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Generation and Trapping of Alkene Radical Cations under Nonoxidizing Conditions: Formation of Six-Membered Rings by *Exo*- and *Endo*-Mode Cyclizations

David Crich* and Santhosh Neelamkavil

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

dcrich@uic.edu

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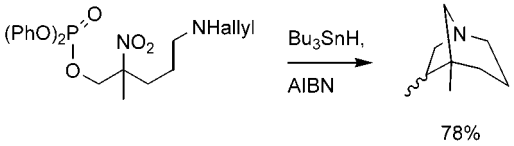
ABSTRACT



78%

It is demonstrated that alkene radical cations generated by the radical ionic fragmentation of *β*-(phosphatoxy)alkyl radicals undergo efficient nucleophilic capture by amines in either the 6-*exo* or 6-*endo* modes, leading to six-membered nitrogen heterocycles. Suitable placement of an alkene enables the juxtaposition of a radical cyclization resulting in the formation of both the indolizidine and 1-azabicyclo[3.2.1]octane skeleta.

β-(Phosphatoxy)alkyl radicals,[1,2] generated from a variety of sources, provide, by rapid radical-ionic fragmentation,[3] a convenient source of alkene radical cations under nonoxidizing conditions.[4] To date we have demonstrated how alkene radical cations obtained in this manner may be trapped inter- and intramolecularly by alcohols and amines leading to the formation of carbon−oxygen and carbon−nitrogen bonds.[5−8] The use of allyl alcohols and amines as nucleophiles permits synthetically useful radical/polar crossover sequences in which nucelophilic attack on the radical cation is followed by radical cyclization,[7,8] as exemplified by our entry into the pyrrolizidine nucleus.[8,9] In the more useful intramolecular sequences we have so far limited ourselves to 5-*exo* processes at the level of both the nucleophilic attack and the subsequent radical cyclization. Here, we describe the extension of the method to the formation of six-membered rings and, additionally, show how even highly stabilized *β*-(phosphatoxy)-alkyl radicals may be induced to undergo the radical ionic fragmentation given the appropriate reaction conditions.

As in the earlier 5-*exo*/5-*exo* synthesis of the pyrrolizidine nucleus,[8] a number of factors combined to focus our attention on the nitro group as the optimal radical precursor. First, *β*-nitro alcohols, the immediate precursors to the phosphates, are very readily assembled by the Henry reaction. Second, the strongly electron-withdrawing nitro group effectively prevents any detrimental solvolysis of the phosphate esters. Third, tertiary nitroalkanes are convenient precursors to free radicals in stannane-mediated systems.[10] Scheme 1 sets out

(1) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273.
(2) Crich, D. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2; p 188.
(3) Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X.; Yao, Q.; Zipse, H. *J. Am. Chem. Soc.* **1999**, *121*, 10685.
(4) For more classical entries into alkene radical cations under oxidizing conditions see: Hintz, S.; Heidbreder, A.; Mattay, J. In *Topics in Current Chemistry*; Mattay, J., Ed.: Springer: Berlin, 1996; Vol. 177, p 77; Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550.
(5) Crich, D.; Gastaldi, S. *Tetrahedron Lett.* **1998**, *39*, 9377.
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(8) Crich, D.; Ranganathan, K.; Huang, X. *Org. Lett.* **2001**, *3*, 1917.
(9) The use of allyl alcohols in this manner was first employed as a probe of mechanism: Giese, B.; Beyrich-Graf, X.; Burger, J.; Kesselheim, C.; Senn, M.; Schafer, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1742.

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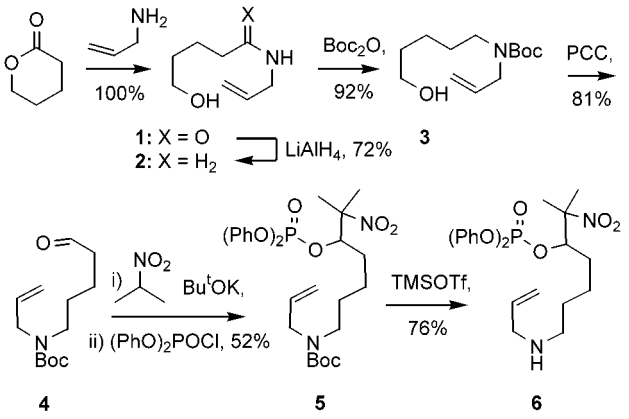
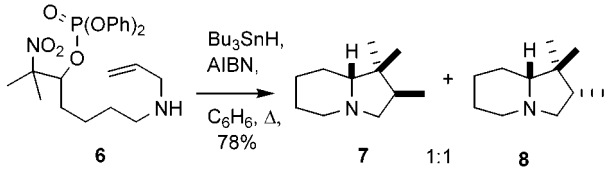
Scheme 1. Preparation of Indolizidine Precursor **6**



