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RADICAL CYCLIZATION AS AN APPROACH TOWARD THE SYNTHESIS OF PYRROLIDINES

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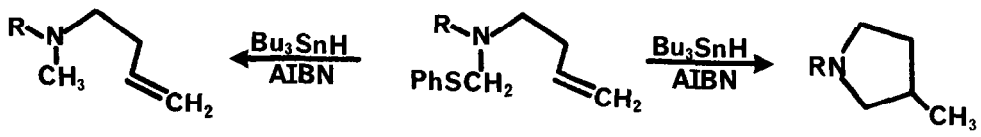
Abstract: Free radical cyclizations of several bromo allyl and diallyl substituted sulfonamides are described. The regiochemical course of these cyclizations depend on the nature of the substituent groups attached to the π-bond.

Free radical cyclizations are attracting renewed interest from synthetic organic chemists for ring construction[1-8] as traditional prejudices against free-radical intermediates are removed. The use of hetero-substituted radicals in C-C bond forming processes, however, has not been widely studied and only a few examples of heterocyclic synthesis via this method are known.[9-17] In connection with an ongoing synthetic program to develop new methods for alkaloid synthesis, we have examined a route to pyrrolidines in which a radical cyclization plays a crucial role. This report describes the initial results of our study and outlines the stereo and regiochemical aspects of the radical cyclization reaction.

We began our studies by treating thiobutenyl amine 1 with tri-n-butyltin hydride (1.4 equiv.) and AIBN (0.04 equiv.) in benzene at reflux. The only material isolated (89%) was the noncyclized amine 2. This result is strikingly different from that encountered with related α-acylamino radicals[9,10] where complete cyclization had occurred. It would seem as though the rate of cyclization is related to the stability of the radical center. Such stabilization has been previously invoked to explain the absence of cyclization products from merostabilized radicals.[18] In an attempt to promote the intramolecular cyclization process, we studied the reaction of the corresponding sulfonamide 3. The reductive cyclization of this material afforded pyrrolidine 4 in 36% yield[19] together with some of the noncyclized amine 5. Although the cyclization of 3 was competitive with reduction, the low yield of 4 imposes a serious limitation to the practicality of the method using butenyl substituted sulfonamides.

Our attention was next given to the possible intramolecular cyclization of the 2-bromoethylallyl-sulfonamide system 6. To our delight, when 6 was treated



2; R=CH_2Ph
5; R=SO_2Ph

1; R=CH_2Ph
3; R=SO_2Ph

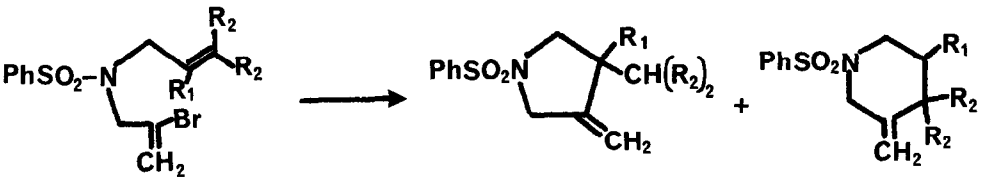
4; R=SO_2Ph

with tri-n-butyltin hydride, a 87% yield of 4 was isolated. An even more interesting result is the exclusive formation of the exo cyclized product 8 (92%)[20] obtained from the reductive cyclization of sulfonamide 7. None of the 6-endo mode of closure could be detected in the crude reaction mixture. This result stands in contrast to Hart's observations with the N-acyl-2-aza-5-hexenyl radical where both modes of cyclization were encountered.[9] Internal olefin substitution generally leads to enhanced endo cyclization.[1,8] Apparently, the stereoelectronic factors governing the cyclization reaction of 6 and 7 are even more stringent than that which occur with the simple 5-hexenyl system. This is probably related to the shorter C-N bond distance which promotes the 5-exo trig cyclization pathway. Reductive cyclization of the prenyl substituted sulfonamide 9 results in exclusive formation of the expected exo-cyclized product 10.

6; $R_1=R_2=H$
7; $R_1=CH_3$; $R_2=H$
9; $R_1=H$; $R_2=CH_3$

4; $R_1=R_2=H$
8; $R_1=CH_3$; $R_2=H$
10; $R_1=H$; $R_2=CH_3$

During the course of this work, we also examined the cyclization of several diallyl substituted sulfonamides of type 11. The vinyl radical cyclizations were all initiated with tributylstannane in the presence of AIBN as the radical initiator. Intramolecular addition of the vinyl radical to the neighboring π-bond at a predictable position would be quite useful since such a process should result in the formation of a nitrogen containing cycloalkene that could be used for further synthetic manipulations. We found that the reductive cyclization of 11 gives a 1:2 ratio of exo and endo cyclization products (73%),[21] respectively, contrary to the considerably larger exo:endo ratios observed by Stork in the closely related carbocyclic system.[22] It would seem that subtle steric and electronic effects, which we do not fully understand, are responsible for the regiochemical outcome of the cyclization reaction. In order to delineate



11; $R_1=R_2=H$
14; $R_1=H$; $R_2=CH_3$
16; $R_1=CH_3$; $R_2=H$

12; $R_1=R_2=H$
15; $R_1=H$; $R_2=CH_3$

13; $R_1=R_2=H$
17; $R_1=CH_3$; $R_2=H$

the effect of olefin substitution on the regiochemical course of the reaction, we studied the cyclization of sulfonamides 14 and 16 and found the reactions to proceed in good yield (60% and 67%) with total stereoselectivity. With these systems, favorable stereoelectronic factors promote the observed selectivity.

Studies of the cyclization process with other substituents and its application toward the synthesis of alkaloids are in progress and will be reported on at a later date.

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(19) Compound 4; NMR (360 MHz,$CDCl_3$) δ 0.91 (d, 3H, J=6.5 Hz), 1.36 (m, 1H), 1.91 (m, 1H), 2.12 (m, 1H), 2.77 (dd, 1H, J=9.7 and 7.9 Hz), 3.24 (ddd, 1H, J=9.7, 7.9 and 7.2 Hz), 3.36 (ddd, 1H, J=9.7, 8.10 and 4.3 Hz), 3.44 (dd, 1H, J=9.7 and 7.2 Hz) and 7.51-7.85 (m, 5H).
(20) Compound 8; NMR (90 MHz,$CDCl_3$) δ 0.88 (s, 6H), 1.52 (t, 2H, J=6.0 Hz), 2.93 (s, 2H), 3.28 (t, 2H, J=6.0 Hz) and 7.3-7.9 (m, 5H).
(21) Compound 12; NMR (360 MHz,$CDCl_3$) δ 1.04 (d, 3H, J=6.5 Hz), 2.63-2.74 (m, 2H), 3.60 (dd, 1H, J=8.1 and 6.5 Hz), 3.76 (ddd, 1H, J=14.0, 3.6 and 1.8 Hz), 3.97 (brd, 1H, J=14.0 Hz), 4.85-4.92 (m, 2H) and 7.5-7.8 (m, 5H); Compound 13; δ 1.69 (m, 2H), 2.11 (t, 2H, J=6.1 Hz), 3.10 (t, 2H, J=5.8 Hz), 3.54 (s, 2H), 4.83 (s, 1H), 4.90 (s, 1H) and 7.5-7.80 (m, 5H).
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