ORGANIC LETTERS

2012
Vol. 14, No. 23
6072–6075

Regioselective Formation of Tetrahydroselenophenes via 5-*exo*-*dig*-Cyclization of 1-Butylseleno-4-alkynes

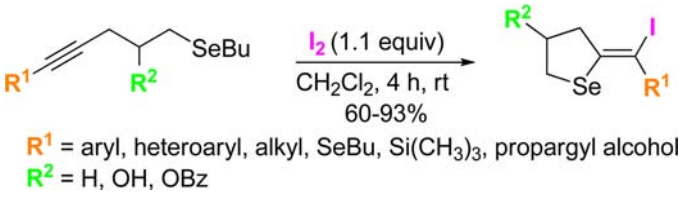
Rafaela M. Gai,[†] Ricardo F. Schumacher,[†] Davi F. Back,[‡] and Gilson Zeni*[,†]

Laboratório de Síntese, Reatividade, Avaliação Farmacológica e Toxicológica de Organocalcogênios, CCNE, UFSM, Santa Maria, Rio Grande do Sul, Brazil, 97105-900, and Laboratório de Materiais Inorgânicos, CCNE, UFSM, Santa Maria, Rio Grande do Sul, Brazil, 97105-900

gzeni@ufsm.br

Received October 28, 2012

ABSTRACT



Results on the synthesis of tetrahydroselenophene derivatives from 1-butylseleno-4-alkynes by electrophilic cyclization using iodine as the electrophilic source are presented. This methodology was carried out via a simple process under mild reaction conditions providing the cyclized products in high yields. Electrophilic sources, such as PhSeBr, $CuCl_2$, and $CuBr_2$, were also used in this study. The tetrahydroselenophenes obtained by this protocol were submitted to cyanation, Suzuki, and Ullmann cross-coupling reactions to afford good yields of a cross-coupled product.

Heterocycles are one of the most important classes of organic compounds with representatives in numerous natural products and medicinal agents. Among the many methods for heterocycle preparation, the ring-closing reactions of an appropriate unsaturated substrate using palladium-catalyzed intermolecular annulation[1] and transition metal catalyzed intramolecular cyclization[2] have proven to be some of the most efficient procedures. More recently, significant advances have been made in the formation of heterocycles using electrophilic cyclization reactions.[3] In these reactions, an alkene, alkyne, allene, conjugated diene, or other carbon–carbon multiple bonds act as nucleophile partners with a number of electrophile-mediated carbon–heteroatom bond formations to give the heterocycle. Thus far, many kinds of reagents and reaction conditions have been reported for the electrophilic cyclization, including IPy_2BF_4,[4] gold reagent,[5] halogens,[6] NXS,[7] trichloroisocyanuric acid (TCCA),[8] $I(coll)_2PF_6/BF_3OEt_2$,[9] and organochalcogen electrophiles.[10] The innovative use of cyclization reactions of appropriated substituted alkynes with $FeCl_3$/PhSeSePh is also a fine achievement in the synthesis of functionalized heterocycles.[11] The electrophilic cylclization reactions, using organochalcogen alkynes as substrate, have proven to be an efficient alternative for the

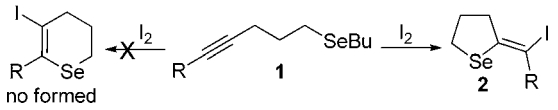
[†] Laboratório de Síntese.
[‡] Laboratório de Materiais Inorgânicos.

