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SYNTHESIS OF INDOLIZIDINES BY THE 1,3-DIPOLAR CYCLOADDITION OF AZIDES WITH METHYLENECYCLOPROPANES FOLLOWED BY CYCLOPROPYLIMINE REARRANGEMENT

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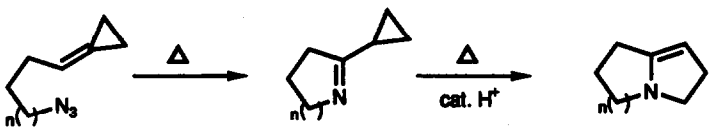
Abstract: Cyclic imines **6a** and **6b** were obtained by the intramolecular 1,3-dipolar cycloaddition of azides with methylenecyclopropanes. Acid catalyzed rearrangement produced bicyclic enamines **7**, which upon reduction provided indolizidines **8**. A similar strategy was used for the synthesis of (-)-8a-epi-desacetoxyslaframine **16**.

The acid catalyzed rearrangement of cyclopropylimines to pyrrolines has been known for over 60 years.[1] Stevens used this rearrangement for the synthesis of a variety of pyrrolidine containing natural products,[2] and other groups have since reported related studies.[1,3] We have been interested in the use of bicyclic enamines for the synthesis of pyrrolizidine and indolizidine alkaloids, and felt that an attractive route to these materials would be possible by the route shown below.[4] Intramolecular 1,3-dipolar cycloaddition of an azide **1** onto a methylene-cyclopropane[5] would provide an intermediate triazoline, which could extrude nitrogen with concomitant 1,2-hydrogen shift[6] to produce a cyclopropylimine **2**. Acid catalyzed rearrangement of **2** would produce the desired bicyclic enamine **3**. Conceptually, the transformation of **1** to **3** could be carried out in one vessel if the acid catalyst were present at the outset of the reaction.



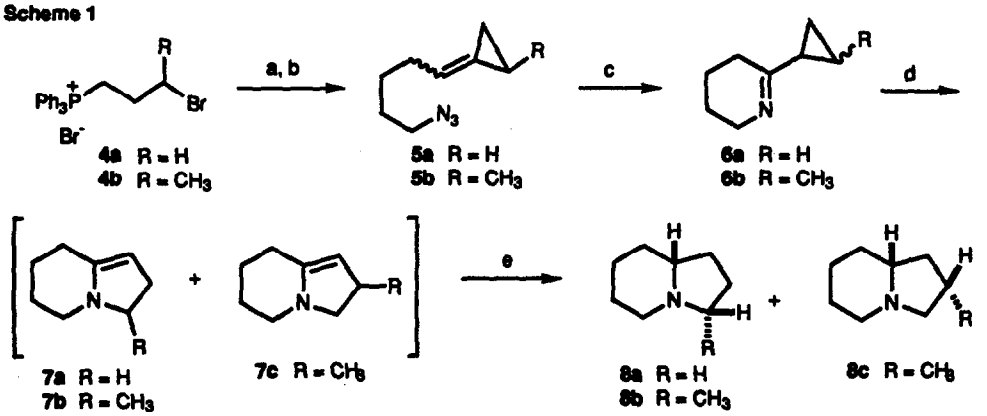
1 **2** **3**

Although cyclopropylimine rearrangements are well known, close precedent for the rearrangement of **2** to **3** is sparse. Examples using simple cyclopropanes are rare, especially with nonaromatic imines.[1,2] Generally, the cyclopropane carbon attached to the imine is substituted by groups such as arylthio,[2,3c] dialkylamino,[3b-d] alkoxycarbonyl,[2,3a,f,4] aryl[2] or vinyl.[1,3g,h] Examples of the acid catalyzed cyclopropylimine rearrangement using cyclic imines are uncommon and require a carboethoxy substituted cyclopropane.[3a,d,f]

Cyclopropyl ylides derived from cyclization of phosphonium salts **4a** and **4b**[7] were used in conjuction with 5-hydroxypentanal to provide two simple cyclization precursors **5a** and **5b** (Scheme 1). Cyclization of either substrate was found to be solvent dependent, with the best yields of cyclopropylimines **6a** and **6b** resulting from the use of polar solvents such as DMF. Nonpolar solvents such as benzene led to the formation of several by products. The rearrangement of imines **6a** and **6b** proceeded in benzene at 145° in the presence of a catalytic amount of ammonium chloride to produce the bicyclic enamines **7**. These compounds were not isolated due to their sensitivity, but ^{1}H NMR analysis showed their presence along with small amounts of products apparently derived from acid catalyzed self condensation of the enamines.[8] Hydrogenation produced δ-coniceine **8a**[9] and the 3- and 2-methylindolizidines **8b** and **8c** in a 1:3 ratio. Attempts at direct cyclization of **5a** or **5b** to enamines **7** were unsuccessful, since the initial 1,3-dipolar cycloadditions and the subsequent NH_4Cl catalyzed rearrangements were best carried out in solvents of different polarity.[10]

