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INDOLIZIDINE AND QUINOLIZIDINE RING FORMATION IN THE SET-PHOTOCHEMISTRY OF α-SILYLAMINES

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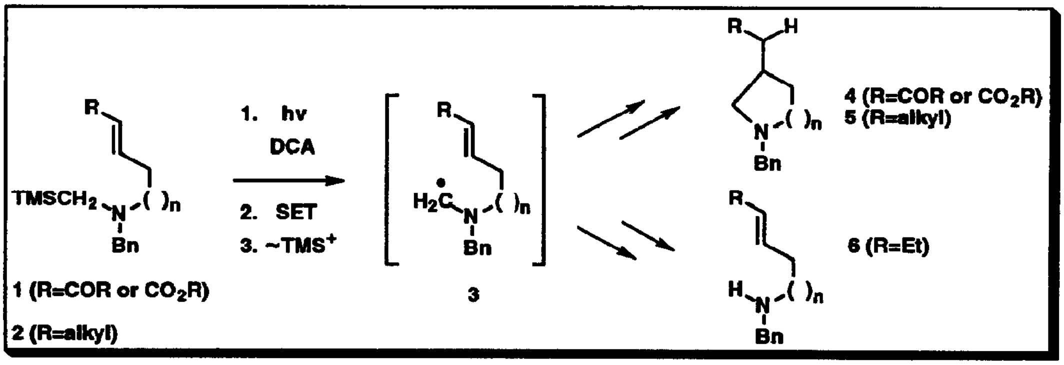
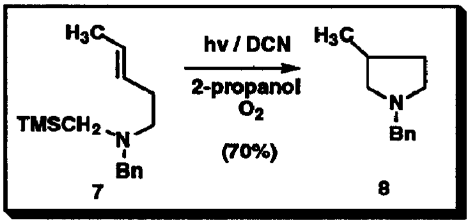
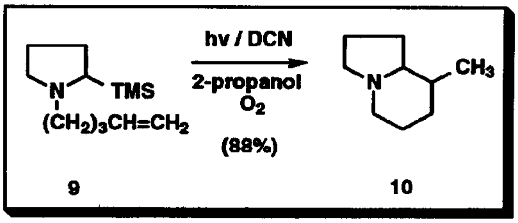
Abstract. The scope and limitations of indolizidine and quinolizidine ring forming, SET-photoinduced, α-amino radical cyclization reactions were explored.

We recently reported the results of a reasonably extensive study of the mechanistic and synthetic aspects of SET-photoinduced, α-amino radical cyclization reactions of tethered α-silylamine-olefin systems.[1,2] In that effort, we found that silylamino α,β-unsaturated esters and ketones **1** undergo SET-photosensitized reactions under anaerobic conditions to produce N-heterocyclic products **4** by a route involving formation and cyclization of intermediate α-amino radicals **3**. Exploration of the scope of this process demonstrated that reaction efficiencies are dependent on the (1) size of the forming ring (*eg.*, 5, 6 > 7), (2) reaction conditions (*eg.*, O_2-free solutions and low SET-sensitizer concentrations), and (3) nature of the olefin-tether (EWG-substitution required). In terms of the last requirement, we observed that related silylamino alkenes **2** are not transformed to cyclization products **5** under conditions where enone and ester analogs **1** react smoothly. For example, 9,10-dicyanoanthracene (DCA) sensitized irradiation (N_2, MeCN, $\lambda > 320$ nm) of **2** (R = Et, n = 2) does not result in formation of the piperidine **5** (R = Et, n = 2). Rather, the dealkylation product **6** is formed mainly. These observations were explained in terms of the slow cyclization rate for α-amino radicals **3** (R = alkyl) (*vs.* their oxidation by DCA to iminium cations)[3] when the olefin-tether lacks activating, EWG-substitution. This parallels the conclusions of an early study by Padwa[4] in which it was shown that α-amino radicals, unlike their α-amido analogs,[5] do not efficiently add intramolecularly to simple-alkenes.



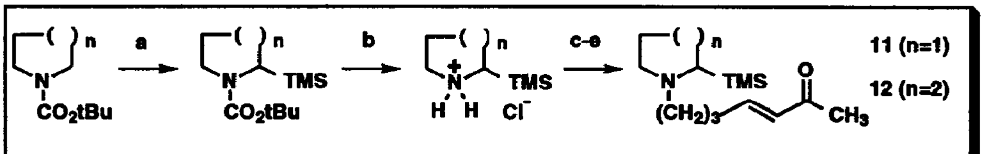
In light of these observations, we were intrigued by the reports by Pandey and his coworkers that primary[6] and secondary[7] α-amino radicals, derived by SET-photosensitized irradiations of simple alkene-silylamine systems, participate in high yielding cyclization reactions. Included in the examples provided by Pandey are the 1,4-dicyanonaphthalene (DCN) sensitized conversions of amines **7** and **9** to products **8** and **10**, respectively. These processes were reported to occur efficiently upon irradiation (λ > 240 nm) of non-deoxygenated 2-propanol solutions containing the amines and DCN.





