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INTRAMOLECULAR PHOTOCYCLIZATIONS OF AMINO KETONES TO FORM FUSED AND BRIDGED BICYCLIC AMINES

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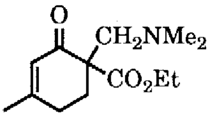
Abstract: *The irradiation of cyclic aminoketones produces bicyclic amines derived from intramolecular electron transfer followed by cyclization.*

The elegant studies by Mariano and others have established that electron transfer reactions have appreciable synthetic utility.[1] In particular, the conjugate addition type reactions of tertiary amines bearing a trimethylsilylmethyl group with cyclic unsaturated ketones constitutes a useful synthetic reaction.[2] In the context of our research using photochemical cyclizations for the formation of heterocyclic compounds, we investigated the photochemical reactions of **1** and related compounds. Our research had already established that the irradiation of ketones **2** and **3** produced useful yields of bicyclic heterocycles.[3]



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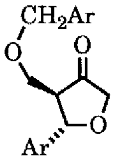

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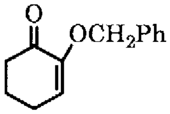

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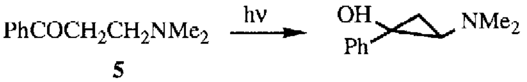
Extension of this annulation strategy by the study of amino ketone **1** might provide an entry to pyrrolidine ring but prediction of the outcome of this reaction was complicated by the likelihood that the mechanistic course of the photoreaction was almost certainly going to be different.

At the outset, we were aware that a number of researchers had studied the intramolecular reactions of amino ketones. Wagner has shown that gamma-amino ketones such as **4** undergo Norrish type II hydrogen atom abstraction followed by fragmentation.[4] Roth had demonstrated that amino ketones such as **5** afford amino cyclopropanols in good yield.[5] Interestingly, this reaction was postulated to proceed via an initial intramolecular

$$\underset{\mathbf{4}}{PhCOCH_2CH_2CH_2\text{-}NMe_2} \xrightarrow{h\nu} PhCOCH_3$$



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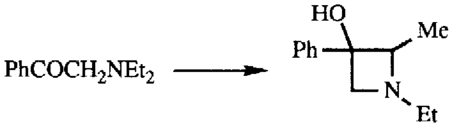
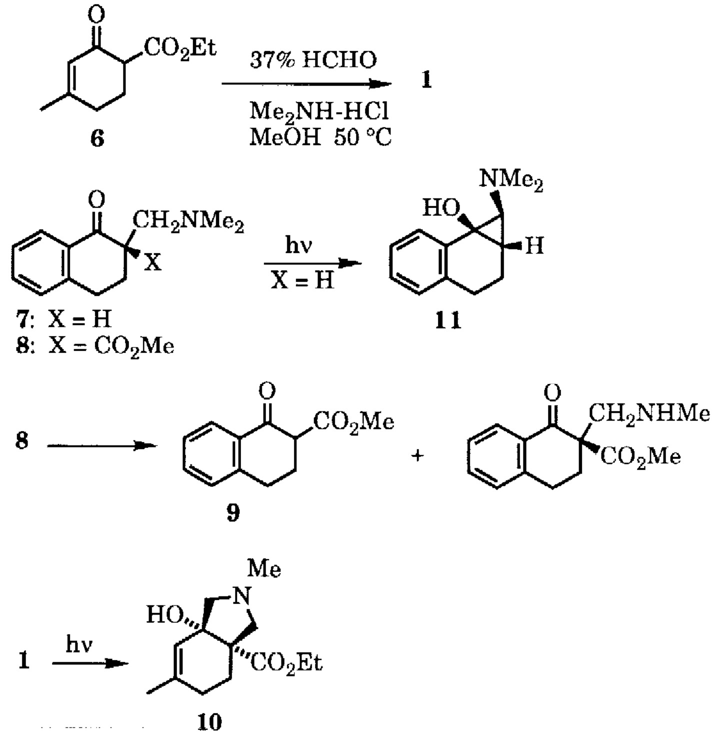
electron transfer followed by an intramolecular deprotonation of the amine radical cation by the radical anion of the ketone. The resulting biradical then cyclized to a cyclopropane. In the case of cyclic amino ketones, this reaction should be strongly influenced by conformational effects which could favor the formation of hydroxy pyrrolidines. Additionally, Searles and coworkers reported an interesting synthesis of hydroxy azetidines from the intramolecular photocyclization of an alpha-amino ketone.[6]



The amino ketones **1**, **7** and **8** were synthesized by Mannich reactions with alpha-tetralone and readily available ketone **6**. The photocyclization of **1** was conducted with a medium pressure Hanovia lamp at ambient temperature. A variety of degased solvents (benzene, tert-butanol, methanol and acetonitrile) and filters (Pyrex, Nonex) were examined to find the combination which afforded the best yield. Irradiation of **1** in MeOH without a filter produced pyrrolidine **10** in 30% yield. However, The yield improved to 56% using a Rayonet reactor equipped with blacklight lamps. No products which contained a cyclopropane ring were isolated.

