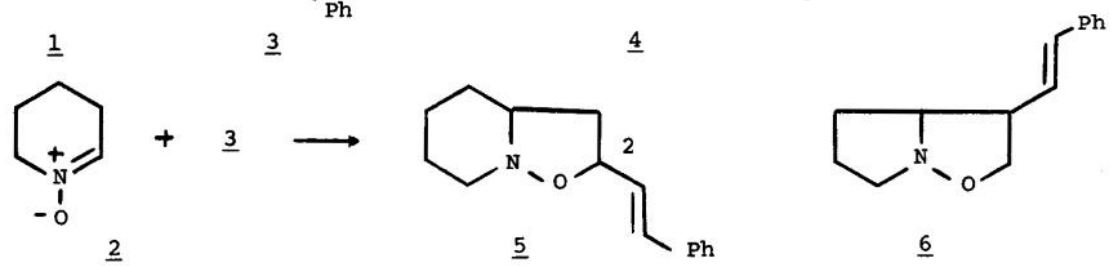
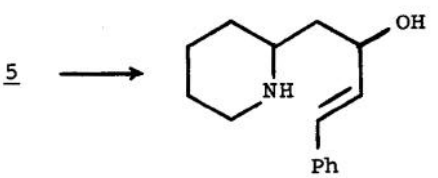


2 5 6

regiochemical integrity. Fortunately, the diastereometric mixture obtained does not adversely affect the synthesis of the quinolizidine nucleus since an oxidation step is involved at a subsequent stage (vide infra) which eliminates the chirality at C-2.

The reductive fission of the nitrogen-oxygen bond in 5 with zinc in 50% aqueous acetic



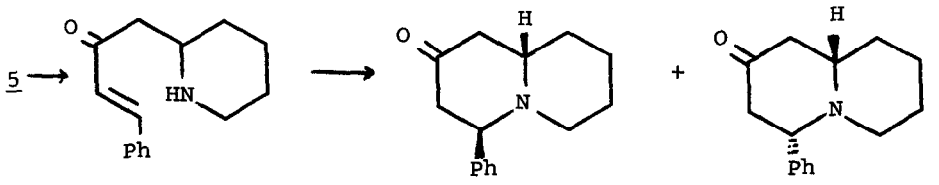
5 7

acid produced amino alcohol 7 in 93% yield. The amino alcohol (pmr($CDCl_3$) δ 8.44 (s,2), 7.07 (m,5), 6.48 (d,1 J = 16 Hz), 6.04 (dd, 1,J = 16 Hz, J' = 4 Hz), 4.48 (m,1), 1.03-3.64 ppm (m,11)) displayed its NH and OH infrared stretching bands at 2.79 and 3.12 μ, respectively.

Our next objective involved the oxidation of the allylic alcohol moiety in 7 to the corresponding α,β-unsaturated ketone (8) without protecting the amino grouping. A subsequent Michael reaction would then produce the desired quinolizidine system (i.e. 9 and 10[9]). We were gratified to find that the oxidation of 7 with activated manganese dioxide[10] (CH_2Cl_2, 1

hour, 25°C) led to the formation of a 76% yield of quinolizidines 9 and 10 as a 2:1 mixture, respectively. This mixture could be readily separated by column chromatography on silica gel (95:5, benzene-acetone) and the individual constituents possessed spectral properties virtually identical to those previously reported for cis- and trans-4-arylquinolizidin-2-ones[9,11,12] Thus, cis-4-phenylquinolizidin-2-one (9) exhibits a pmr ($CDCl_3$) signal at δ 4.21 ppm (dd, 1,J = 6, 4.5 Hz)[9,11] while its trans-isomer 10 displays the corresponding signal at δ 3.20 ppm (dd, 1, J = 12, 3.5 Hz)[9,11]. Moreover, the trans-quinolizidine 10, but not 9, reveals Bohlmann bands (3.58 and 3.61 μ)[9,11,12] in its ir spectrum. The mass spectrum (70 ev) of trans-4-phenylquinolizidin-2-one (10), m/e 229 (M^+) and 84 (100), is consistent with that of a 4-arylquinolizidin-2-one[11,12].

The quinolizidine 9 was epimerized to 10 (97% yield) using sodium hydroxide in methanol[11,12]. We have since carried out the epimerization process on the crude product mixture



8 9 10

obtained from the manganese dioxide oxidation and obtained isomer 10 exclusively, as determined by pmr and tlc examination, in 72% yield from the amino alcohol 7.

The methods described above provide an efficient entry into the 4-substituted quinolizidine system present in a host of alkaloids. We are currently extending our synthetic efforts in those directions.

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