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A Novel Method for Synthesis of Functionalized Piperidines

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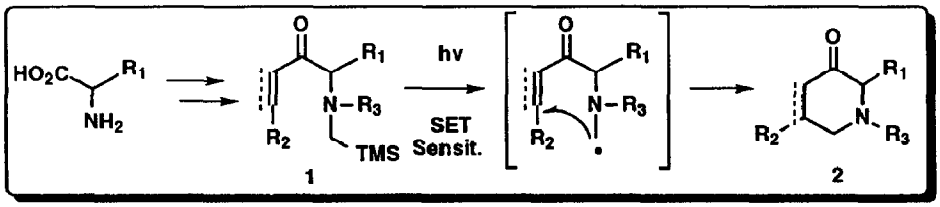
Abstract. A new methodology for synthesis of functionalized piperidines which employs photoinduced radical cyclization of α-silylamino-enones and ynones is described.

Earlier, we described the results of studies which showed that α-silylamine α,β-unsaturated ketone systems upon direct irradiation undergo SET-initiated photoaddition and photocyclization reactions.[1] In addition, we uncovered an SET-photosensitization methodology to promote related α-amino radical cyclization processes. Several of the advantages of the SET-sensitization *vs.* direct irradiation protocol were highlighted in this early work[1] and in more recent studies of silylamino- and silylamido-2,5-cyclohexadienone photocyclization reactions.[2] A program designed to explore the synthetic potential of this chemistry has led to a recent investigation of a new strategy for synthesis of functionalized piperidines (Scheme 1). We report here the preliminary results of this effort which show that α-silylamino-enones and -ynones **1** can be prepared from an amino acid precursor and that 6-endo radical cyclizations of these substances occur under SET-photosensitization conditions to produce piperidines **2** with high degrees of regiochemical and stereochemical control.

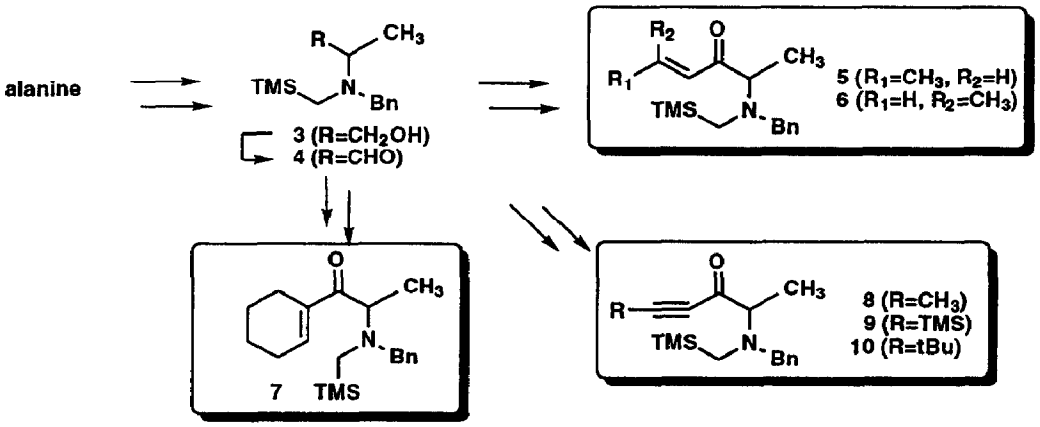
Scheme 1.



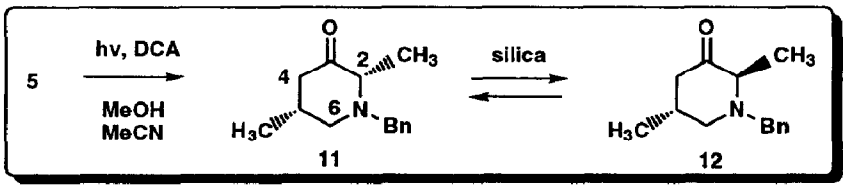
Silylamino-enones **5-7** and -ynones **8-10** were used to test various features of this piperidine synthesis strategy. Preparation of these substances started with sequential conversion of L-alanine to amino-alcohol **3** and -aldehyde **4**[3a] (Scheme 2). Addition of $LiC{\equiv}CCH_3$ to **4** followed either by Red-Al reduction and Swern oxidation gives **5**[3b] (28%) or by hydrogenation (Lindlar) and TPAP/NMO oxidation[4] gives **6**[3c] (10%). In a similar fashion, addition of 1-cyclohexenyl lithium to **4** followed by Swern oxidation gives **7**[3d] (32%). Finally, independent addition of $LiC{\equiv}CCH_3$, LiC≡CTMS and LiC≡CtBu to **4** followed by Swern oxidation of each of the resulting ynols provides the respective ynones **8-10**. By these procedures the amino-enones are prepared as

chromatographically pure substances. The ynones (> *ca.* 80% purity), on the other hand, are labile materials and, therefore, must be used in the photoreactions described below without purification.