the synthesis of a substrate for a 6-*exo*/5-*exo* tandem nucleophilic/radical cyclization protocol whereas the cyclization itself is shown in Scheme 2.

Scheme 2. Formation of Indolizidines by a Tandem Nucleophilic 6-*Exo*/Radical 5-*Exo* Cyclization Protocol



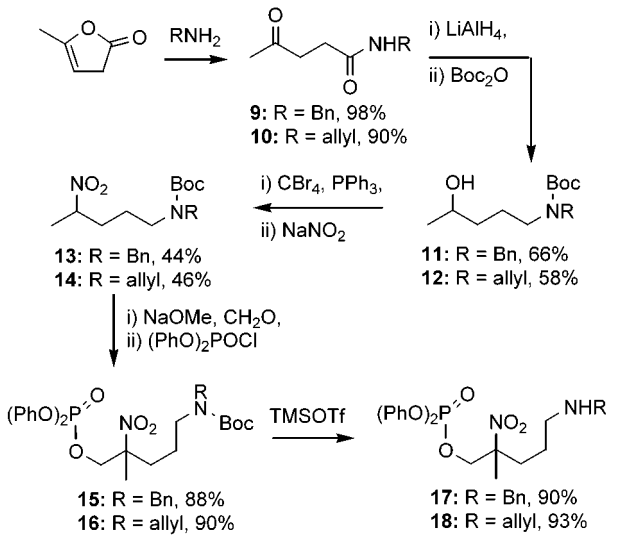
Aside from the successful high-yielding nature of the tandem cyclization (Scheme 2), and the associated increase in molecular complexity typically seen in sequenced reactions, this approach to the indolizidine nucleus is noteworthy for the rapid assembly of the very simple acyclic radical cation precursor **6** from three readily available components: δ-valerolactone, allylamine, and 2-nitropropane.

Having demonstrated the feasibility of the 6-*exo* nucleophilic trapping of the alkene radical cations, we turned our attention to the 6-*endo* mode and the concomitant need to suppress the competing 5-*exo* cyclization. We reasoned that this might best be addressed through the use of steric hindrance and so constructed the simple probe **17** as outlined in Scheme 3. Again we stress the very straightforward chemistry used to assemble this substrate and the availability of the three key building blocks: angelicalactone, benzylamine, and formaldehyde.

Treatment of **17** in benzene at reflux with tributyltin hydride and AIBN provided the known *N*-benzylpiperidine **19** in 90% yield (Scheme 4). There was no evidence for the formation of the known isomeric pyrrolizidine **20** in this reaction. The 5-*exo* cyclization mode may therefore be readily suppressed in favor of the 6-*endo*-mode through the

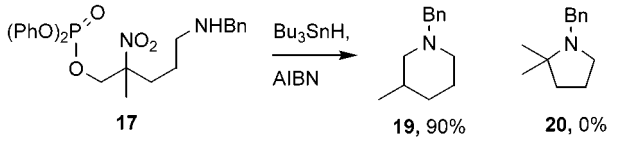
(10) Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, I.; Tamura, R.; Kaji, A. *Tetrahedron* **1985**, *41*, 4013.

Scheme 3. Preparation of Precursors for 6-*Endo* Ring Closures



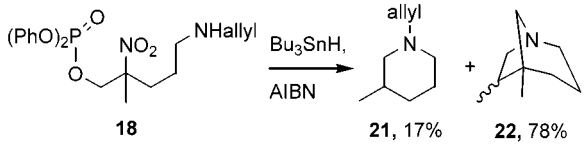
introduction of a substituent at the proximal position of the alkene radical cation.

