ORGANIC LETTERS

2004
Vol. 6, No. 7
1135−1138

Hydroselenation of Alkynes by Lithium Butylselenolate: An Approach in the Synthesis of Vinylic Selenides

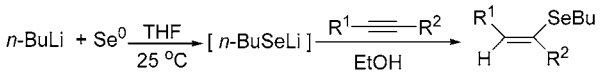
Gilson Zeni,*,[†] Marcelo P. Stracke,[†] Cristina W. Nogueira,[†] Antonio L. Braga,[†] Paulo H. Menezes,[‡] and Helio A. Stefani[§]

Laboratório de Síntese, Reatividade, Avaliação, Toxicológica e Farmacológica de Organocalcogenios−CCNE-UFSM, 97105-900 Santa Maria RS, Brazil, Departamento de Química Fundamental−UFPE, Recife. Brazil, and Faculdade de Ciências Farmacêuticas−USP, São Paulo, Brazil

gzeni@quimica.ufsm.br

Received January 17, 2004

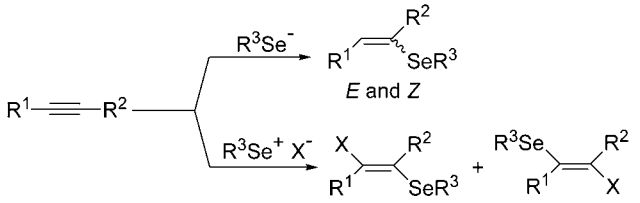
ABSTRACT



Vinylic selenides were prepared in good yields by hydroselenation of alkynes with lithium butylselenolate generated by reaction of *n*-butyllithium with elemental selenium. The regio- and stereochemistry of the hydroselenation depend on the nature of the substituents bonded to the alkyne.

Organoselenium compounds have become attractive synthetic targets because of their chemo-, regio-, and stereoselectivity reactions[1] and their useful biological activities.[2] On this way, vinylic selenides play an important role in the synthesis of organoselenium compounds, especially in the development of many convenient methods for the stereoselective preparation of functionalized alkenes.[3] Although various methods are mentioned for the preparation of vinylic selenides, a more useful procedure has centered on the nucleophilic or electrophilic organoselenium addition to terminal or internal alkynes.[4] For example, the nucleophilic addition of selenophenol to alkynes affords, preferentially, the *Z*-vinylic selenides after longer reaction times at room temperature. The reaction is faster at a high temperature; however, the mixture of *Z*- and *E*-vinylic selenides was obtained in an almost 1:1 ratio (Scheme 1).[5] On the other hand, the eletrophilic addition of organoselenenyl halides to alkynes gave a mixture of Markownikov and anti-Markownikov

Scheme 1



[†] CCNE-UFSM.
[‡] UFPE.
[§] USP.

(1) (a) *Organoselenium Chemistry*, *Topics in Current Chemistry 208*; Wirth, T., Ed.; Springer-Verlag: Heidelberg, 2000. (b) Krief, A. In *Comprehensive Organometallic Chemistry II*; Abel, E. V., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol. 11, Chapter 13. (c) Paulmier, C. In Organic Chemistry Series 4. Baldwin, J. E., Ed.; *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986.

(2) (a) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125−2179. (b) Parnham, M. J.; Graf, E. *Prog. Drug Res.* **1991**, *36*, 9−47. (c) Nogueira, C. W.; Quinhones, E. B.; Jung, E. A. C.; Zeni, G.; Rocha, J. B. T. *Inflammation Res.* **2003**, *52*, 56−63.

(3) Comasseto, J. V.; Ling, L. W.; Petragnani, N.; Stefani, H. A. *Synthesis* **1997**, 373−403.

(4) (a) Comasseto, J. V. *J. Organomet. Chem.* **1983**, *253*, 131−181. (b) Barros, O. S. D.; Lang, E. S.; de Oliveira, C. A. F.; Peppe, C.; Zeni, G. *Tetrahedron Lett.* **2002**, *43*, 7921−7923. (c) Dabdoub, M. J.; Dabdoub, V. B.; Pereira, M. A. *Tetrahedron Lett.* **2001**, *42*, 1595−1597. (d) Dabdoub, M. J.; Baroni, A. C. M.; Lenardão, E. J.; Gianeti, T. R.; Hurtado, G. R. *Tetrahedron* **2001**, *57*, 4271−4276. (e) Dabdoub, M. J.; Cassol, T. M.; Batista, A. C. F. *Tetrahedron Lett.* **1996**, *37*, 9005−9008.

