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Cyclization Reactions of α-Amino Radicals Derived from N-(N',N'-Dialkylaminoalkenyl)benzotriazoles and Samarium Diiodide

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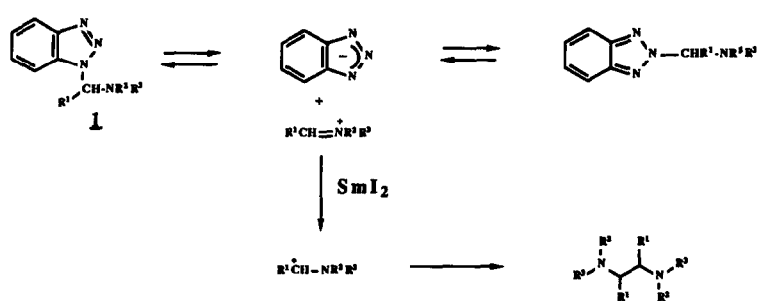
Abstract: N-(N',N'-Dialkylaminoalkenyl)benzotriazoles, derived from secondary amines and unsaturated aldehydes, reacted with samarium diiodide (SmI_2) to afford, through an α-amino radical intermediate, 5-exo and 6-exo cyclization products with good diastereoselectivity.

Methods based on free radical chemistry have enjoyed increasing popularity in recent years[1-5] and are now commonplace in any rationally designed synthetic endeavor. Cyclization reactions of derivatives of the 5-hexenyl radical have proven to be particularly useful in the synthesis of carbocycles. To a lesser extent, the heteroatom-stabilized 5-hexenyl radicals have also found useful applications in the synthesis of carbocycles and heterocycles[6-14]. Thus, 2-aza-5-hexenyl radicals afford pyrrolidines when the olefinic portion of the radical is activated and / or the nitrogen substituent is part of an electron-withdrawing group[8,10-14].

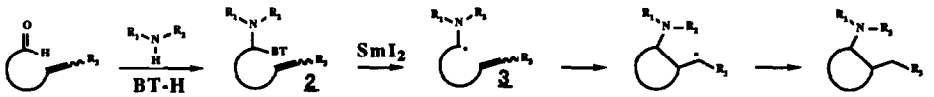
While the tin hydride method remains the most frequently employed for radical generation, the use of the one-electron reducing agent samarium diiodide (SmI_2) has recently seen a rapid growth[15]. 2-Azaalkyl radicals have been generated by the action of SmI_2 on iminium salts[11] or *o*-iodobenzyl tertiary amines[16], but only in the former case was the radical used in a subsequent cyclization step leading to various nitrogen-containing heterocyclic systems.

We have recently shown[17] that α-dialkylaminoalkylbenzotriazole derivatives **1**, when treated with equimolar amounts of SmI_2 under mild conditions, afford 2-azaalkyl radicals, which undergo dimerization to form vicinal diamines (scheme 1). The key feature of this reaction is the fast dissociation in solution of substrates **1** to afford reactive iminium cations[18] which readily accept one electron from SmI_2. As an extension of this new methodology, we now report on the intramolecular trapping of α-amino carbon radicals, generated in this fashion, with suitably positioned tethered electron deficient olefins (scheme 2). 5-Exo- and 6-exo cyclization products are in this way obtained in moderate yields.



Scheme 1

The α-dialkylaminoalkenylbenzotriazole cyclization substrates **2** are easily prepared from an aldehyde, benzotriazole and a secondary amine by stirring overnight at 25°C in the presence of 4 Å molecular sieves. These substances cannot be conveniently purified and are used as crude products in the cyclization step[19]. As expected[18], their ^{1}H- and ^{13}C-NMR spectra indicate that these adducts exist in solution as equilibrium mixtures of 1- and 2-substituted benzotriazoles and, therefore, that they readily dissociate into an iminium cation and the benzotriazolyl anion (scheme 1).



