Tetrahedron Letters,Vol.29,No.51,pp 6685-6688,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

APPLICATION OF REDUCTIVE, SINGLE ELECTRON TRANSFER PROCESSES TO THE GENERATION AND CYCLIZATION OF ω-UNSATURATED α-AMINO RADICALS

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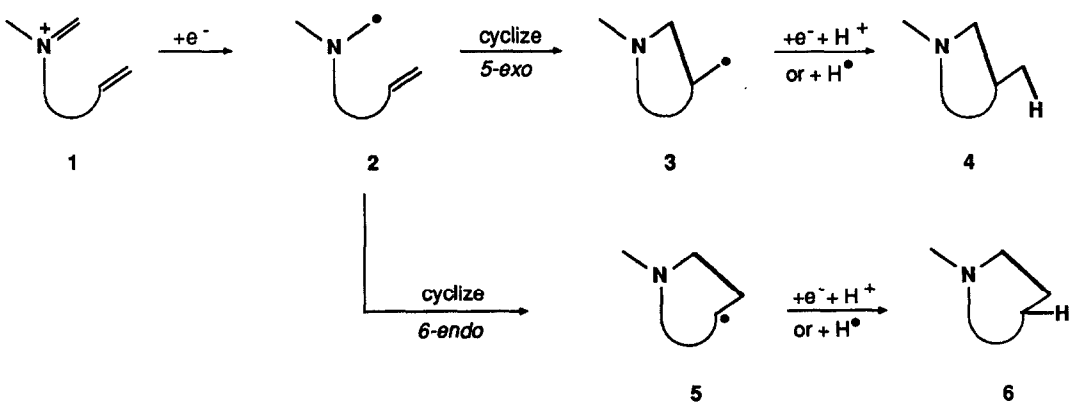
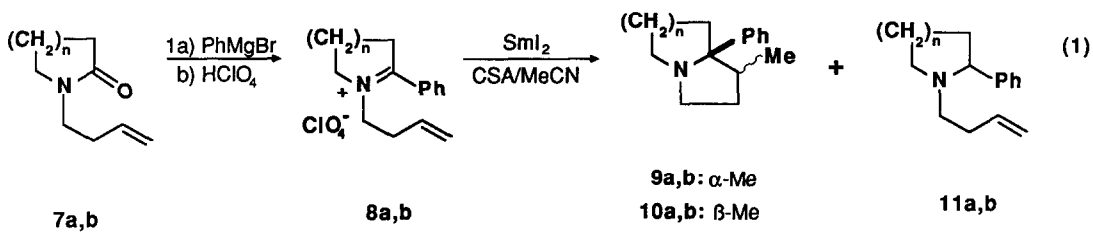
Abstract. Subjection of ω-unsaturated iminium salts **1** to dissolving metal reduction with samarium diiodide in the presence of camphorsulfonic acid afforded the corresponding α-amino radicals **2**, which underwent facile cyclization via a 5-*exo* mode of closure leading to heterocyclic products of the general type **4**.

Within the general context of inventing novel methods for the construction of pyrrolidine and piperidine rings, which are structural subunits common to numerous alkaloid families, we were intrigued by the possibility that these arrays might be elaborated by a sequence that featured a radical process[2] for the construction of a new carbon-carbon bond alpha to a *basic* nitrogen atom.[3,4] The central feature of this strategy for alkaloid synthesis entailed the initial single electron transfer to suitable iminium salt acceptors **1** via either a chemical[5,6] or a electrochemical[7,8] reduction to generate the ω-unsaturated-α-amino radicals **2**. Cyclization of these unsaturated radicals via an *exo* mode would then furnish the cyclic radicals **3**, which would be transformed into **4** by either sequential transfer of an electron and a proton or more directly by simple hydrogen atom transfer (Scheme 1). Based upon the evidence that was available at the outset of this work,[2] we anticipated that the alternative closure of the radical **2** via an *endo* mode to give the intermediate radical **5** leading to the formation of **6** would constitute a minor reaction pathway. We now wish to disclose some of our initial results in this area, the significance of which is underscored by the *previous report that certain ω-unsaturated α-amino radicals did not undergo cyclization*,[3j] an observation that stands in marked contrast to the behavior of the *N*-acyl[3a-i] and *N*-sulfonylamino[3j] analogues of **2**.

