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Inhibition of Stannane-Mediated Radical Rearrangements by a Recoverable, Minimally Fluorous Selenol

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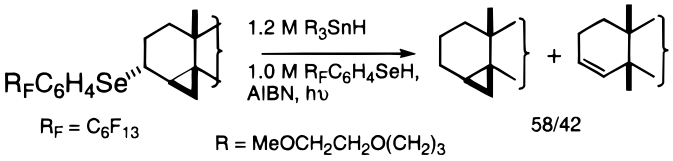
ABSTRACT



The preparation of a minimally fluorous diaryl diselenide is described. It is demonstrated that this diselenide, reduced in situ to the corresponding selenol, may be used in conjunction with stannanes to prevent a number of radical rearrangements. A 1 M solution of this selenol used in admixture with Breslow's water-soluble stannane can be used to significantly inhibit a cyclopropylcarbinyl ring opening. The combination of the fluorous selenol and the polar stannane permits recovery of the selenol by continuous fluorous extraction and isolation of a stannane-free hydrocarbon product.

We have previously described how a number of radical rearrangements may be inhibited by the inclusion of catalytic quantities of diphenyl diselenide in stannane-mediated reductions of alkyl halides and aryl and vinyl iodides.[1] This phenomenon, which is an extension of Robert's concept of polarity reversal catalysis,[2] arises from the in situ reduction of the diselenide to benzeneselenol (eq 1), the approximately 1000-fold difference in rates of trapping of alkyl radicals by Bu_3SnH[3] and PhSeH,[4] and the operation of the chain sequence illustrated in eqs 2−4. We have also demonstrated how the same chain sequence may be used to vastly improve propagation efficiency in radical reductions involving stabilized allyl, cyclohexadienyl, and benzyl radicals.[1d,e]

$$Bu_3SnH + PhSeSePh \rightarrow Bu_3SnSePh + PhSeH \quad (1)$$

$$R^\bullet + PhSeH \rightarrow RH + PhSe^\bullet \quad (2)$$

$$PhSe^\bullet + Bu_3SnH \rightarrow PhSeH + Bu_3Sn^\bullet \quad (3)$$

$$Bu_3Sn^\bullet + RX \rightarrow Bu_3SnX + R^\bullet \quad (4)$$

Currently we are interested in extending this methodology to the prevention of very rapid radical rearrangements such as the cyclopropylcarbinyl/homoallyl fragmentation. Consideration of the rate equations for the opening of the cyclopropylmethyl radicals,[5] and for the trapping of alkyl radicals by benzeneselenol,[4] provides an estimate that the selenol concentration needed to prevent these extremely fast rearrangements would be in the molar range. Such high concentrations are obviously no longer catalytic and pose the problem of product purification and recovery of the selenol/diselenide. We reasoned that the answer to these problems lay in the use of a fluorous areneselenol that, after the reaction, could be extracted in a fluorous phase.[6] Here, we describe the successful implementation of this concept.

(1) (a) Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84. (b) Crich, D.; Jiao, X.-Y.; Yao, Q.; Harwood: J. S. *J. Org. Chem.* **1996**, *61*, 2368. (c) Crich, D.; Hwang, J.-T.; Liu, H. *Tetrahedron Lett.* **1996**, *37*, 3105. (d) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765. (e) Crich, D.; Mo, X.-S. *J. Am. Chem. Soc.* **1998**, *120*, 8298. (f) Crich, D.; Hwang, J.-T.; Gastaldi, S.; Recupero, F.; Wink, D. J. *J. Org. Chem.* **1999**, *64*, 2788.

(2) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.

(3) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

(4) (a) Newcomb, M.; Varick, T. R.; Ha, C.; Manek, M. B.; Yue, X. *J. Am. Chem. Soc.* **1992**, *114*, 8158. (b) Newcomb, M.; Choi, S.-Y.; Horner, J. H. *J. Org. Chem.* **1999**, *64*, 1225.

(5) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.

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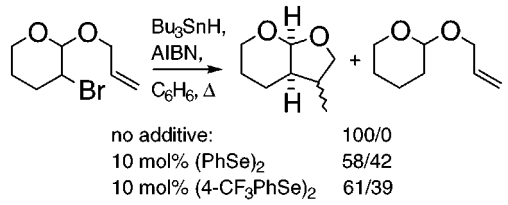
In the first instance the ability of 4-trifluoromethylbenzeneselenol, obtained in situ from bis(4-trifluoromethylphenyl) diselenide,[7] to quench alkyl radicals was assessed. As shown in Scheme 1, this selenol is slightly less efficient

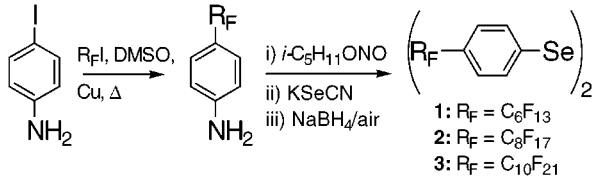
Scheme 1. Effect of a *p*-CF_3 Group



than benzeneselenol itself in preventing a simple radical rearrangement. This slight loss of activity was considered a reasonable price to pay for the simplified synthesis of fluorous derivatives with the fluorous chain directly bound to the arene as opposed to those with an insulating spacer.