The rearrangement of **6b** was of special interest since the regioselectivity of the rearrangement of unsymmetrically substituted cyclopropanes has not been studied. In addition, indolizidines of the type **8b** would be useful for the synthesis of a variety of alkyl substituted alkaloids such as monomorine. The mechanism of the acid catalyzed rearrangement of cyclopropylimines is proposed to be N-protonation followed by a homoconjugate addition of chloride ion, resulting in an intermediate γ-chloroenamine. This then cyclizes by an intramolecular N-alkylation.[1,2] The predominance of 2-methylindolizidine **8c** (35% overall from **6b**) over the 3-methyl isomer **8b** (12%) after reduction supports such a mechanism, since chloride ion attack would be expected to occur at the least hindered cyclopropane carbon. An alternative mechanism where the cyclopropyliminium ion undergoes ionization prior to chloride ion attack would be expected to produce **8b** as the major product via a more stabilized cation. One diastereomer of each indolizidine **8b** and **8c** was observed by ^{13}C NMR. The stereochemistry of **8b** was determined by comparison with literature chemical shift values.[11] The stereochemistry of **8c** was not determined, but presumably results from the addition of hydrogen from the least hindered face of the enamine, producing the isomer shown.[12] The effect of reaction conditions, cyclopropane substitution and stereochemistry on the regioselectivity of these cyclizations are currently under examination.

Scheme 1



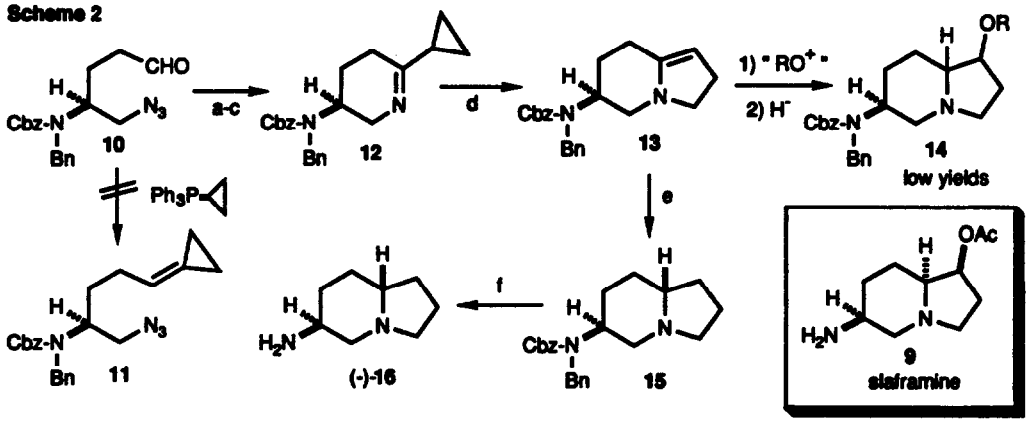
(a) For **4a**: 2 eq. KO^{t}Bu, THF, reflux, 3h; add 5-hydroxypentanal, reflux 17h, 84%. For **4b**: 2 eq. NaH, THF, 25°; add 5-hydroxypentanal, reflux 18h, 86%, ca. 1:1 mixture of *E* and *Z*. (b) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 25°, 1h; NaN_3, DMF, 25°, 24h. **5a**, 96%; **5b**, 60%. (c) DMF, 120°, 17h. **6a**, 66%; **6b**, 60%, ca. 3:1 mixture of isomers. (d) PhH, cat. NH_4Cl, sealed tube, 145°, 4h for **7a**; 20h for **7b/7c**. (e) H_2 (1atm), cat. PtO_2, Et_2O, 25°, 8h. **8a**, 42% overall from **6a**. **8b+8c**, 47% overall from **6b** (1:3 mixture).