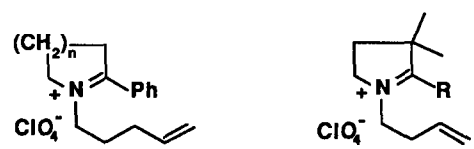
Scheme 1



In order to assess some of the general aspects of this approach to nitrogen heterocycles, our initial experiments were directed toward an examination of the feasibility of preparing substituted pyrrolizidine and indolizidine rings by effecting the cyclization of α-amino radicals derived from the iminium salts **8a,b**. Synthesis of the requisite substrates **8a,b** was readily achieved in excellent yield by reaction of the lactams **7a,b** with phenylmagnesium bromide followed by workup with aqueous perchloric acid. Reduction of **8a** with samarium diiodide in anhydrous acetonitrile *in the presence of at least one equivalent of camphorsulfonic acid* (CSA) produced a mixture (10:1) of the cyclized products **9a** and **10a** in 82% yield together with traces of the reduced product **11a** (eq 1).[9] In the absence of camphorsulfonic acid, lower yields of the cyclized products were obtained together with dimers and larger quantities of the amine **11a**. This observation suggests that protonated, unsaturated α-amino radicals may undergo cyclization somewhat more readily than their unprotonated counterparts.[10] In a similar fashion, treatment of the homologue **8b** with samarium diiodide under identical conditions furnished a mixture (1:1) of **9b** and **10b** in 60% yield together with 5-10% of **11b**. One interesting feature of these reactions is that the cyclization of the radical generated upon single electron transfer to **8a** (n = 1) is considerably more efficient and stereoselective than the corresponding process involving the homologue **8b** (n = 2). Use of other reductive methods, including Co(I)[5d,e] and electrochemical,[11] for effecting the cyclization of radicals derived from the iminium salts **8a,b** have also been examined in preliminary experiments. Although the reaction conditions and hence the yields employing these alternative techniques have not been optimized, similar results have been obtained.



Series a: n = 1
Series b: n = 2

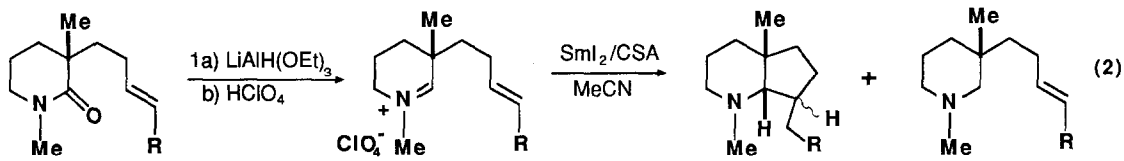


12: n = 1
13: n = 2

14: R = H, Ph

Further experiments with the related *N*-alkenyl substituted iminium salts **12** - **14** have revealed several apparent limitations in this process (Scheme 1). For example, when the *N*-4-pentenyl derivatives **12** and **13** were treated with samarium diiodide under a variety of conditions, only uncyclized, reduction products were obtained. The radical cyclization of these unsaturated α-amino radicals also seems to be sensitive to retardation by increased steric bulk adjacent to the radical center since radicals generated from the iminium salts **14** (R = H, Ph) also failed to cyclize.

Inasmuch as a number of fused nitrogen heterocycles not bearing a bridgehead nitrogen atom occupy a position of some importance in alkaloid chemistry, we elected to ascertain whether the cyclizations of ω-unsaturated α–amino radicals could be exploited to construct such ring systems. For example, when the iminium salt **16a** was treated with samarium diiodide in anhydrous acetonitrile in the presence of camphorsulfonic acid, a mixture of the two epimeric bicyclic amines **17a** and **18a** (46% combined yield; approximately 2.5:1 by capillary GLC) and the monocyclic amine **19a** (33%) was obtained (eq 2). On the other hand, reaction of the related styryl derivative **16b** with samarium diiodide under similar conditions afforded a single bicyclic product (78%) that has been identified as **17b** with only trace amounts of the monocyclic amine **19b** being formed. Not surprisingly, it thus appears that the presence of an activating group on the acceptor double bond not only increases the yield of the cyclization but the stereoselectivity of the reaction as well.



15a,b **16a,b** **17a,b:** α-H **18a,b:** ß-H **19a,b**

Series a: R = H
Series b: R = Ph

Thus, these preliminary investigations have revealed some interesting and unusual chemistry of ω-unsaturated α-amino radicals, and further studies to ascertain the synthetic potential of the method and to establish some of the mechanistic details together with the scope and limitations of these processes are under current investigation.

Acknowledgment. We thank the National Institutes of Health (CA 37929) and the Robert A. Welch Foundation for generous financial support of this research. We are also grateful to the NSF (CHE 8305785) and the NIH (RR 01912) for NMR facilities.

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