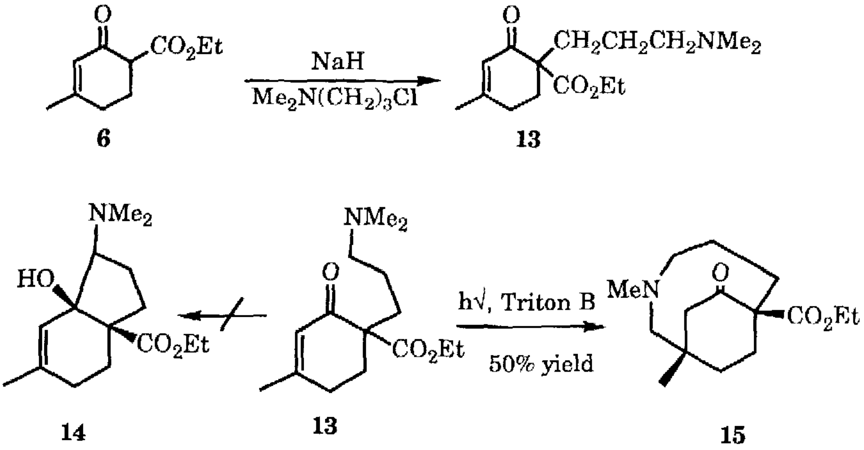
Scheme 1



We next turned our attention to tetralone **7**. Although irradiation using the Hanovia apparatus generated several products, irradiation in a Rayonet system in acetonitrile produced cyclopropanol **11** in 70% isolated yield as a single stereoisomer as evidenced by 300 MHz proton NMR and 75 MHz carbon NMR. Infrared absorptions suggested that the amine and the hydroxyl group were intramolecularly hydrogen bonded. Interestingly, irradiation of the analogous keto ester **8** provided 2-carboxymethyl-1-tetralone (**9**) as the major product and a product derived by N-demethylation of **8** in low yield. The cleavage of the CH_2NMe_2 group was unexpected and to the best of our knowledge does not have any precedent in the photochemical literature.

We next prepared the keto ester **13** by the reaction of the sodium salt (NaH, THF, 0°C) of 6 with 3-chloropropyldimethylamine (**12**) in boiling THF. Ketoester **13** was irradiated in MeOH using a medium pressure Hanovia lamp for three hours. In analogy with our earlier results, we had expected to obtain aminoalcohol **14**. However, we actually produced ketone **15** in approximately 30% yield. When the photoreaction was conducted in the presence of one equivalent of Triton B, a 50% isolated yield of **15** was obtained. The structure determination of **15** was based on resonances supporting a quaternary methyl group and one N-Me signal in the 300 MHz proton NMR spectrum and resonances corresponding to a saturated ketone in the 75 MHz carbon spectrum and an absorption at 1729 cm^{-1} (saturated ketone) in the infrared spectrum.[7]

Scheme 2



To the best of our knowledge, the production of nine-membered rings by electron transfer followed by cyclization has little precedent in the photochemical literature. Aside from some fascinating photoreactions of aminoketoamides,[8] there does not appear to be any close precedent.

Although a coherent mechanistic picture has not yet emerged, it is clear that intramolecular interactions of certain unsaturated ketones and amines have considerable synthetic potential. The selective formation of annulation products **10** and **15** by a tandem alkylation/photocyclization sequence is of both mechanistic and synthetic interest.

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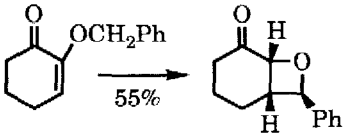
   The photolysis of **3** (Rayonet reactor) provided the interesting bicyclic ketone shown below (Li Chen, unpublished results).



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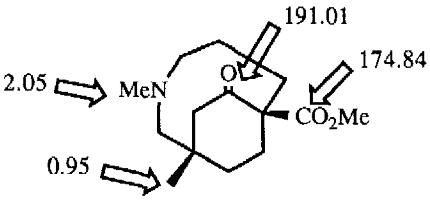

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