ORGANIC LETTERS

2001
Vol. 3, No. 12
1917−1919

Generation and Reaction of Alkene Radical Cations under Nonoxidizing Conditions: Synthesis of the Pyrrolizidine Nucleus

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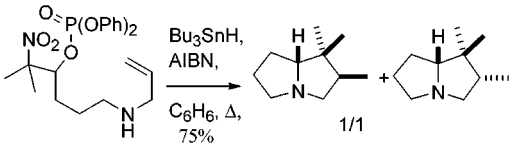
Received April 9, 2001

ABSTRACT

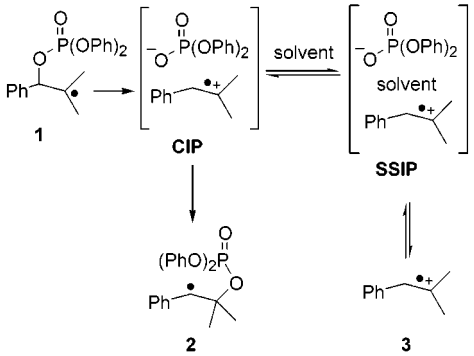


Stable β-phosphatoxy nitroalkanes, readily assembled by the Henry reaction and subsequent phosphorylation, serve as good precursors to alkene radical cations on treatment with triphenyltin or tributyl hydride and AIBN in benzene at reflux. When the β-phosphatoxy nitroalkane is suitably functionalized with nucleophilic groups, substitutions can be achieved with the formation of heterocyclic rings. When the nucleophile is an allylamine, tandem processes occur giving pyrrolizidines.

Direct spectroscopic evidence for the fragmentation of β-aryl-β-(phosphatoxy)alkyl radicals (**1**)[1] into styrene radical cations (**3**) in polar solvents has recently been provided. In nonpolar solvents the same radicals are observed to undergo rearrangement to the benzylic radicals **2**, but the linearity of plots of log(k) for the fragmentation and/or rearrangement against the $E_T(30)$ solvent polarity scale lead to the conclusion that all such reactions of **1** have the same rate-determining step, viz. radical ionic fragmentation to an alkene radical cation/phosphate anion contact ion pair (**CIP**).[2] In nonpolar solvents the caged radical ion pair rapidly collapses to give the benzyl radicals (**2**), whereas in more polar solvents it is in equilibrium with solvent separated ion pairs (**SSIP**) and, eventually, observable free ions (Scheme 1).[2] Subsequent experiments, in which the diffusion-controlled oxidation of triarylamines by alkene radical cations was used to probe the formation of the latter, revealed that α-alkoxy-β-(phosphatoxy)radicals behave in a comparable manner.[3]

Given that the initial radicals (**1**) may be generated from a wide variety of precursors, it may be readily appreciated that a new versatile source of alkene radical cations is at hand. Such alkene radical cations have only previously been

Scheme 1. General Mechanistic Scheme for Fragmentation and Rearrangement of β-(Phosphatoxy)alkyl Radicals



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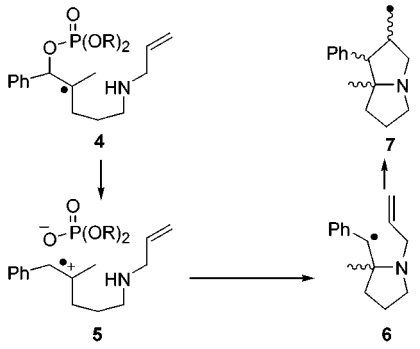
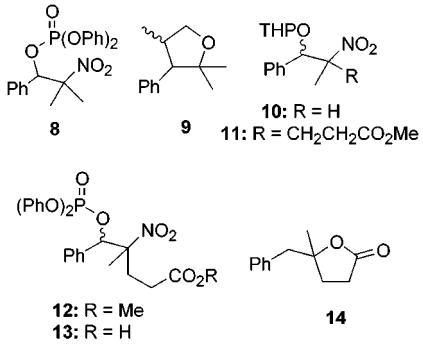
10.1021/ol015965h CCC: $20.00
Published on Web 05/22/2001

accessible from alkenes under strongly oxidizing conditions, which has limited practical applications of their colorful chemistry.[4] In a first demonstration of the potential of the new method, we studied trapping by alcohols, both intra- and intermolecularly, leading to the formation of tetrahydrofurans.[5] We now describe our preliminary results on the extension of this chemistry to a radical/ionic cascade sequence involving intramolecular nucleophilic capture of the radical cation by an allylamine followed by radical cyclization leading, overall, to the formation of pyrrolizidines (Scheme 2).