Accordingly, three simple fluorous diselenides were prepared as outlined in Scheme 2. Only one of these (**3**) at

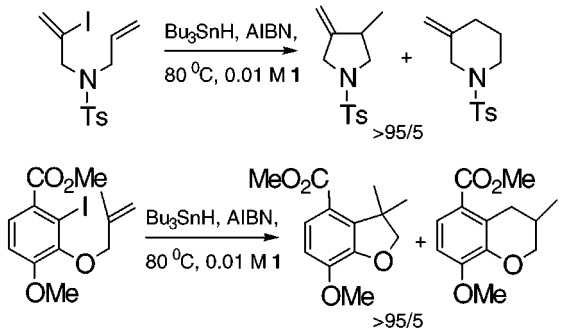
Scheme 2. Preparation of Fluorous Diselenides



59% F by weight approximated the 60% fluorous character usually considered a minimum[6] for efficient fluorous extraction. Unfortunately, with its 1346 molecular weight, this substance proved to be insoluble in most organic and even fluorous solvents. Diselenide **2** at 56% was somewhat more soluble, but certainly not to the molar concentrations required here. Only **1** (MW 946, 52% F) was sufficiently soluble for our purposes, but it was not fluorous enough for simple extractive purification. We have recently developed a modified continuous flow extractor to overcome exactly this type of problem[8] and fortunately, it enabled the ready, complete extraction of **1** from CH_2Cl_2 or toluene into perfluoromethylcyclohexane.

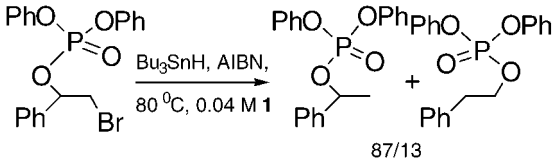
The ability of significant concentrations of **1** to inhibit various radical rearrangements was next tested. As shown in Scheme 3, a 0.01 M solution of **1**, and therefore of the corresponding selenol, was able to completely inhibit the homoallyl/cyclobutyl and neophyl type rearrangements ($k \sim 10^4\ s^{-1}$),[9,10] which typically complicate vinyl and aryl radical cyclizations,[10,11] without detriment to the initial cyclizations.[12]

Scheme 3. Inhibition of Homoallyl and Neophyl Rearrangements



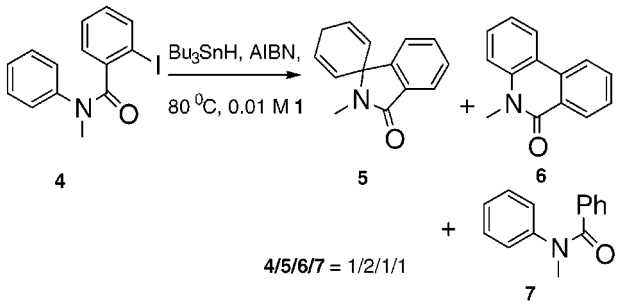
Subsequently, a reduced 0.04 M solution of diselenide **1** was found to be capable of almost completely inhibiting a rapid ($k_{80} = 8 \times 10^5\ s^{-1}$)[13] β-(phosphatoxy)alkyl rearrangement[14] (Scheme 4).[10]

Scheme 4. Inhibition of a β-(Phosphatoxy)alkyl Rearrangement



Scheme 5[10] is intended to show that the selenol derived by reduction of **1**, like PhSeH,[1d] is capable of transferring

Scheme 5. Improvement of Chain Transfer



hydrogen to a resonance-stabilized cyclohexadienyl and therefore of improving propagation efficiency. In the absence of selenol, chain propagation is poor, very significant

(6) Reviews on fluorous chemistry: (a) Curran, D. P. *Angew Chem., Int. Ed. Engl.* **1998**, *37*, 1174. (b) de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev.* **1999**, *28*, 37. (c) Horvath, I. T. *Acc. Chem. Res.* **1998**, *31*, 641.

(7) Schmid, G. H.; Garratt, D. G. *J. Org. Chem.* **1983**, *48*, 4169.

(8) Crich, D.; Hao, X. Unpublished.