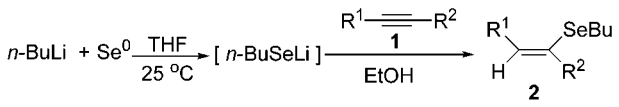
10.1021/ol0498904 CCC: $27.50
Published on Web 03/09/2004

adducts, depending on the nature of the substituents at the triple bond (Scheme 1).[6] Conversely, vinylic selenides can be prepared by palladium-catalyzed hydroselenation of alkynes to afford the Markownikov adduct in good yields.[7]

There are some limitations associated with the methodologies to prepare vinylic selenides illustrated above; procedures described employ diorganoyl diselenides[8] or selenophenol[9] as starting materials, which are volatile and unstable and have an unpleasant odor. Also, the preparation of these compounds is complex.

We now wish to report our results on the preparation of vinylic selenides via hydroselenation of terminal and internal alkynes, avoiding the previous preparation of diorganoyl disselenides or selenophenol. Thus, a solution of alkyne in deoxygenated ethanol was added dropwise to a solution containing *n*-BuSeLi (generated in situ by addition of *n*-butyllithium to a suspension of elemental selenium and THF at room temperature). The resulting solution was refluxed for 24 h and monitored by TLC to produce the desired vinylic selenides in good yields and high regio- and stereoselectivity (Scheme 2).[10]

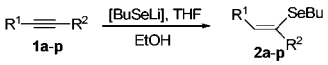
Scheme 2



Our investigation began with the addition of lithium *n*-butylselenolate to internal alkynes, and the results are shown in Table 1. The hydroselenation of symmetrical internal alkynes (entries a−e) readily produces, stereoselectively, the *Z*-vinylic selenides **2a**−**e** in good yields, except for dibutylacetylene, which did not give the desired vinylic selenides (Table 1, entry e). Under the same reaction conditions, the hydroselenation of unsymmetrical internal alkynes (Table 1, entries f−i) produced the corresponding vinylic selenides in good yields and in high stereo- and regioselectivity. The regio-and stereoselectivities obtained in the products described in Table 1 could be justified by both steric and electronic effects of the substituents on the triple bond. We have also therefore performed a series of reactions to test whether unsymmetrical internal alkynes bearing a heteroatom such as Si, Te, Sn, Se, S, or P would react in the same fashion with lithium butyl selenenolate (Table 1, entries j−p). As a result, the phenylthio acetylene **1j** gave the *Z*-vinylic selenides **2j** with the addition of the organoselenium group at the β-position relative to methylthio substituent as a single regio-, and stereoisomer in 59% yield (Table 1, entry j). The hydroselenation of 1-alkynylphosphonate (Table 1, entry l) gave regioselectively the β-butylseleno vinyl phosphonate in 64% yield. However, considerable loss of stereoselectivity was verified (the *Z*- and *E*-β-butylseleno vinyl phosphonates were obtained in a 1:1 ratio). The hydroselenation did not proceed with unsymmetrical internal alkynes bearing an organoselenium, tellurium, tin, or silicon group bonded directly at the triple bond (Table 1, entries m−p). In these cases we observed only the cleavage of the carbon-heteroatom bond. Thus, the products were phenylacetylene together with organoselenium compounds **3** containing the heteroatom bonded directly at the selenium atom, probably as the result of a direct attack of *n*-BuSeLi to the heteroatom (Se, Si, Sn, Te) (Scheme 3).

Next we decided to expand the scope of this method to include terminal alkynes. Thus, a solution of 1-alkyne in

Table 1. Hydroselenation of Internal Alkynes



entry	R^1	R^2	yield[a] (%)
a	Ph	Ph	60
b	≡—C(Me)(Et)OH	C(Me)(Et)OH	55
c	≡—CH_2OH	CH_2OH	69
d	≡—Ph	Ph	67
e	C_4H_9	C_4H_9	NR
f	C_4H_9	Ph	48
g	Ph	CH_2OH	65
h	≡—C_4H_9	Ph	66
i	≡—Ph	$C(Me)_2OH$	63
j	SCH_3	Ph	59
l	$PO(OEt)_2$	C_4H_9	60[b]
m	Ph	$SeCH_3$	NR
n	Ph	$SiMe_3$	NR
o	Ph	TeBu	NR
p	Ph	$SnBu_3$	NR

[a] Yields are given for isolated products. [b] The reaction produced a 1:1 mixture of *Z*- and *E*-isomers.

(5) Comasseto, J. V.; Ferreira, J. T. B. *J. Organomet. Chem*. **1981**, *216*, 287−294.

(6) (a) Filer, C. N.; Ahern, D.; Fazio, R.; Shelton, E. J. *J. Org. Chem*. **1980**, *45*, 1313−1315. (b) Garratt, D. G.; Beaulieu, P. L.; Morisset, U. M. *Can. J. Chem*. **1981**, *59*, 927−934.

