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DIRECTING AND STABILIZING EFFECTS OF SUBSTITUTED ACETYLENES IN HETEROCYCLISATION. EFFICIENT SYNTHESIS OF PYRROLIZIDINE ALKALOIDS.

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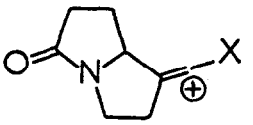
Abstract: (±)-Trachelanthamidine and (±)-isoretronecanol have been synthesized via reductive cyclisation of the phenylthioacetylene imid 5.

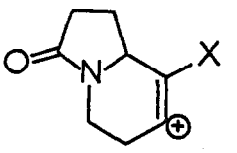
The overall high reactivity of the cyclic α-acyliminium ion towards triple bonds has been proven of great practical value in biogenetic heterocyclisation[1]. Acetylene ring closure, however, is not always site specific although a substituted triple bond located in a 5,6 relationship to a developing cationic centre strongly prefers to form a five-membered ring[2].

The occurrence of a wide variety of alkaloids of the pyrrolizidine type coupled with the current high interest in its synthesis[3] necessitated the development of a method for preferential formation of five-membered rings. The latter objective is achieved via the introduction of suitably functionalized triple bond synthons[4] as is exemplified by a short and efficient synthesis of (±)-trachelanthamidine and (±)-isoretronecanol.

As was envisaged on the basis of previous experiences substitution of the terminal acetylene hydrogen atom by a group X capable of stabilizing an exocyclic vinyl cationic species A could lead to pyrrolizidine derivatives. In the latter way the slightly unfavorable ringstrain effects associated with the intermediacy of A thereby favouring the endocyclic species B are adequately compens-



A

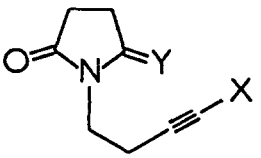


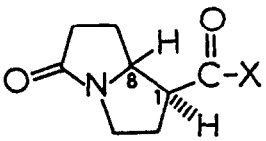
B

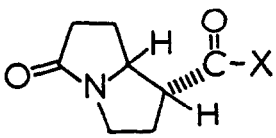
ated by mesomeric stabilization of the linear vinyl cation[5].

Indeed it was found that for X = phenyl exclusive formation of pyrrolizidine products occurred. Thus upon reduction of the imid 1[6] and cyclisation of the so-obtained ethoxylactam 2 in formic acid (144 hr, r.t.) and subsequent acid hydrolysis (2M HCl) a quantitative formation of a 55:45 mixture of the epimers 3 and 4 was observed. According to ^{1}H NMR and TLC analysis no trace of a 5,6 fused product appeared detectable. Base treatment of the epimer mixture (K_2CO_3/ DMF, 96 hr, r.t.) effected a complete isomerisation of 4 into 3. M.p. 3 91-93°C (diisopropylether), ^{1}H NMR ($CDCl_3$): δ 7.38-8.02 (m, 5H, ArH); 4.34 (m, 1H, H_8, $J_{1,8}$= 8.0 Hz); 3.76 (m, 1H, H_3); 3.50 (m, 1H, H_1); 3.21 (m, 1H, H_3); 2.15-2.87 (m, 4H); 1.71-2.00 (m, 1H, H_7). No attempt to purify 4 was made while tentative assignment of stereochemistry of 3 occurred on the basis of a 360 MHz ^{1}H NMR analysis and upon comparison with other results (vide infra).

Upon substitution of X = Sphenyl and following the analogous procedure for the imid 5[6] the conversion (HCOOH, r.t. 72 hr 1.5 M HCl) of the ethoxylactam 6 furnished a 4:1 mixture of epimers 7 and 8 in 80% yield after purification. Chromatographic separation afforded the pure C-1 epimers: 7, m.p. 69.0-70.5° (ether), ^{1}H NMR ($CDCl_3$): δ 7.42 (m, 5H, ArH); 4.11 (m, 1H, H_8), $J_{1,8}$= 8.2 Hz); 3.67 (m, 1H, H_3); 3.22 (m, 1H, H_3); 2.88 (m, 1H, H_1); 2.78-2.67 (m, 1H, H_6); 1.96 (m, 1H, H_7). The data of 8 are: m.p. 94.5-95°C (dip), ^{1}H NMR ($CDCl_3$): δ 7.36 (m, 5H, ArH); 4.16 (m, 1H, H_8, $J_{1,8}$= 7.2 Hz); 3.75 (m, 1H, H_3); 3.25 (m, 1H, H_1); 3.06 (m, 1H, H_3). The $J_{1,8}$ values were determined from a 250 MHz ^{1}H NMR analysis. Of additional interest in this cyclisation is the fact that the synthetically valuable phenylthioesters[8] are formed and can be isolated which may be of



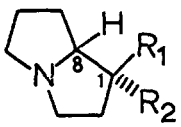




1 X = Phenyl ; Y = O
2 X = Phenyl ; Y = H, OEt
5 X = SPhenyl ; Y = O
6 X = SPhenyl ; Y = H, OEt

3 X = Phenyl
7 X = SPhenyl

4 X = Phenyl
8 X = SPhenyl



9 $R_1 = CH_2OH$; $R_2 = H$
10 $R_1 = H$; $R_2 = CH_2OH$

further use in the synthesis of more complex systems.

The trans $H_{1,8}$ configuration of 7 is ascertained by LAH-redn (4 hr, 70°C, THF) to (±)-trachelanthamidine (9); m.p. picrate 173-174.5° (ipa)[9], spectral data in accordance with literature assignments. Similarly 8 was reduced to (±)-isoretronecanol (10)[3b]; m.p. picrate 189-191°C (EtOH).

The foregoing results convincingly demonstrate the utility of α-acyliminium ions in this conceptually new type of heterocyclisation.

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6. The starting imides are obtained via the oxidation-reduction coupling technique[7] of succinimide with the appropriate alcohols. 1-Phenylbut-1-yn-4-ol is easily prepared by reaction of lithium phenylacetylide with ethyleneoxide followed by hydrolysis.
Phenylthiolation of the dianion of but-3-yn-1-ol with diphenyldisulfide yields 1-phenylthio-1-but-1-yn-4-ol.
All new compounds gave correct analytical data.

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