(9) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

(10) In each of these experiments **1** was recovered in a minimum of 85% yield by continuous fluorous extraction with the modified continuous extractor.

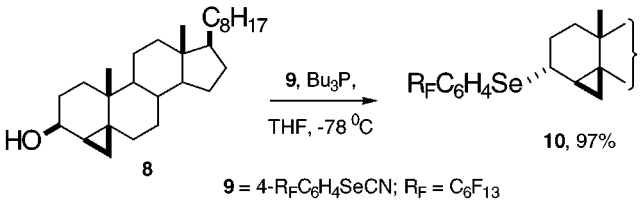
(11) (a) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525. (b) Stork, G.; Mook, R. *Tetrahedron Lett.* **1986**, *27*, 4529. (c) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072.

amounts of substrate are recovered, and the only isolable cyclized product obtained is the thermodynamic phenanthridinone **6**.[1d]

Returning to the rapid type (k 10^6-10^7 s^{-1})[9] of 5-hexenyl radical closing set out in Scheme 1, we found that a 0.07 M reduced solution of **1** resulted in an approximately 1/1 ratio of reduced and rearranged products. However, when the concentration of reduced **1** was increased to 0.6 M, the rearrangement was completely inhibited with only the reduction product being observed in the ^{1}H NMR spectrum of the crude reaction mixture. Again, **1** could be recovered in good yield by the continuous fluorous extraction protocol.

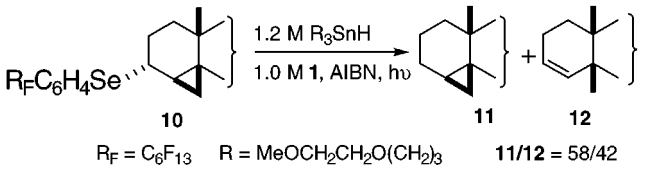
Finally, we returned to our objective of preventing cyclopropylcarbinyl rearrangements. Thus, the known[15] cyclopropanated sterol **8** was treated with 2 molar equiv of the fluorous selenocyanate **9** (the precursor to **1**, Scheme 2) and Bu_3P in THF at −78 °C. Filtration of the crude reaction mixture on silica gel gave a mixture consisting of the anticipated inverted, fluorous selenide **10**,[16] and diselenide **1**. Partitioning of this mixture between toluene and perfluoromethylcyclohexane in the modified continuous extractor enabled the recovery of **1** and the isolation of analytically pure **10** (only 28% fluorous and therefore not extracted) in 97% yield (Scheme 6).

Scheme 6. Preparation of Selenide **10**



Irradiation of **10** in benzene with a combination of diselenide **1** (1.0 M), Breslow's stannane[17] (1.2 M), and AIBN in benzene at room temperature for 30 min resulted in a complex reaction mixture which was first treated with benzoyl peroxide at reflux[18] and then partitioned between toluene and perfluoromethylcyclohexane in the continuous extractor.[8] In this manner 90% of the total diselenide **1** was recovered from the fluorous phase for reuse. The toluene phase was filtered on silica gel with hexanes to give a mixture of the known[19] reduced and ring-opened products **11** and **12**, respectively, in 65% yield and a 58/42 ratio (Scheme 7). Thus, the molar concentration of fluorous selenol enables

Scheme 7. Inhibition of a Cyclopropylcarbinyl Opening



trapping of a typical cyclopropylcarbinyl radical in preparatively significant yield. Moreover, isolation of the hydrocarbon products was facilitated by the continuous extraction of the minimally fluorous selenide and the use of the more polar tin hydride.

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

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(12) The selenol does not catalyze the reduction of the initial vinyl or aryl radical owing to the already very high rate constants for trapping of these types of radical by the stannane. For discussions of this point, see refs 1c and 1f.

(13) Crich, D.; Jiao, X.-Y. *J. Am. Chem. Soc.* **1996**, *118*, 6666.

(14) (a) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **1993**, *115*, 1165. (b) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273.

(15) Sampson, N. S.; McCann, A. E. *J. Org. Chem.* **1997**, *62*, 5893.

(16) Preparation and stannane-mediated opening of a related phenyl selenide: Clive, D. L. J.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 3801.

(17) (a) Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957. (b) Light, J.; Breslow, R. *Org. Synth.* **1993**, *72*, 199.

(18) This treatment cleaves the stannyl selenides: Schiesser, C. H.; Fong, M. C. *J. Org. Chem.* **1997**, *62*, 3103.

(19) (a) Cerny, V.; Budesinsky, M.; Sorm, F. *Collect. Czech. Chem. Commun.* **1973**, *38*, 565. (b) Muchmore, D. C. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. 6, p 762.