Scheme 2. Cascade Sequence for the Formation of Pyrrolizidines from β-(Phosphatoxy)alkyl Radicals

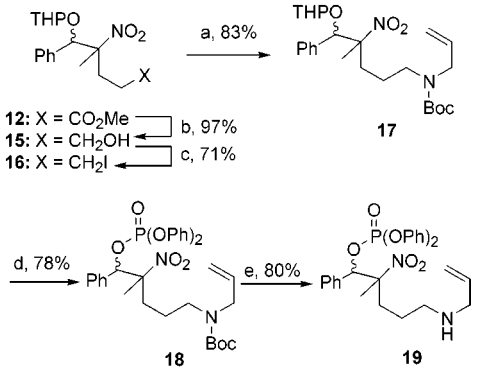


In reducing Scheme 2 to practice, we were immediately confronted by the need for a precursor to radical **4** compatible with the presence of the nucleophilic amine. Evidently, halides were not suitable, nor were Barton esters,[6] which would be likely to undergo lactamization. Phenyl sulfides were considered insufficiently reactive toward stannyl radicals[7] to permit smooth chain propagation, and we have generally found 2-phenylselenoalkyl phosphates to be unstable, with respect to alkene formation,[8] unless formation of an episeleninium ion is stereochemically prevented.[9] Ultimately tertiary nitroalkanes were selected as the precursors of choice, being readily accessible, electron withdrawing and therefore likely to stabilize the benzylic phosphates, and good radical precursors in tin hydride mediated chain sequences.[10] To test this idea, **8** was assembled by condensation of 2-nitropropane with benzaldehyde followed by reaction with diphenyl chlorophosphate. As expected, it was found to be stable in benzene at reflux, to silica gel chromatography and, on reaction with allyl alcohol and triphenyltin hydride[11] in benzene at reflux, to afford the tetrahydrofuran **9**[5b] in 59% yield. This product arises from regioselective trapping of the β,β-dimethylstyrene radical cation by allyl alcohol and subsequent radical cyclization.[5b] In a second proof of concept, benzaldehyde was condensed with nitroethane and the resulting nitroaldol converted to the THP derivative **10** in 99% overall yield. Stirring of **10** with DBU and methyl acrylate in acetonitrile then afforded **11** in 80% yield. Removal of the THP group in the standard manner and phosphorylation provided **12** in 63% yield, which on saponification gave **13** quantitatively. When this substance was exposed to triphenyltin hydride,[11] with AIBN initiation in benzene at reflux, the γ-lactone **14** was obtained in 90% yield. In this chemistry the vicinal nitrophosphate serves as the precursor to the alkene radical cation, which suffers nucleophilic attack by the acid. The benzyl radical, formed in the course of the cyclization, is quenched by the stannane. This example serves to highlight the further significant advantage of the use of the nitro group as radical precursor, namely, the ease with which the substrates can be assembled by simple condensations and alkylations using very well known chemistry.



A suitable precursor (**19**) to radical **4** was readily assembled from **12** as outlined in Scheme 3. Treatment of **19** with triphenyltin hydride and AIBN in benzene at reflux gave, after recycling of the tin hydride with sodium borohydride[12] and silica gel chromatography, four diastereomeric

Scheme 3. Preparation of Radical Precursor **19**[a]



[a] (a) (i) Allylamine, (ii) Boc_2O; (b) $LiAlH_4$; (c) Ph_3P, I_2, imidazole; (d) (i) TsOH, (ii) $(PhO)_2POCl$, DMAP; (e) tmsOTf, lutidine.

(3) Newcomb, M.; Miranda, N.; Huang, X.; Crich, D. *J. Am. Chem. Soc.* **2000**, *122*, 6128.

(4) (a) Mattay, J. *Synthesis* **1989**, 233. (b) Hintz, S.; Heidbreder, A.; Mattay, J. In *Topics in Current Chemistry*; Mattay, J., Ed.; Springer: Berlin, 1996; Vol. 177, p 77. (c) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550. (d) Bauld, N. L.; Bellville, D. J.; Harirchian, B.; Lorenz, K. T.; Pabon, R. A.; Reynolds, D. W.; Wirth, D. D.; Chiou, H.-S.; Marsh, B. K. *Acc. Chem. Res.* **1987**, *20*, 269. (e) Lewis, F. D. *Acc. Chem. Res.* **1986**, *19*, 401.

