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Stereoselectivity in The Cyclisation of Photoinduced Electron Transfer (PET) Generated Cyclic α -Amino Radicals: First General Stereoselective Entry to 1-Azabicyclo (m:n:o) Alkane Systems

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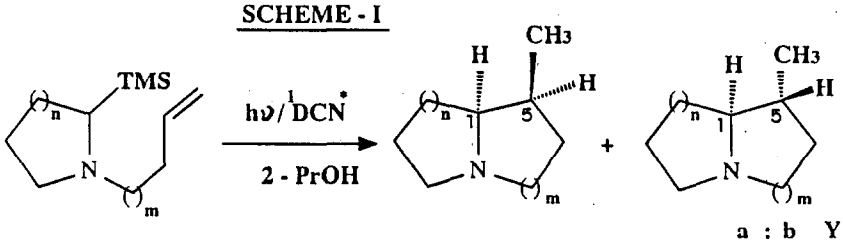
Abstract: *Stereoselectivity in the intramolecular cyclisation of PET-generated cyclic α-amino radicals and its application to the synthesis of 1-azabicyclo (m:n:o) alkane systems is reported.*

Although carbon-carbon bond formation strategy for carbocyclisation via radical reactions has grown enormously during the past decade[1], the use of α-amino radicals in the construction of N-heterocycles is limited[2]; though they constitute the most ubiquitous heterocyclic ring systems endowed with biological activity. This limitation may be attributed mainly to the difficulty in generating α-amino radicals for efficient heterocyclisation[3]. The use of α-acylamino or β-amino radicals[4,5], generated by conventional reductive cleavage of -C-X (X= Se, S, halogen) bond using tributyl tinhydride, has circumvented this problem to the large extent but difficulty associated in precursor synthesis coupled with removal of toxic tin residue from the reaction mixture has restricted their practical utility. We[6] and Mariano etal[7] have reported recently α-amino radical generation from PET promoted desilylation of α-methyl silyl amines via longer lived solvent separated ion pairs (SSIP). However, in sharp contrast to carbocyclisation stereochemistry of 3-substituted hex 5-enyl radicals[8], cyclisation of analogous acyclic α-amino radicals was found to be non-stereoselective possibly due to low energy barrier between the two "chair like " transition states[9,10]. In this communication we extend our study

SCHEME - I



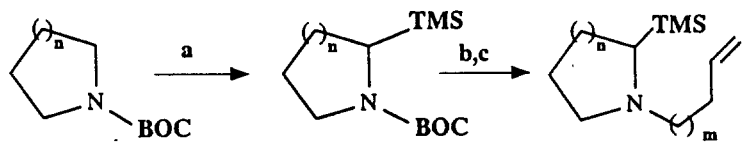
			a : b	Yield (%)
1	n = m = 1	5 a	5 b	97 : 3	90
2	n = m = 2	6 a	6 b	0 : 100	88
3	n = 1, m = 2	7 a	7 b	2 : 98	85
4	n = 2, m = 1	8 a	8 b	95 : 5	87

to probe the stereoselectivity of cyclic α-amino radical cyclisations from silylamines (1-4) and also to dem-

onstrate a general stereoselective synthetic methodology for wide spread biologically active quinolizidine, indolizidine and pyrrolizidine ring systems [1-azabicyclo (m:n:o) alkanes][11]. Our results, are summarised in SCHEME-I.

The starting silyl amines (**1-4**) were synthesized (>90% yield overall) by following the simple steps as shown in SCHEME-II.

SCHEME - II



9 **10** (95 %) **1 - 4** (90 %)

a) i) Sec-Bu Li / TMEDA, ether, -78°C, TMSCl, 3h

b) TFA, DCM, 5°C, 30 min

c)  . CH_3CN, K_2CO_3, reflux, 2h

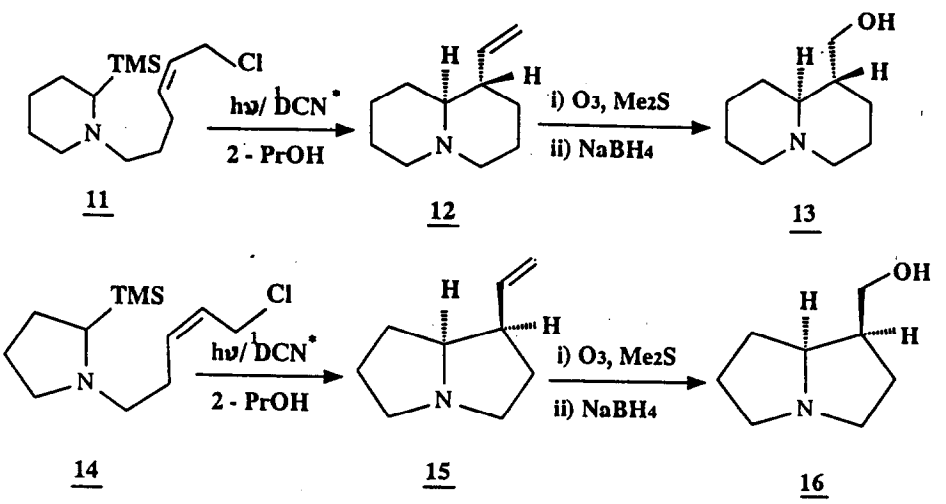
In general we used a photolysis procedure similar to the one used by us for earlier reactions[6]. Irradiation (2-3 hrs) of a 2-propanol solution of amines **1-4** (15 m.mol) and 1,4-dicyanonapthalene (DCN, 4.5 m.mol) through a pyrex filter light (>280 nm, all light absorbed by DCN) with 450-W Hanovia medium pressure lamp, without removing dissolved oxygen from the solution and usual workup and chromatographic purification gave corresponding cyclized products (**5a-8b**) in high yields (85-90%)[12] with quantitative recovery of DCN[13]. The products were characterised by ^1H NMR, ^{13}C NMR and mass spectral analysis.