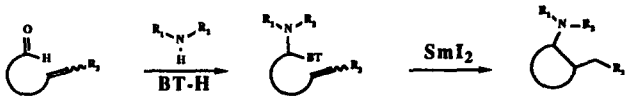
BT = 1- or 2-Benzotriazolyl

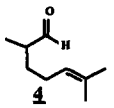
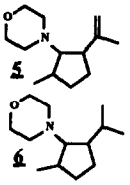
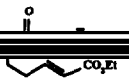
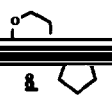
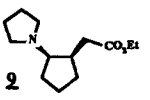
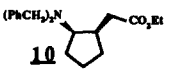
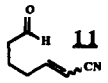
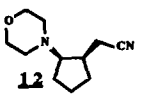
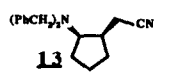
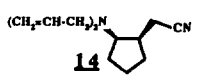
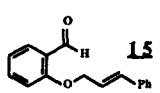
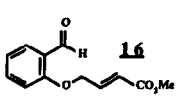
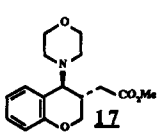
Scheme 2

Initial cyclization studies were conducted on a substrate **2** derived from the aldehyde **4** (Table 1, entry 1), which contains an unactivated olefin moiety. When this benzotriazole derivative was treated at 25°C with a 0.1 M THF solution of SmI_2, two equivalents of the reagent were rapidly consumed but the yield of cyclized products **5** and **6** (Table 1) amounted to only a combined 29 %[20,21]. Unidentified side products accounted for most of the remaining mass. A likely explanation is that a radical **3** (scheme 2) formed but was not reactive enough to undergo cyclization with an unactivated olefin. Similar observations have been reported on 2-aza-5-hexenyl radicals generated by the tin hydride method[10,13,14]. The transformation of the amine functionality into amide[10], sulfonamide[13,14] or carbamate[8] in order to reduce its stabilizing[22] effect on the radical has been succesfully used to overcome this problem. Similarly, the protonation[11,22] of the α-amino radical results in a faster cyclization step, as does the activation by a radical-stabilizing group on the olefinic double bond[10,11].

Our results using double bonds activated by phenyl, carbalkoxy or cyano groups are collected in Table 1. Clean reactions and good yields of 5- and 6-exo cyclization products are realized when the strong electron-withdrawing groups CO_2Et or CN are used. The phenyl group does not seem to provide enough activation, as only diamine[17] products were obtained for the substrate derived from the aldehyde **15** (Table 1, entry 8). The reactions leading to cyclopentane derivatives appear to be highly diastereoselective. The cis diastereoisomer was the predominant product in all reactions of adducts derived from the aldehydes **7** and **11** (Table 1, entries 2-7) and in some cases the only one obtained (Table 1, entries 2-3). Furthermore, the diastereomeric ratios obtained in cyclopentanes derived from the aldehyde **11** are very close to the ratio of geometric isomers in the starting aldehyde. It is therefore tempting to suggest that there is a correlation between the product stereochemistry and the olefin geometry. The diastereoselectivity drops, however, in the single 6-exo process studied and now the trans product predominates (Table 1, entry 9). Nevertheless, the reasonable yield obtained for the benzopyran derivative **17** is remarkable for this kind of a 6-exo cyclization[23]. The cis stereochemistry of the cyclopentane derivatives has been assigned on the basis of the available experimental[24] and theoretical[25,26] data reported in the literature for 5-hexenyl radical cyclizations. The assignments are supported by N.O.E. studies performed on **14**, and the observation of γ-gauche effects[6,27-29] in the ^{13}C-NMR spectra of **12-14**. The stereochemistry of the rest of the cyclopentane products was assigned by analogy to these. The stereochemistry of **17** was deduced by coupling constant analysis and the observation of a ^{13}C-NMR γ-gauche effect.