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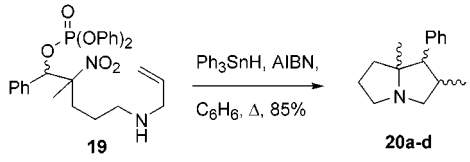
(6) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

pyrrolizidines (**20a**−**d**) in a combined yield of 85% and ratio 2.7:1.6:1:1 (Scheme 4). The general concept of Scheme 2 was therefore shown to be viable.

Scheme 4. Cyclization of **19**



The four diastereomers were separated by careful chromatography and assigned the structures in Figure 1 on the basis of extensive NOE studies. The two major isomers (**20a**,**b**) have the phenyl group on the *exo*-surface of the bicyclic system and differ in the relative configurations of the two stereocenters formed in the final cyclization. As is typical in 1-phenyl-5-hexenyl-type cyclizations,[13] the major isomer (**20a**) has the *trans*-configuration about the newly formed bond. We propose therefore that the major isomer arises from a boatlike transition state (**21a**) that is a consequence of the preference of the phenyl group for the *exo*-surface and of the nascent bond to be *trans*. The second major product issues from the chairlike transistion state **21b**, whereas the two minor products are the result of chair- and boatlike transition states with the phenyl group on the more hindered *endo*-surface of the bicyclic system.

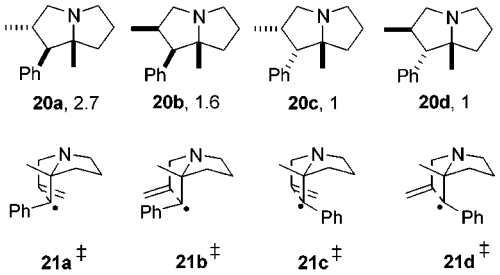
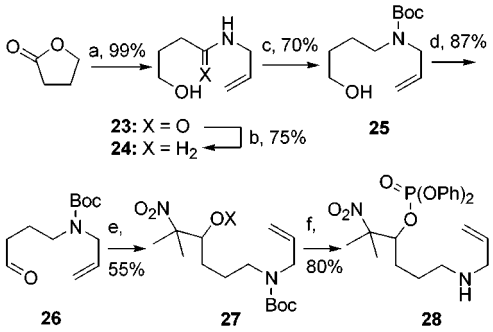


Figure 1. Products (**20a**−**d**) and corresponding transition states (**21a**−**d**) for the cyclization of **19**.

A further substrate (**28**) for cyclization was readily prepared as outlined in Scheme 5 with the key feature again being the rapid assembly by the Henry reaction with a simple aldehyde and subsequent phosphorylation.

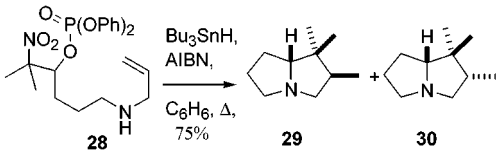
Scheme 5. Preparation of Radical Precursor **28**[a]



[a] (a) Allylamine; (b $LiAlH_4$; (c) Boc_2O; (d) PCC; (e) (i) Me_2CHNO_2, $KOBu^t$, (ii) $(PhO)_2POCl$, DMAP; (f) tmsOTf, lutidine.

Treatment of **28** with tributyltin hydride[11] and AIBN in benzene at reflux led to a 75% isolated yield of the pyrrolizidines **29** and **30** as a 1:1 mixture of two diastereoisomers (Scheme 6).

Scheme 6. Cyclization of **28**



This last example serves to focus attention on two key points. First, benzylic stabilization is not necessary in this chemistry. Second, and very important in terms of synthetic planning, the key radical cation intermediates may be entered from both sides. More explicitly, the departing phosphate may be displaced in either a *cine* fashion, as in Schemes 2 and 4, or directly as in Scheme 6.[5b] Further cascade type polycyclizations of reductively generated alkene radical cations are under investigation and will be reported on in due course.

Acknowledgment. We thank the NSF (CHE 9986200) for support of this work.

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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