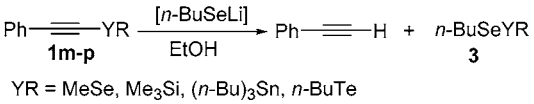
(7) Kuniyasu, H.; Ogawa, A.; Sato, K. I.; Ryu, I.; Sonoda, N. *Tetrahedron Lett*. **1992**, *33*, 5525−5528.

(8) (a) Krief, A.; Derock, M. *Tetrahedron Lett*. **2002**, *43*, 3083−3086. (b) Back, T. G. *Organoselenium Chemistry: A Practical Approach*; Oxford University Press: Oxford, 1999.

(9) Gosselck, J. *Angew. Chem., Int. Ed. Engl*. **1963**, *2*, 660−669.

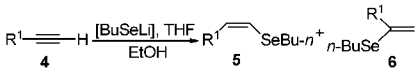
(10) **Typical Procedure for Hydroselenation of Alkynes by BuSeLi.** To a suspension of elemental selenium (0.079 g; 1 mmol) in dry THF (5 mL) under argon and with magnetic stirring was added *n*-butyllithium (0.4 mL of a 2.5 M solution in hexane; 1 mmol). A yellow solution was formed. To this solution was added the appropriate alkyne (1 mmol) in deoxygenated ethanol (5 mL). The mixture was then heated at reflux for 24 h. After this time, the mixture was cooled to room temperature and treated with NH_4Cl (10 mL) solution and ethyl acetate (100 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography and eluted with hexane or hexane/ethyl acetate (80:20).

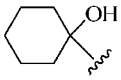
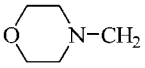
Scheme 3



deoxygenated ethanol was added dropwise to a solution containing *n*-BuSeLi. The resulting solution was stirred at room temperature for the time indicated in Table 2 and

Table 2. Hydroselenation of Terminal Alkynes



Entry	R^1	Time (h)	Yield[a] (%)	Ratio[b] **5**:**6**
a	Ph	12	80[c]	-
b	C_4H_9	48	trace[d]	
c	$HO(Me)_2C$	30	63	6:1
d	HO(Et)(Me)C	30	62	9:1
e	HO(Et)HC	30	66	1:1
f		30	60	10:1
g		24	51	1.5:1
h	$HOCH_2$	30	79	1:8

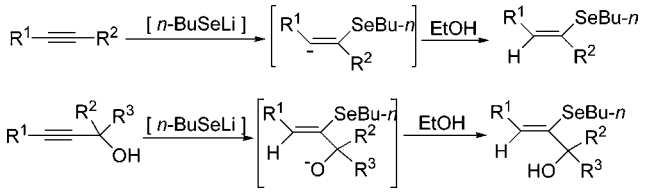
[a] Yields are given for isolated products. [b] The ratios were determined on the basis of ^{1}H NMR data. [c] Using 20 mmol scale the product was obtained in 77% yield. [d] The reaction was refluxed.

monitored by TLC to produce the desired vinylic selenides in good yields; the results are summarized in Table 2. We can see in Table 2 that the hydroselenation of phenylacetylene gave the *Z*-vinylic selenides **5a** in good yield and in a shorter reaction time, as an exclusive regio- and stereoisomer (Table 2, entry a). In addition, when the hydroselenation of phenylacetylene was carried out on a large scale (20 mmol), the product **5a** was obtained in a similar yield. This result indicates that our method can be employed in the large-scale synthesis of vinylic selenides **5a**, which are important intermediates in organic synthesis.[11] In contrast, when 1-hexyne was employed as starting material, the hydroselenation afforded the vinylic selenides **5b** only in small amounts, even though heating and longer reaction times were employed (Table 2, entry b). In this case we recovered the 1-hexyne jointly with large amounts of dibutyl diselenide. The effect of the hydroxyl group at the propargyl position of 1-alkynes was also examined, and the results are summarized in Table 2. The hydroselenations proceed at room temperature, affording stereoselectively the corresponding *Z*-vinylic selenides; however, a significant loss in the regiochemistry was observed. With a bulky alkyl group in the propargyl position (Table 2, entry g) the regioisomer **5g** was obtained as a major product with *Z*-stereochemistry exclusively. However, an inversion in the regiochemistry was observed when the hydrogen (small group) was present in the propargyl position (Table 2, entry h). This set of experiments demonstrated that the ratio of regioisomers is dependent on the steric effect of the alkyl group in the propargyl position.

