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SUBSTITUENT EFFECTS ON 2-AZA-5-HEXYNYL RADICAL CYCLIZATION REGIOCHEMISTRY

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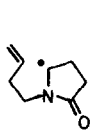
Summary: Cyclizations of several N-acyl-2-aza-5-hexynyl radicals are described. The regiochemical course of these cyclizations depend on the nature of substituents at the alkyne terminus.

We recently showed that the cyclization of N-acyl-2-aza-5-hexenyl radicals of type 1 provides a promising new entry to pyrrolizidinones and indolizidinones.[1] During the course of this work, we also examined the cyclization of several N-acyl-2-aza-5-hexynyl radicals of type 2. This report describes the initial results of this study and in particular documents the influence that substituents exert on the cyclization regiochemistry.



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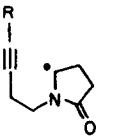
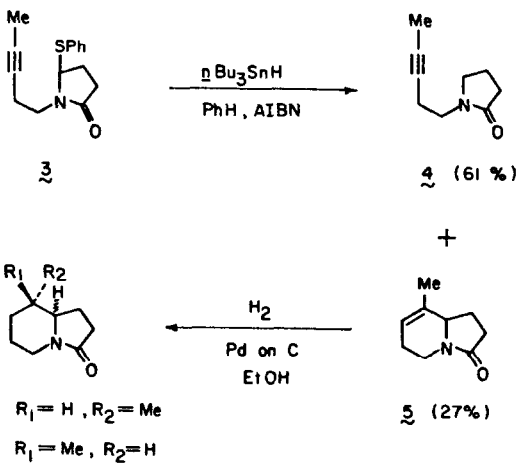


2

a R = Me
b R = $SiMe_3$
c R = CMe_3

We began our studies by examining the behavior of α-acylamino radical 2a. Thus, treatment of thiophenoxylactam 3[2] with tri-n-butyltin hydride and AIBN in benzene under reflux[3] gave a 61% yield of reduction product 4 and 27% of the endo cyclization product 5, presumably via the inter-



3

4 (61 %)

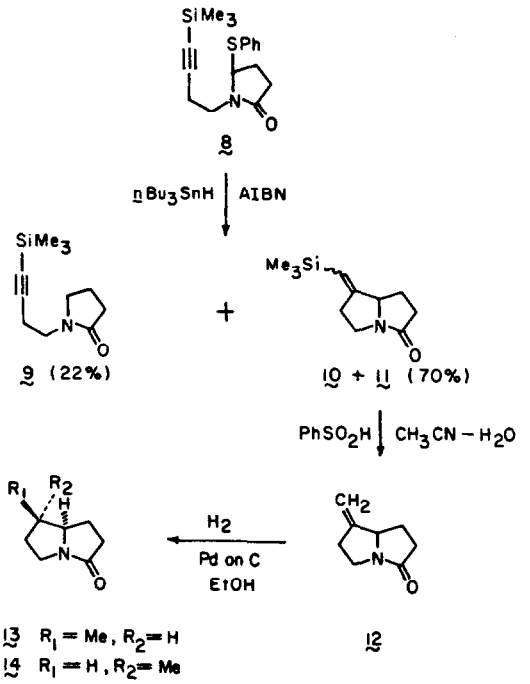
5 (27%)

6 R_1 = H, R_2 = Me

7 R_1 = Me, R_2 = H

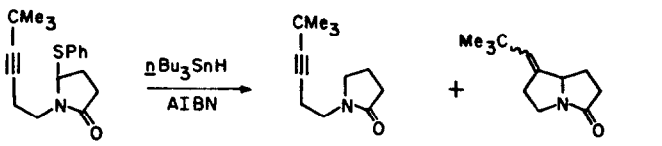
mediacy of radical 2a.[4] The structure of 5 was established by its conversion to a separable mixture of known indolizidinones 6 and 7 upon catalytic hydrogenation.[1,5,6] It is noteworthy that no products derived from exo cyclization were detected. Although only a few examples of 5-hexynyl radicals have been reported, in all cases only exo cyclization products were obtained.[7]

Although reduction of α-acylamino radical 2a by tri-n-butyltin hydride was competitive with cyclization, even under high dilution conditions, we undertook a substituent study to explore the generality of this approach to indolizidinones.[8] To our surprise, when α-thiophenoxylactam 8[2,3] was treated with tri-n-butyltin hydride, a 92% yield of a 2:7 mixture of 9 and 10 + 11, respectively, was obtained.[9,10] The structures of 10 and 11 were proven by protode-



silylation[11] to afford olefin 12 followed by catalytic hydrogenation to a separable mixture of the known pyrrolizidinones 13 and 14.[1,12] Two effects of trimethylsilyl substitution are apparent from this result. First, the rate of cyclization, relative to reduction, is raised to a synthetically useful level.[13] Second, exo cyclization becomes the predominant regiochemical course of the reaction.[14,15]

