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FREE RADICAL CYCLIZATIONS OF TERMINAL ALKYNES WITH OXIME ETHERS

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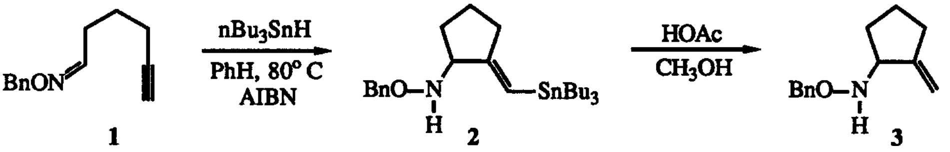
Abstract: A benzyl oxime ether tethered to a terminal alkyne efficiently undergoes a free radical hydrostannylation reaction to afford five- and six-membered rings bearing a protected amine and a vinyl stannane functionality. These products were subsequently protiodestannylated to obtain the unsubstituted exo-methylene compounds.

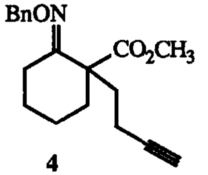
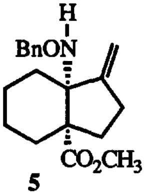
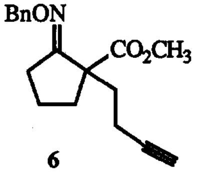
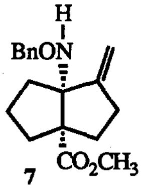
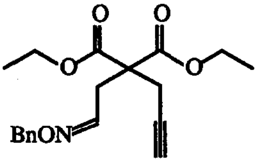
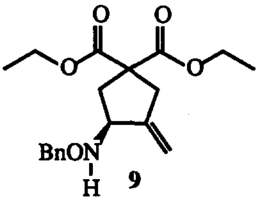
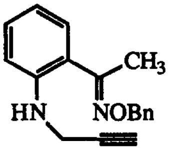
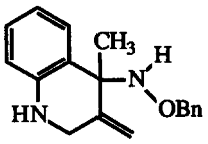
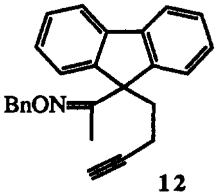
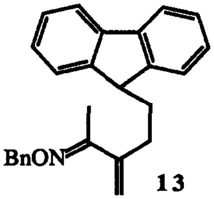
Free radical reactions are germane to practical synthetic construction and this has led to their rapid growth in total synthesis.[1] An important variation of these reactions is the hydrostannylation reaction which invokes vinyl tin radicals, preparable from a terminal alkyne and tributyltin radical, to produce five-membered rings when utilized with a suitably disposed free radical acceptor.[1,2] An alkene[2] and a carbonyl[3] have both been examined as acceptors in this reaction, however, oxime ethers have not.[4] In this Letter we describe a synthetic study which combines the effective radical trapping ability of an oxime ether with a vinyl stannane radical in an efficient cyclization reaction.



The simplest version of this process involves the intramolecular coupling of a terminal alkyne tethered to an oxime ether **1** which was promoted by tributyltin hydride under free radical conditions, to produce the cyclized product **2**.[5] A subsequent protiodestannylation[2(b)] with acetic acid in methanol then afforded the desired cyclopentane ring bearing a versatile exo-methylene subunit and a benzyl ether-substituted amine functionality.[6] Several examples of this sequence are shown in Table 1. The yields for the radical reactions were generally good, ranging from 56% to 90%. In every example except entry 5, a well-functionalized cyclopentane ring was obtained. This methodology should be directly applicable to the preparation of various natural products containing nitrogen, such as alkaloids. Although the tributyltin function was removed with acetic acid in each example, the intermediate vinyl stannane compound is isolable[5] and can provide a useful functionality for further manipulations to access vinyl anions, carbonyl compounds, vinyl halides, and Pd(0)-catalysed coupling reactions.[7]