Scheme 4. Formation of a Piperidine by a Nucleophilic 6-*Endo* Cyclization of an Alkene Radical Cation



Cyclization of **18** under the same conditions resulted in the formation of the 1-azabicyclo[3.2.1]octane **22** in 78% yield along with 17% of **21** (Scheme 5). The bicyclic product

Scheme 5. Formation of the 1-Aza[3.2.1]bicyclooctane Nucleus by a Tandem Nucleophilic 6-*Endo*/Radical 5-*Exo* Cyclization



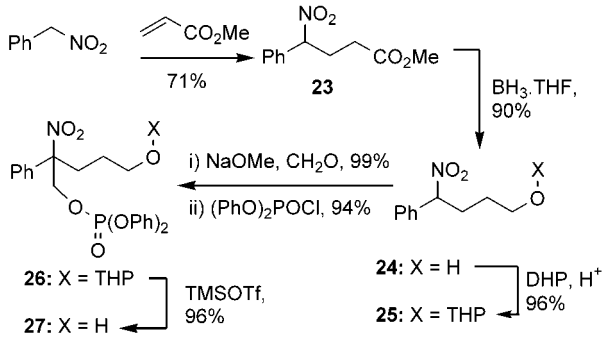
22 was isolated as an inseparable mixture of two stereoisomers in the ratio of 2:1. It is noteworthy in this tandem process that it is the radical cyclization[11] which is responsible for slight reduction in yield with respect to the prototype of Scheme 4, and not the radical ionic fragmentation and 6-*endo*

(11) For a rare, related example of the cyclizations of a 3-allylcyclohexyl type radical leading to the formation of the bicyclo[3.2.1]octane type skeleton, see Hart, D. J.; Tsai, Y. M. *J. Org. Chem.* **1982**, *47*, 4403.

cyclization. The 1-azabicyclo[3.2.1]octane skeleton constitutes the nucleus of the 5,11-methanomorphanthridine (montanine) class of the *Amaryllidaceae* alkaloids[12] and of the novel *Lycopodium* alkaloid lyconadin A.[13] Moreover, 1-azabicyclo[3.2.1]octane derivatives have been found to be potent muscarinic agonists with antipsycotic-like activity[14] and to be dopamine transporter inhibitors.[15,16] The basic tandem cyclization set out in Scheme 5 therefore provides a novel entry into a valuable class of molecules and has the potential to provide access to new substitution patterns for medicinal chemistry research.

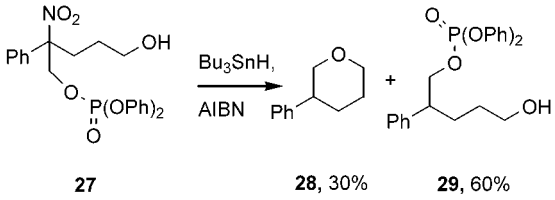
Finally, the limits of the radical ionic fragmentation were pushed through the synthesis (Scheme 6) and cyclization

Scheme 6. Preparation of the Tetrahydropyran Precursor **27**



(Scheme 7) of a probe for the formation of tetrahydropyrans via 6-*endo*-cyclization of an alcohol onto a proximally substituted alkene radical cation. In this example the proximal substituent driving the regioselectivity of the cyclization is the phenyl ring which also provides a severe test for the radical ionic fragmentation. In effect, the radical formed on homolytic removal of the nitro group from **27** is a relatively stable tertiary benzylic one and the C−O bond to be heterolyzed a primary one. This cleavage is therefore the most uphill of all the radical ionic fragmentations that we have examined to date.

Scheme 7. 6-*Endo*-Mode Cyclization Illustrating a Relatively Unfavorable Radical Ionic Fragmentation



27 **28**, 30% **29**, 60%

In the event attempted cyclization in benzene at reflux failed and resulted only in the formation of **29**, thereby emphasizing the difficulty inherent in this particular fragmentation. However, when the reaction was conducted in a mixture of benzene and acetonitrile at reflux the tetrahydropyran **28** was obtained in a yield of 30%. Given the difficulty of the fragmentation in this case, this result bodes well for the further development of the general methodology.

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Supporting Information Available: Description of experimental procedures and full characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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