Table 1. Preparation[a] of Cyclic Products from Aldehydes, Benzotriazole, and Amines



Entry	Aldehyde	Amine	Product(s)[30]	Yield[b] (%)
1	 4		 5 6	29
2			 8	[illegible]
3	7		 9	70
4[c]	7	$(PhCH_2)_2NH$	 10	39 (cis:trans = 81:19)
5	 11 (E : Z = 65:35)		 12	60 (cis:trans = 68:32)
6	11	$(PhCH_2)_2NH$	 13	63 (cis:trans = 67:33)
7	11	$(CH_2{=}CH\text{-}CH_2)_2NH$	 14	65 (cis:trans = 70:30)
8	 15		Diamine[d]	
9	 16		 17	42(60) (trans:cis = 60:40)

a Cyclization reactions were conducted by dropwise addition of 0.1M SmI_2 to the benzotriazole adduct in THF at 25°C, unless otherwise noted. b Yields refer to isolated purified material and are given for two steps, starting from the aldehyde. Numbers within brackets indicate actual cyclization yields for the second step in cases where substantial mass loss ocurred during the preparation of the benzotriazole adducts. c Reaction run at 0°C. d No cyclic product was obtained. See reference 17.

In conclusion, radicals generated by reduction of N-(N',N'-dialkylaminoalkenyl)benzotriazoles (**2**) with SmI_2 effectively participate in 5-exo and 6-exo cyclizations to afford carbocycles and heterocycles with good stereochemical control. Since substrates **2** are readily obtained[18] from aldehydes and secondary amines the method represents a convenient entry into amino-substituted cyclic products from simple starting materials. Further work, aimed at delineating the full scope of this process and its application to the synthesis of nitrogen heterocycles is currently underway.

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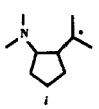
References and Notes

1. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.
2. Curran, D. P. *SynLett* **1991**, 63.
3. Curran, D. P. *Synthesis* **1988**, 417.
4. Curran, D. P. *Synthesis* **1988**, 489.
5. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.
6. Yadav, V.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 779.
7. Lolkema, L. D. M.; Hiemstra, H.; Al Ghouch, A. A.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 1491.
8. Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1990**, *31*, 759.
9. Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem.* **1991**, *56*, 5245.
10. Choi, J. K.; Ha, D. C.; Hart, D. J.; Lee, C. S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279.
11. Martin, S. F.; Yang, C. P.; Laswell, W. L.; Rüeger, H. *Tetrahedron Lett.* **1988**, *29*, 6685.
12. Kano, S.; Yuasa, Y.; Asami, K.; Shibuya, S. *Chem. Lett.* **1986**, 735.
13. Padwa, D., W.; Nimmesgern, H.; Venkatramanan, M. K.; Wong, G. S. K. *Chem. Ber.* **1986**, *119*, 813.
14. Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620.
15. For a recent review see: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.
16. Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1992**, *57*, 793.
17. Aurrecoechea, J. M.; Fernández-Acebes, A. *Tetrahedron Lett.* **1992**, *33*, 4763.
18. Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.
19. The mass obtained in their preparation was always in the range 92-100% of the theoretical amount (see Table 1 for two exceptions) and the purity was estimated by ^{1}H- and ^{13}C-NMR to be always superior to 90%. Further characterization was obtained by MS data.
20. The complexity of the reaction mixture allowed only a partial purification of these materials.
21. The formation of **5** and **6** is the result of the disproportionation of the radical *i*. For a similar observation see Curran, D.P.; Totleben, M.J. *J. Am. Chem. Soc.* **1992**, *114*, 6050.



i

22. Pasto, D. J.; Krasnanski, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062.
23. See, for example, reference 11.
24. RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.
25. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.
26. Spellmeyer, D. C.; Houk, K. M. *J. Org. Chem.* **1987**, *52*, 959.
27. Schneider, H. J.; Nguyen-Ba, N.; Thomas, F. *Tetrahedron* **1982**, *38*, 2327.
28. Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 225.
29. RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.
30. All new cyclization products have been characterized by their spectroscopic (^{1}H-, ^{13}C-NMR, IR, MS) data.

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