Tetrahedron Letters,Vol.30,No.44,pp 6059-6062,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

PHOTOINDUCED SET GENERATION OF α-AMINERADICALS : A PRACTICAL METHOD FOR THE SYNTHESIS OF PYRROLIDINES AND PIPERIDINES

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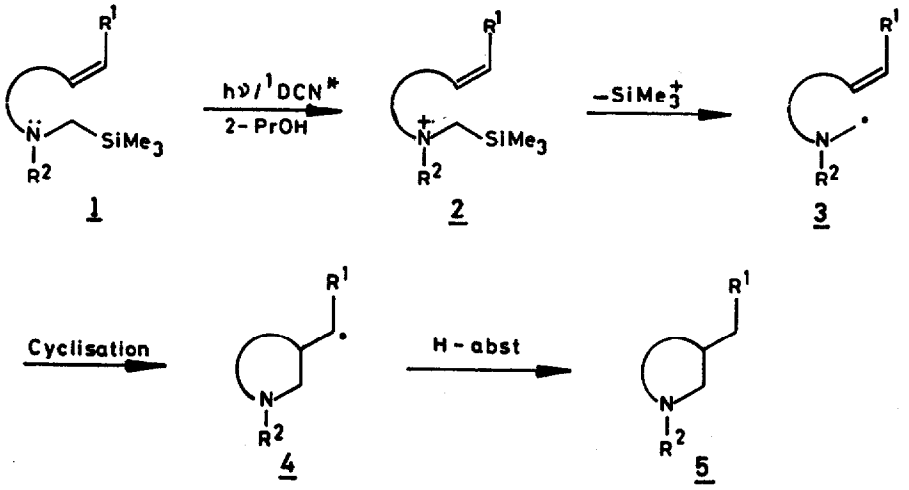
ABSTRACT: Selective desilylation to generate α -amineradicals from α -alkyl silylamine radical cation and their intramolecular cyclisation is reported.

In our ongoing research programme of photoinduced SET reactions of synthetic importance[1], we have recently reported the convenient methodology for the generation of nitrones (1,3-dipoles)[1c], iminium cations[1d] and azomethine ylides[1i] from the appropriate amineradical cation produced by SET employing singlet excited state of dicyano naphthalene (DCN) as electron acceptor. These reactive intermediates have resulted primarily by efficient proton loss from amine radical cation at sites adjacent to nitrogen.

Since ion radicals often serve as precursors for neutral radicals by loss of electrofugal or nucleofugal groups, we envisioned to create α -amineradical by selective desilylation from radical cation 2 generated by photolysing 1 and DCN as shown in Scheme I, although α-amineradicals have been reported by proton loss from simple unsymmetrical tert-amine cation radical[2,3] and reduction of iminium salts by samarium iodide[4] in modest to low regioselectivity. Further, we envisaged to

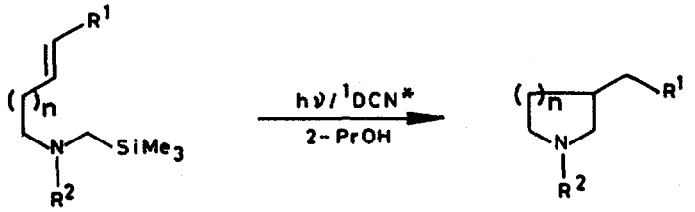


SCHEME - I

construct pyrrolidines and piperidines, which are common subunits of many naturally occurring alkaloids[5], by intramolecular cyclisation of thus generated -amine radical. Herein, we report our success in this area.

RRL-H Communication No.2354.

Photolysis (>280 nm, 450-W Hanovia lamp, 2 h) of a mixture of 6a-b (15 m mol) and DCN (45 m mol) in 2-propanol gave 7a-b in high yields (70-78 %)[6] Scheme II. The DCN was recovered almost quantitatively after the reaction as noted earlier[1c]. The study with a variety of substrates indicated reaction to be quite general (Scheme II).



6a-b 7a-b

a) n = 1 , R^1 = H , R^2 = C_4H_9

n = 1 , R^1 = CH_3 , R^2 = C_4H_9

n = 1 , R^1 = H , R^2 = $CH_2-C_6H_5$

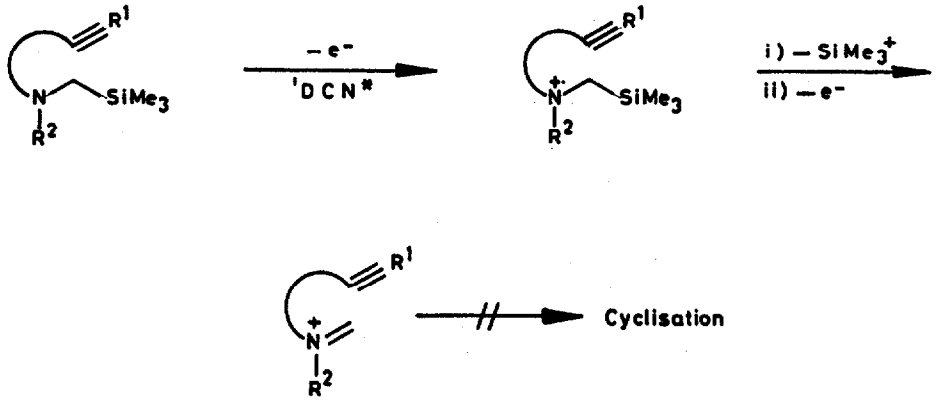
b) n = 2 , R^1 = H R^2 = C_4H_9

SCHEME-II

It is appropriate to mention here that ∝ -amineradicals generated by conventional tributyl n-tin hydride and AIBN reaction of N-alkenyl-N-(phenylthio)methyl amines have failed to yield cyclisation product, instead, gave corresponding uncyclised reduced amine[7]. However, in the present case no trace of reduced amine was observed. Therefore, this result stands in the sharp contrast of the Padwa's observation and disapproves the notion that merostabilised ∝ -amine radicals do not take part in cyclisation.