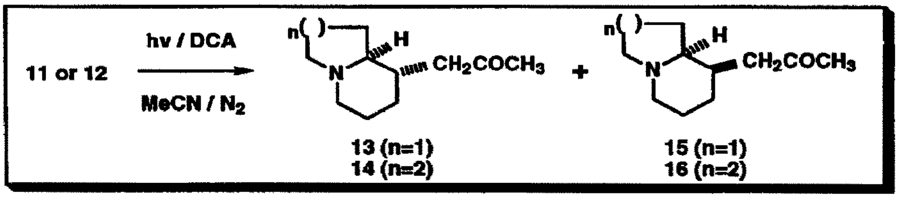
To gain insight into the source of these disparate results, we have subjected the pentenyl-pyrrolidine **9**[7] and related amino-enones **11** and **12** to photochemical study. The amino-enones **11** and **12** were prepared by the sequences shown in Scheme 1 which advantageously use the Beak[8] method to install the α-TMS function.

Scheme 1.

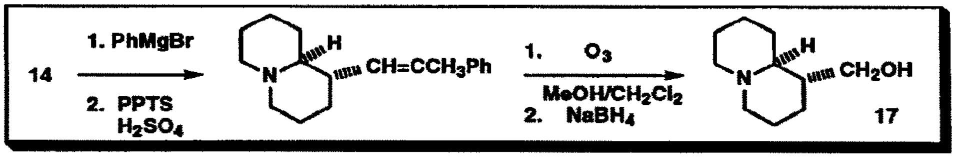


(a) sBuLi,TMEDA, Et$_2$O, -78°C; TMSCl; (b) 2N HCl, EtOH, 25°C; (c) 1N NaOH, 5-bromo-pentene, MeCN, 80°C; (d) O$_3$, CH$_2$Cl$_2$-CH$_3$OH; DMS; (e) Ph$_3$P=CHCOCH$_3$

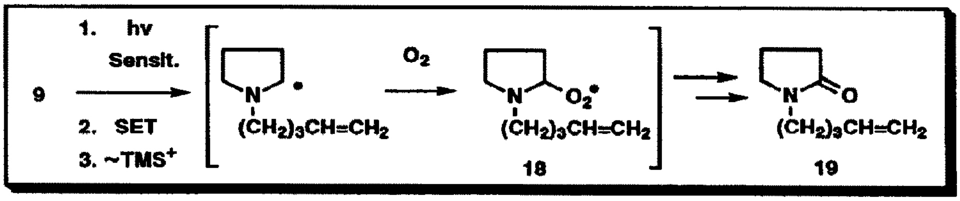
Consistent, with our earlier findings,[1] we observe that DCA-sensitized irradiation (λ > 320 nm, MeCN, N_2) of the pyrrolidine **11** leads to a separable mixture of the indolizidines **13** (42%) and **15** (43%). In addition, photocyclization of the piperidine **12** occurs efficiently under these conditions to produce the quinolizidines, **14** (81%) and **15** (18%). Stereochemical assignments to **14** and **16** are based on their contrasting ^1H and ^{13}C NMR properties, comparisons of these with those of the structural analogs, epilupinine and lupinine,[9] and the chemical transformation of the major epimer **14** to epilupinine **17** (Scheme 2).



Scheme 2.



In contrast, DCA-sensitized irradiation of the pentenyl-pyrrolidine **9** fails to promote formation of the indolizidine **10**. Instead, a mixture of unidentifiable products is obtained. Moreover, when **9** is subjected to DCN-sensitized irradiation under conditions which match (albeit in our hands) those reported by Pandey[6,7] (non-deoxygenated 2-propanol), it is efficiently (75%) converted to the pyrrolidinone **19**.[10]



The current results are consistent with those found in our earlier studies[1,2] of α-silylamine SET-photochemistry. The high yielding photocylization reactions of the silylamino-enones are a result of the high reactivity of efficiently formed, α-amino radical intermediates in intramolecular additions to tethered, EWG-substituted olefins.[11] That this process occurs slowly in systems containing "unactivated" (*i.e.*, electron rich) olefins follows from Padwa's original work[4] and our efforts,[1] and is in accord with electronic considerations. As a consequence, the α-amino radical formed in the photoreaction of **9** by an SET-desilylation sequence undergoes alternative processes involving oxidation either by DCA (in a deoxygenated solution) to produce an iminium cation[3] or by O_2 (in a non-deoxygenated solution) to yield a hydroperoxy radical **18**. The latter species serves as a precursor to the pyrrolidinone **19** while the former intermediate should be sufficiently labile to prevent its detection.

When taken together, the above and earlier results emphasize that the application of SET-photoinduced, α-amino radical cyclization reactions to N-heterocyclic synthesis appears restricted to α-silylamine substrates that contain EWG-substituted alkene tethers. They also bring into question the results reported by Pandey and his coworkers.

Acknowledgment.

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(10) Prepared from 2-pyrrolidinone by reaction with NaH and 5-bromopentene in MeCN.

(11) (a) This reactivity (*i.e.* β-addition to enones) even allows reversal of the normal selectivity for 5-exo over 6-endo radical cyclizations (ref. 11b); (b) Khim, S.K.; Mariano, P.S. *Tetrahedron Lett.*, **1994**, *35*, 999.

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