To further explore the potential of this cyclization sequence, an approach to slaframine **9** was attempted (Scheme 2). A bicyclic enamine such as **13** could allow the introduction of the required acetoxy group. Slaframine is a potent cholinomimetic isolated from the fungus *Rhizoctonia leguminicola*.[13,14] The aldehyde **10** was prepared in optically active form from glutamic acid.[15] Attempted formation of methylenecyclopropane **11** proved to be unsuccessful due to the very low reactivity of cyclopropylidinetriphenylphosphorane.[7] A simple alternative was the addition of cyclopropyllithium, oxidation of the resultant alcohol and an intramolecular Staudinger reaction,[17] affording the cyclopropylimine **12**. Upon subjection of this imine to the normal rearrangement conditions, enamine **13** was produced and was best used without purification. A variety of electrophilic oxygen sources were used to

attempt the conversion of 13 into an iminium ion, which upon reduction with sodium borohydride would produce 14. For example, oxidation of 13 with benzoyl peroxide, mCPBA or 2-(phenylsulfonyl)-3-phenyloxaziridine was followed by sodium borohydride. Low yields of derivatives 14 of undefined stereochemistry were observed, even though model studies on 1-pyrrolidinocyclohexene were successful in such a transformation.[18]

Although this route to slaframine was unsuccessful, reduction of 13 with acidic $NaBH_3CN$ produced the indolizidine 15 as a single stereoisomer in 66% overall yield from 12. Deprotection of 15 gave 8a-epi-desacetoxyslaframine 16, $[\alpha]_D^{20}$ -10.5° (c= 0.64, 3 N HCl),[20] which should be useful for SAR studies on slaframine. The overall efficiency of the cyclopropylimine rearrangement is considerably higher in this case than the examples in Scheme 1.

Scheme 2



(a) c-C_3H_5Li, Et_2O, -78°, 30min 89%. (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78° (2h), 25° (1h), 85%. (c) Ph_3P, THF, 25°, 18h, 78%. (d) 145°, xylene, cat. NH_4Cl, 2h. (e) $NaBH_3CN$, AcOH, 0° (1h), 25° (18h), 66% from 12. (f) H_2 (1atm), cat. 10% Pd/C, AcOH, 25°, 6h, 73%.

In summary, cyclic imines bearing simple unsubstituted (or alkyl substituted) cyclopropanes bear promise for the synthesis of indolizidine alkaloids, whether obtained by intramolecular azide cyclizations with methylenecyclopropanes or by more conventional imine formation methods.

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10. Whereas polar solvents were best for the 1,3-dipolar cycloadditions, nonpolar solvents such as benzene and xylene were crucial for the acid catalyzed cyclopropylimine rearrangement. The rearrangement in a polar solvent such as DMF led to decomposition.
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12. ^{13}C NMR of 8c (75 MHz, $CDCl_3$): δ 65.6, 61.2, 53.1, 40.5, 30.7, 29.1, 25.2, 24.2, 22.0.
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15. Azidoaldehyde **10** was prepared from N-benzylglutamic acid[16] by the following sequence: (1) $PhCH_2OCOCl$ (Cbz-Cl), $NaHCO_3$, H_2O, 67%. (2) 2 eq. BH_3THF, THF, 25°, 18 h, 60%. (3) 0.6 eq. $Me_2tBuSiCl$, pyridine, 88%. (4) $(PhO)_2P(O)N_3$, $EtO_2CN{=}NCO_2Et$, Ph_3P, 83%. (5) nBu_4NF, THF, 96%. (6) $(COCl)_2$, Me_2SO, Et_3N, 92%.
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18. Although oxidation of enamines with such reagents is known to afford α-hydroxyketones after hydrolysis,[19a-c] reduction of the intermediate iminium ions to give β-aminoalcohols is rare.[19d] We have observed that the reaction of 1-pyrrolidinocyclohexene with mCPBA followed by reduction with $NaBH_4$ gave 2-pyrrolidinocyclohexanol (41%).
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20. Data for **16**: ^1H NMR (300 MHz, DMSO-d_6) δ 3.22 (dd, 1H, J=9.9, 3.4 Hz), 3.01 (m, 1H), 2.9 (dt, 1H, J=7.8, 2.5 Hz), 1.97 (m, 3H), 1.81-1.57 (m, 5H), 1.33-1.1 (m, 3H). ^{13}C NMR (90 MHz, DMSO-d_6) δ 62.5, 54.4, 52.8, 47.1, 29.3, 28.6, 28.1, 20.9. J_{H6H5ax} (10 Hz) and J_{H6H5eq} (3.4 Hz) as well as H_6 $W_{1/2}$ = 24 Hz, (c.f. slaframine equatorial H_6 $W_{1/2}$ = 7 Hz) indicates that H_6 is axial in **16**. No NOE was observed between H_6 and H_{8a}, providing evidence for a trans relationship of these two hydrogens. This stereochemistry is consistent with axial hydride delivery to an iminium ion.

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