Scheme 2.

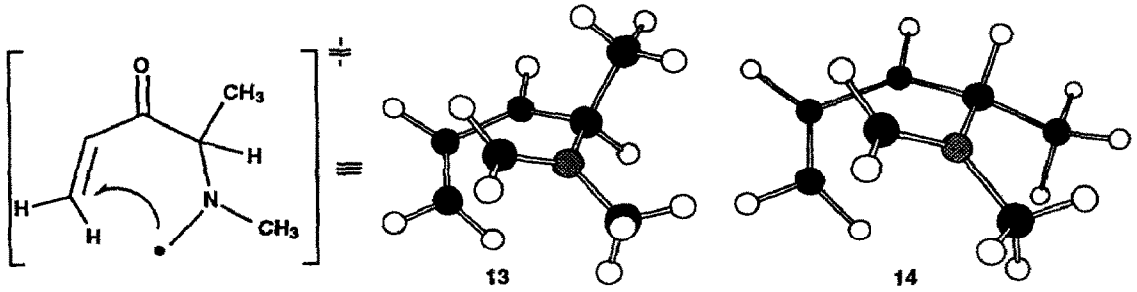


SET-photosensitized reactions were conducted by irradiation (λ>320 nm) of 9,10-dicyanoanthracene (DCA) (*ca.* 0.1 mM) in 15% MeOH-MeCN solutions of the enones or ynones (*ca* 1 mM). Under these conditions, the *trans*-propenyl amino-ketone **5** is transformed to a single, diastereomerically pure piperidine **11** in a yield which varies with the extent of conversion (*e.g.* 73% at 6% conversion of **5**, 23% at 73% conversion). Chromatography of the photolysate on silica gel yields an equilibrium mixture of **11** and its stereoisomer **12** in an *ca.* 1:1 ratio. The piperidines, **11** and **12**, are characterized as the respective *cis*- and *trans*-stereoisomers on the basis of their distinctive spectroscopic properties. For example, the ^{13}C NMR chemical shifts of C-6 and C-4 in **11** (52.7 and 44.7 ppm) and **12** (57.6 and 47.0 ppm) are characteristic of gauche-effects associated with the axial C-2 methyl conformer which contributes to the *cis*-isomer **11**. Moreover, the silica gel induced conversion of **11** to **12** by enolization suggests their C-2 epimeric relationship. In this process as well as those discussed below, both glc and ^1H NMR analyses of the crude photolysates at varying conversion indicate that <95% of the alternative stereo- or regio-isomers are produced.

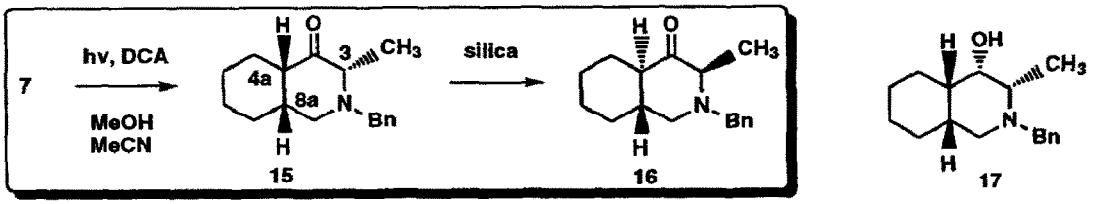


The high degree of *cis*-diastereoselectivity for the radical cyclization step in the conversion of **5** to **11** is consistent with a predictive model. Specifically, the model transition states, **13** and **14** were derived by molecular mechanics minimization (Macromodel/MM2) using constrained approach distances and angles calculated in earlier[5] *ab initio* treatments of radical addition processes. The greatly different energies of **13** (17.5 kcal/mol) *vs.* **14** (19.5 kcal/mol), resulting from a combination of $A^{1,2}$-strain (N-CH_3-C-CH_3) and transannular steric (H-H *vs.* H-CH_3) interactions, indicate that radical cyclization in the photoreaction of **5** should lead to preferential formation of the

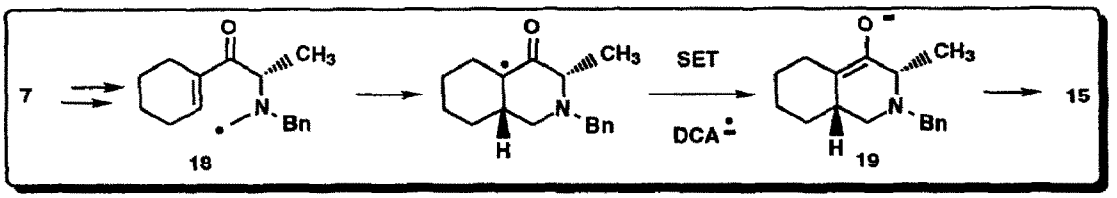
α-keto radical precursor of **11**. Moreover, similar considerations suggest that the *cis*-propenyl amino ketone **6** should resist radical cyclization owing to a highly congested transition state. This seems to be a correct forecast since no piperidine products are formed when **6** is subjected to the DCA-sensitized irradiation conditions.