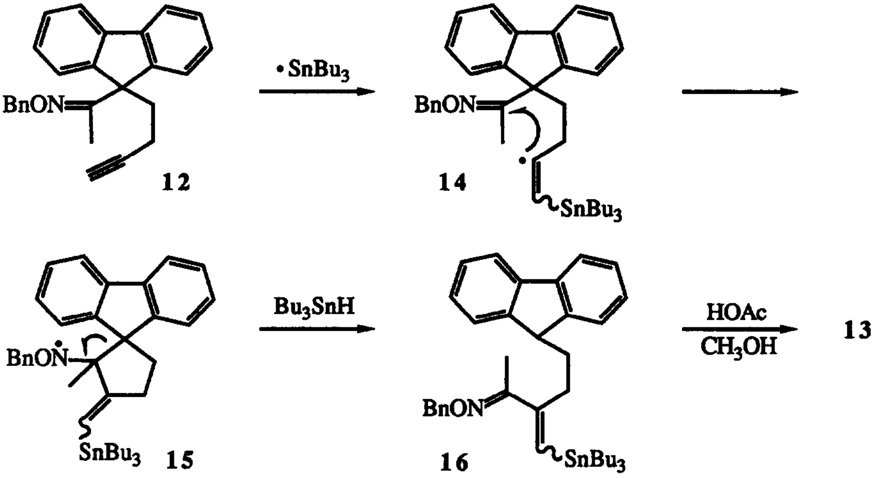
Table 1

Intramolecular Radical Reactions of Alkynes and Oxime Ethers

Entry	Starting Substrate[a]	Product[b]	Yield[c]
1	 4	 5	82%
2	 6	 7	90%
3	 8	 9	56%[d]
4	 10	 11	60%
5	 12	 13	58%

[a] All new compounds produced IR, ^{1}H NMR, ^{13}C NMR, mass spectrum, combustion analysis and/or accurate mass data consistent with the structure shown; All compounds are racemic; in some cases, a single enantiomer is shown for clarity; [b] Typical experimental procedures are given in the references[5,6]; [c] Yield data is for chromatographically homogeneous materials; [d] Based on recovered starting material.

Fused bicyclo[4.3.0]- and bicyclo[3.3.0]-ring systems can be achieved by directed annulation using this methodology as entries 1 and 2 demonstrate, respectively. The aldo-oxime ether starting substrate **8** in entry 3 smoothly cyclized to the desired cyclopentane product **9** and other examples show that the method also functions well for several keto-oxime ethers. It should be noted that the geometry of the oxime ether apparently did not adversely influence the outcome of the reactions, and mixtures were used in most cases. Entry 4, in which a six-membered ring is formed, demonstrates that access to quinolinoid-type skeletons is feasible from the ortho-disubstituted aniline compound **10**.



The last example in Table 1, entry 5, did not lead to a cyclized product. A plausible mechanistic explanation for the formation of **13** emanates from the initial formation of vinyl tin radical intermediate **14**, by addition of tributyltin radical to the terminal acetylene in **12**. A subsequent cyclization with the sp^2 carbon of the oxime ether affords the nitrogen-centered free radical species **15**. After undergoing ring cleavage to produce the fluorene-stabilized radical, a transfer of hydrogen radical from tributyltin hydride renders the ring-opened oxime ether **16**. It is interesting to note that none of the cases in entries 1, 2, and 4 resulted in a similar bond cleavage reaction and this is likely due to the superior radical-stabilizing effect of the fluorene ring system.

In conclusion, a general method for the intramolecular coupling of a benzyl oxime ether tethered to a terminal alkyne has been developed. The overall sequence utilizes tributyltin hydride in a free radical reaction to prepare substituted cyclopentane rings. The application of these methods to the synthesis of natural products is in progress.[8]

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(2) (a) Stork, G. in "Radical-Mediated Cyclization Processes," in "Selectivity- a Goal for Synthetic Efficiency," Bartmann, W.; Trost, B. M., Eds. Verlag Chemie, Weinheim, **1984**; (b) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829.

(3) Examples of the use of carbonyls as free radical acceptors: (a) Fraser Reid, B.; Vite, G. D.; Yeung, B. -W. A.; Tsang, R.; *Tetrahedron Lett.* **1988**, 1645; (b) Nishida, A.; Takahashi, H.; Takeda, H.; Takada, N.; Yonemitsu, O. *J. Am. Chem. Soc.* **1990**, *112*, 902; (c) Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am . Chem. Soc.* **1987**, *109*, 3484; (d) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102.

(4) Other uses of oxime ethers as free radical acceptors: (a) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, 2821; (b) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631; (c) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633, and references therein.

(5) In a typical experiment, the oxime ether starting material was dissolved in benzene (0.02 M solution) and a catalytic amount of AIBN (0.20 eq.) and nBu_3SnH (1.20 eq.) was added. After degassing the solution with a stream of argon for 30 min., it was heated to 80° C for 18-24 h and the reaction was monitored by TLC until the starting material was consumed. After removing the benzene under reduced pressure, ^1H NMR indicated the product was generally clean and was subjected directly to protiodestannylation without purification. It is possible to chromatograph the vinyl stannane, however, reduced yields often result because the silica gel causes protiodestannylation.

(6) In a typical experiment, the cyclic vinyl stannane was dissolved in methanol (0.5 M solution) and a catalytic amount of acetic acid was added to the solution. The reaction was stirred at 23° C and was monitored by TLC until the starting material was consumed. Compound **11** required heating to reflux for 48 h to remove the stannane moiety. After evaporation of the solvents, the crude mixture was chromatographed over silica gel to afford the desired cyclopentane products.

(7) For a review on several examples of vinyl tin elaborations, see: Pereyre, M; Quintard, J. -P.; Rahm, A. in "Tin in Organic Synthesis," Butterworth & Co., London, **1987**.

(8) More details on these studies will be published in a subsequent full paper.

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