In an attempt to determine whether silicon played a major role in the observed regiochemical reversal, the behavior of α-acylamino radical 2c was examined. Treatment of α-thiophenoxylactam 15[2,3] with tri-n-butyltin hydride gave an 84% yield of roughly a 1:1.4 mixture of 16 and 17 + 18.[16] Thus radicals 2b and 2c behave similarly and the role played by silicon appears to be minor.[17]



15 16 (35 %) 17 + 18 (49 %)

From a mechanistic standpoint, it is apparent that subtle steric and electronic effects which we do not yet thoroughly understand are responsible for the regiochemical results presented above and we defer speculation until further experimental information is obtained. From a synthetic standpoint, the cyclization of radical 2b provides a potentially useful route to 1-methylene pyrrolizidin-5-ones and applications of this chemistry to alkaloid synthesis are in progress.

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REFERENCES AND NOTES

1. Hart, D. J.; Tsai, Y.-M. J. Am. Chem. Soc., 1982, 104, 1430.

2. α-Thiophenoxylactams 3,8 (mp 42-43°C), and 15 were prepared from the corresponding imides via the route described in reference 1 in overall yields of 76%, 83%, and 36%, respectively.

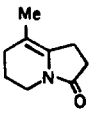
3. A 0.25M solution of tri-n-butyltin hydride (1.3 equivalents) in benzene containing 0.04 equivalents of AIBN was added to a 0.058M solution of the thiophenoxylactam (1.0 equivalents) in benzene via syringe pump over a 19 h period.

4. For the definition of endo and exo cyclization see Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. J. Chem. Soc., Chem. Commun., 1980, 482.

5. Enamide i was also produced during the catalytic hydrogenation. The ratio of 6:7:i was 1.8:1:1.2 by GC.

6. All compounds reported herein gave IR, mass, ^{1}H-NMR and in some cases ^{13}C-NMR spectra consistent with the assigned structures.

7. For references see Beckwith, A. L. J.; Ingold, K. V. in "Rearrangements in Ground and Excited States"; deMayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp. 202-203.



i

8. For some indolizidine alkaloids with substituent patterns related to 5 see Johns, S. R.; Lamberton, J. A. in "The Alkaloids", Manske, R. H. F., Ed.; Academic Press, New York, Vol. 14.

9. A terminal trimethylsilyl heptynyl radical cyclization has been reported: Büchi, G.; Wüest, H. J. Org. Chem., 1979, 44, 546.

10. Product ratios were obtained by integration of appropriate signals in a 200 MHz ^{1}H-NMR spectrum of a purified mixture of products. Pure samples of 9-11 were obtained by a combination of GC and LC techniques. The ratio of 10:11 was approximately 1.7 although the identity of the major vinylsilane remains unknown.

11. Büchi, G.; Wüest, H. Tetrahedron Lett., 1977, 4305. Both 10 and 11 independently gave 12 upon protodesilylation.

12. The ratio of 13:14, separable by GC, was 3.5.

13. Pyrrolizidinone 12 was prepared in a 50% overall yield from 8 on a 10 mmol scale.

14. It has been suggested that trialkylsilyl groups stabilize adjacent alkyl radical centers relative to their all carbon counterparts,[15a] although this effect has not been observed for alkenyl radicals.

15. (a) Wilt, J. W.; Aznavoorian, P. M. J. Org. Chem., 1978, 43, 1285 and references cited therein. (b) For several applications of this radical-stabilizing effect to synthetic problems see: Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. J. Org. Chem., 1981, 46, 4825; Chenard, B. L.; Slapak, C.; Anderson, D. K.; Swenton, J. S. J. Chem. Soc., Chem. Commun., 1981, 179.

16. Product ratios were obtained as described in reference 10. The ratio of 17:18 was 2.2 although the identity of the major vinylsilane remains unknown.

17. Preliminary experiments have shown that 2 [R=C(OMe)Me_2] cyclizes only to pyrrolizidinones while 2 (R=CH_2OMe) and 2 (R=nC_3H_7) afford roughly equal mixtures of pyrrolizidinones and indolizidinones. In all cases, reduction of 2 is the major reaction pathway under the conditions outlined in reference 3.

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