The high diastereoselectivity of this 6-endo radical cyclization is further demonstrated by the SET-sensitized photochemistry of the cyclohexenyl ketone **7**. DCA-induced photoreaction of this substance leads to efficient (69% at 86% conversion) and stereoselective formation of a single decahydroisoquinoline **15**. The *cis,cis*-stereochemistry assignment to this substance follows from its characteristic spectroscopic properties (*eg.*, ^{13}C NMR 47.9 (C-4a), 37.6 (C-8a); ^{1}H NMR 2.73 (dd, J=11.7, 3.7 Hz, H-1ax), 2.51 (dd, J=11.7, 2.6 Hz, H-1eq)), its facile epimerization on silica gel to form the *trans*-fused hydroisoquinoline **16** (*eg.*, ^{13}C NMR 49.3 (C-4a), 42.1 (C-8a); ^{1}H NMR 2.67 (dd, J=12.3, 10.8 Hz, H-1ax), 2.54 (dd, J=12.3, 4.1 Hz, H-1eq)) and its stereoselective reduction to give a single alcohol stereoisomer **17**.

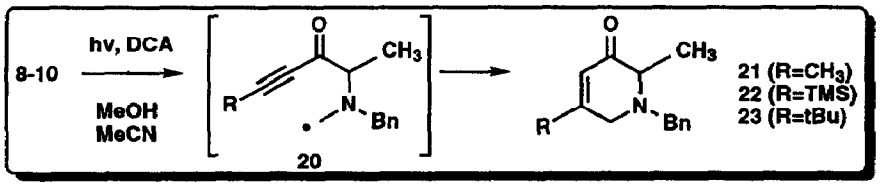


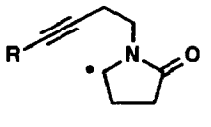
The *cis*-stereochemistry at C-3 and C-8a in **15** is consistent with the results of transition state modeling for cyclization of the radical **18** and the *cis*-relationship at C-4a and C-8a is as expected based on least hindered approach control in protonation of the final intermediate, enolate **19**.



Finally, the endo-radical cyclization protocol is applicable to the synthesis of unsaturated piperidinones. Accordingly, DCA-sensitized irradiations of the amino-ynones **8-10** in MeOH-MeCN

leads to production of the respective piperidines **21-23** (*ca.* 25% yields starting with ynol precursors of **8-10**). 6-Endo rather than 5-exo radical cyclization regiochemistry is adhered to in all three cases. This result stands in contrast to related cyclizations of the α-amido alkynyl radicals **24** probed earlier by Hart[6] where the 6-endo route is followed preferentially by the propynyl system but where the t-butyl-ethynyl analog reacts by a 5-exo mode exclusively. One of several possible reasons for this difference might be that α-amino-ynone (**20**) as compared to α-amido-alkynyl (**24**) radical cyclization reactions might be influenced to a greater extent by polar (*i.e.*, FMO-coefficients) rather than steric effects.





The results summarized above show the viability of SET-photoinduced, 6-endo radical cyclization processes in methodolgy for for functionalized piperidine synthesis. Further efforts are needed to improve the efficiency and develop the potential enantiospecificity of the strategy.

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(3) (a) Aldehyde **4** ($[\alpha]_D^{29°}$ +1.5°) derived from L-alanine has a >95% ee as determined by Mosher ester analysis of the alcohol **3** obtained by $NaBH_4$ reduction of **4**; (b) $[\alpha]_D^{25°}$ -6.5°, 22% ee determined by reduction ($NaBH_4$, $CeCl_3$) of **5** which gives the anti and syn alcohol diastereomers in a 1:2 ratio. Mosher ester analysis of the minor isomer ($[\alpha]_D^{25°}$ +6.4°) gives a 21% ee. This same anti alcohol isomer ($[\alpha]_D^{25°}$ +30.9°, *ca.* 90% ee) is formed as the near exclusive product of sequential reaction of aldehyde **4** with $LiC{\equiv}CCH_3$ and Red-Al; (c)$[\alpha]_D^{29°}$ -0.6°; (d) $[\alpha]_D^{28°}$ -25.7°.

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