This cyclisation strategy gave efficient entry to 1-azabicylo ring (m:n:o) systems **5a-8b** with remarkable regio-and stereoselectivity. The diastereomeric ratios of these products were determined by capillary GC (methyl silicone, fused silica, 25 mts) analysis. The diastereomers have also been resolved in pure form by column chromatography. The 1,5-stereochemistry of major diastereomers **5a, 6b, 7b** and **8a** is ascertained by comparing the ^{13}C NMR chemical shift values of methyl group for major and minor isomers. This may be illustrated here by taking **5** as an example. In the ^{13}C NMR of **5a** methyl signal appeared[14] at δ 13.07, whereas in **5b** it was present at δ 14.86. Since it is well known that within a given series the sterically more congested methyl group (axial) always appears upfield[15], therefore the major isomer (**5a**) can be assigned with 1,5-cis stereochemistry whereas minor isomer **5b** with 1,5-trans. This assignment is further supported by comparing the ^{13}C and ^1H NMR values of **5a** with natural product (±)-heliotridane[16,4b].

The 1,6-trans stereochemistry of **6b** is suggested based on the similar pattern by observing the low field ^{13}C chemical shifts[17] for CH_3 group at δ 18.00 which is further confirmed by noticing C_5 chemical shift at δ 34.00 as reported for the lupin series of alkaloids[18]. The stereochemistry of other compounds (**7a-8b**) have been suggested following the similar logic.

In order to demonstrate the synthetic potential of these findings and to confirm our stereochemical assignments, biologically active natural products (±)-epilupinine(13), and (±)-isoretronecanol(16) were synthesized by following the steps as shown in SCHEME III. The comparision of ^{1}H NMR and ^{13}C NMR spectra

SCHEME - III



of these products with the reported values[19,4a] confirmed our stereochemical assignments.

From the above observations it may be concluded that ring closure stereochemistry of cyclic α-amino radicals is more stereoselective compared to acyclic analogue and depends upon the size of the new ring formed i.e 1,5-stereochemistry is predominantly cis (**5a, 8a**) while 1,6-is exclusively trans (**6b, 7b**).

These diastereoselectivities can be rationalised by invoking the "chair-like" transition state analogous to the ring closure of cyclic 2-but-3 enyl cyclo alkyl radicals[8,20]. The origin of trans-stereochemistry of **6b** may also involve "chair-like" transition state but for effective overlap between the MO of the radical center and olefin π-orbitals 1,6-trans stereochemistry results[8,20].

Based on the above strategy total synthesis of (±)-Tashiromine[21] and (±)-Platynecine[22] is in progress and will be published alongwith the full stereochemical details later.

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12. Isolated yields, not optimised.

13. True sensitized role of DCN in PET reaction of amines have been discussed in ref.10.

14. Spectral data of **5a** ^{1}H NMR (200 MHz, $CDCl_3$) : 1.07 (d, J = 6.9 Hz, 3H); 1.3 - 1.4 (m, 2H); 1.6 - 1.8 (m, 2H); 1.9 - 2.2 (m, 2H); 2.4 - 2.6 (m, 1H); 2.7 - 2.85 (m, 1H); 2.95 - 3.1 (m, 1H); 3.4 - 3.6 (m, 1H); 3.85 - 3.95 (m, 1H); 4.12 - 4.3 (m, 1H). ^{13}C NMR (50.4 MHz, $CDCl_3$): 70.07, 55.85, 53.65, 34.4, 30.31, 25.5, 25.4, 13.07. MS M$^+$ 125, 110, 97, 83, 55.

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17. Spectral data of **6b** ^{1}H NMR (200 MHz, $CDCl_3$): 0.9 (d, J = 6.8 Hz, 3H); 1.5 - 2.2 (m, 11H); 2.3 - 2.4 (t, 1H); 2.55 - 2.75 (m, 2H); 3.35 - 3.55 (m, 2H). ^{13}C NMR (50.4 MHz, $CDCl_3$): 69.9, 55.87, 55.7, 34.0, 31.5, 26.6, 22.5, 22.37, 22.28, 18.0. MS M$^+$: 153, 138, 98, 55, 41.

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