Analysis of the ^{1}H and ^{13}C NMR spectra showed that all of the vinylic selenides presented data in full agreement with their assigned structures. The stereochemistry of the disubstituted vinylic selenides was easily established. As an example, the ^{1}H spectrum of compound **5a** showed a doublet centered at 6.89 ppm with a coupling constant of 9.2 Hz. The other vinylic hydrogen resonates at 6.62 ppm as a doublet, with a coupling constant of 9.2 Hz attributed to the *cis*-related olefinic hydrogens. The geometry of the trisubstituted vinylic selenides was determined by NOE experiments. For example, when the compound **2c** was irradiated at the signal attributed to vinylic hydrogen (6.35 ppm), an enhancement of the allylic hydrogens (2.42 ppm) was observed, showing a *cis* relationship between them.

The reaction pathway leading to vinylic selenides seems to depend on the substitution pattern of the triple bond and is controlled by both steric and electronic effects. We believe that in the case of non-hydroxyled alkynes, the vinylic selenides are formed by the addition of the selenolate anion onto the triple bond, with subsequent trapping of the vinyl anion with a proton from ethanol. However, in the case of propargyl alcohols we believe that the vinylic hydrogen came from the acidic proton of the hydroxyl group (Scheme 4).

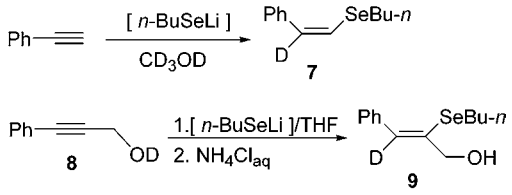
Scheme 4



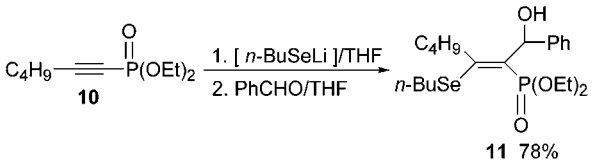
To support this mechanistic description, we have carried out the hydroselenation of phenylacetylene in MeOH-d_4, where **7** was isolated as the major product (Scheme 5). We also used the deuteration experiments to determine if the vinylic hydrogen is donated by the alcohol or if it could come from the hydroxyl group in the propargyl alcohols. As the result, the hydroselenation of deuterated propargyl alcohol **8**, in the absence of a protic solvent, produces the vinylic selenides **9** (Scheme 5). These results suggest that the

(11) (a) Tingoli, M.; Tiecco, M.; Testaferri, L.; Temperini, A.; Pelizzi, G.; Bacchi, A. *Tetrahedron* **1995**, *51*, 4691−4700. (b) Hevesi, L.; Hermans, B.; Allard, C. *Tetrahedron Lett.* **1994**, *35*, 6729−6730.

Scheme 5



Scheme 6



hydroselenation across to the triple bond follows an *anti*-pathway addition with the effective participation of ethanol and the hydroxyl group of propargyl alcohols.

Finally, an application of our method in the preparation of tetrasubstituted vinylic selenides from internal unsymmetrical alkynes, based on the sequence of hydroselenation and trapping of the vinyllithium intermediate with benzaldehyde, has been briefly investigated. Thus, 1.0 equiv of 1-alkynylphosphonate **10** was reacted with 1.0 equiv of *n*-BuSeLi at room temperature for 1 h. Then the solution of 1.2 equiv of benzaldehyde in 2 mL of THF was added. The reaction was stirred at room temperature for 4 h to give the tetrasubstituted vinylic selenides **11** in 78% yield (Scheme 6).

In summary, we present here the hydroselenation of terminal or internal, unsymmetrical or symmetrical alkynes by lithium selenolate anion. The nature of the substituents (steric and electronic effects) on the triple bond plays an important role in the regio- and stereoselectivity of the vinylic selenides formed. Additionally, by our method the use of diorganoyl diselenides or selenophenol is avoided. We expect that these findings would be useful in choosing a method for the synthesis of vinylic selenides containing different functional groups. This reaction associated with the nickel-catalyzed cross-coupling of vinylic selenides with terminal alkynes[12] can contribute to an interesting alternative route to the regio- and stereoselective preparation of functionalized alkenes. Studies on the capture of vinyllithium intermediate with different electrophiles are in progress in our group, and the results will appear soon in a full paper.

Acknowledgment. We are grateful to CNPq, CAPES and FAPERGS for financial support. CNPq is also acknowledged for a MS fellowship (to M.P.St).

Supporting Information Available: Spectroscopic data for all new compounds and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0498904

(12) Silveira, C. C.; Braga, A. L.; Vieira, A. S.; Zeni, G. *J. Org. Chem.* **2003**, *68*, 662−665.