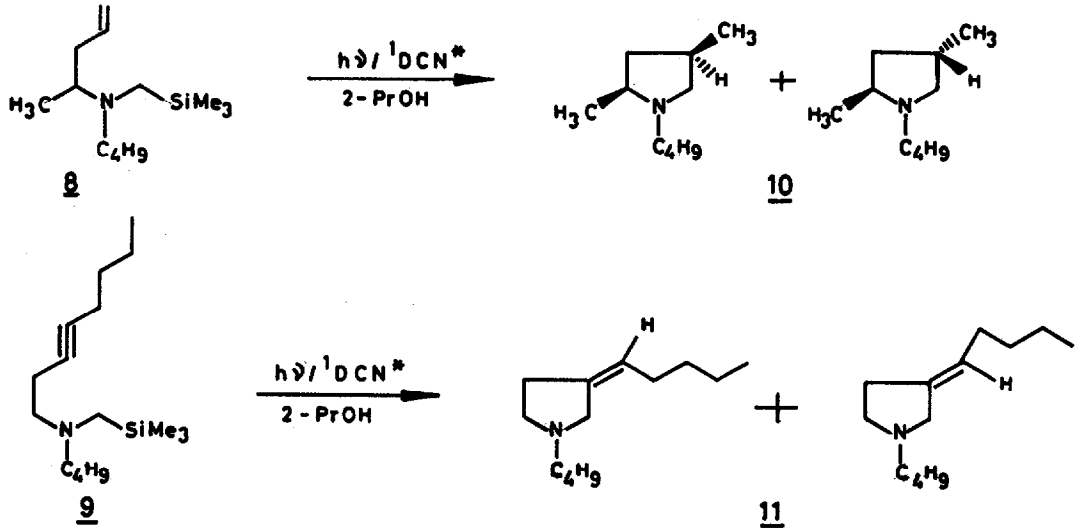
In our hand we have always received the most favourable exo-cyclisation product[8]. The majority of intramolecular radical addition reactions are known where radical adds to the α-position yielding exo-radical rather than addition to the β-position resulting endo-radical[8]. An alternative ionic mechanism (Scheme III) involving iminium cation intermediacy in these cyclisations have been ruled out on the basis of Overman's observation that simple alkynes and non-activated alkenes are immune to intramolecular reactions with weak electrophiles such as iminium cations in non-nucleophilic environment[9].

To gain insight into the stereochemical course of these cyclisations, substrates of type 8 and 9 were selected. Upon reacting compound 8 gave cyclised product 10 which was found to be



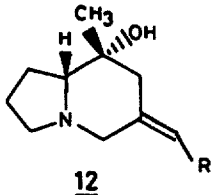
SCHEME-III

1:1 diastereomeric mixture (Scheme IV)[10]. The diastereomeric ratio of 10 was confirmed by ^{13}C MR (Chemical shifts at 62.04 ppm and 61.53 ppm of equal intensity for C-2) and capillary column (methyl silicone, 50 metres) GC-Mass. It was anticipated that the cyclisation might show cis-stereoselectivity by keeping in mind the chairlike transition state similar to that of 5-hexenyl radical cyclisation, however, no stereoselectivity is observed in these cyclisations. Similarly, the reaction of 9 gave equal mixture of Z- and E-isomer, confirmed by ^{13}C MR (chemical shifts at 121.0 and 120.65 ppm of equal intensity)[11].



SCHEME-IV

A total synthesis of (+) pumiliotoxin alkaloid 12 based on this methodology will be published separately.



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ACKNOWLEDGEMENT: One of us (GK) is thankful to CSIR, New Delhi, for the award of Senior Research Fellowship.

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6. Isolated yields but not optimised. Although GC yield was found more than 90%, the products were characterised by ^{1}H NMR (300 MHz) and mass sepctrometry.

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10. ^{1}H NMR ($CDCl_3$) δ 2.73(m, 1H), 2.24-1.98(m, 4H), 1.56-1.21(m, 7H), 1.01(d, 3H), 0.89(m, 6H); ^{13}C NMR ($CDCl_3$) 62.04 & 61.53(equal intensity), 59.65, 52.21, 44.75, 42.60, 40.09, 28.91, 20.52, 19.59, 14.00

11. ^{1}H NMR ($CDCl_3$) δ 6.35-5.39(m, 1H), 2.71-2.52(m, 2H), 2.49-2.28(m, 4H), 2.15(m, 2H), 1.92(m, 2H), 1.2-1.45(m, 8H), 1.00-0.95(m, 6H), ^{13}C NMR ($CDCl_3$) 138.3,121.0 & 120.65 (equal intensity), 59.71, 56.7, 54.4, 31.59, 29.3, 27.7, 22.3, 20.76, 18.4, 16.9 and 14.00.

(Received in UK 18 September 1989)