(1) Majumdar, K. C.; Samanta, S.; Sinha, B. *Synthesis* **2012**, *44*, 817.
(2) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
(3) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.
(4) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2003**, *5*, 4121.
(5) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208.
(6) Okitsu, T.; Sato, K.; Wada, A. *Org. Lett.* **2010**, *12*, 3506.
(7) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769.
(8) Sniady, A.; Morreale, M. S.; Wheeler, K. A.; Dembinski, R. *Eur. J. Org. Chem.* **2008**, *20*, 3449.
(9) Okitsu, T.; Nakazawa, D.; Taniguchi, R.; Wada, A. *Org. Lett.* **2008**, *10*, 4967.
(10) Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1128.
(11) Yu, L.; Ren, L.; Yi, R.; Wu, Y.; Chen, T.; Guo, R. *J. Organomet. Chem.* **2011**, *696*, 2228.

10.1021/ol302919b
Published on Web 11/19/2012

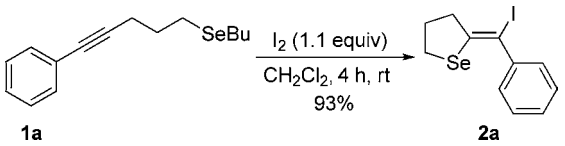
preparation of chalcogenophene derivatives.[12] The ability of the selenium atom to stabilize both electron-deficient and electron-rich centers is crucial for the high regioselectivity observed in chalcogen cyclizations.[13] It has been recognized that an *endo*-cyclization is generally preferred over an *exo*-ring closure in systems having the chalcogen atom at the 5- or 6-position relative to the C(sp) or C(sp^2) center.[14] For example, benzyl 3-butynyl sulfide, upon treatment with an electrophilic source, exclusively gave the thiophene derivatives via 5-*endo-dig* iodocyclization.[15] However, despite many reports about such reactions, the electrophilic *exo-dig* cyclization of organochalcogen substrates bearing an alkyne partner has been scarcely reported and the regioselectivity control has not been well-documented. Here, as part of our study of the application of organochalcogens as substrates in cyclization reactions,[16] we would like to report a detailed study of the *exo-dig* electrophilic cyclization of the 1-butylseleno-4-alkynes **1**, instead of typical *endo-dig* cyclization (Scheme 1).

Scheme 1



In our initial screening experiments, 1-butylseleno-5-phenyl-pent-4-yne **1a**[17] and I_2 (1.1 equiv) were selected as the reactant/reagent standard to determine the optimal reaction conditions. Usually the solvents play an important role for a successful electrophilic cyclization. To select the most efficient solvent, CH_2Cl_2, MeOH, CH_3CN, THF, and toluene were tested at room temperature. Dichloromethane was the best among the solvents tested, and tetrahydroselenophene derivative **2a** was isolated in 93% yield. The solvents CH_3CN and THF also showed good behavior under the same conditions (87 and 90% yield, respectively), whereas MeOH and toluene gave lower yields (both 76%) of the target product. Afterwards, the optimized conditions were established using the combination of 1 equiv of selenide **1a** and 1.1 equiv of I_2, in CH_2Cl_2 as solvent at room temperature for 4 h (Scheme 2).

Scheme 2



As can be seen, this protocol is rather general, as it is applicable for the reactions of a variety of 1-butylseleno-4-alkynes bearing an aryl group as well as a heteroaryl, propargyl alcohol, an alkyl, and a heteroatom directly bonded to the triple bond. There are some important features of these results. For example, the reactions were efficient with a variety of aryl bearing neutral and both electron-rich and electron-deficient groups giving the cyclized products in high yields (Table 1, entries 1−7). The bulkiness of the *ortho*-methyl and naphthyl moieties had no effect on the reactivity, affording products **2b** and **2h** in 90 and 85% yields, respectively (Table 1, entries 2 and 8). When 1-butylseleno-4-alkynes **1b**, **1d**, and **1e** were used as substrates, the *exo-dig* products **2b**, **2d**, and **2e** were obtained in a ratio of 5.5:1, 4.3:1, and 3.2:1, repectively, favoring the *E*-isomer.[18] It is also important to point out that 1-butylseleno-4-alkynes **1e** with a methoxyl group at the ortho position of an aryl group would give a competitive cyclization when a cyclizing agent, such as I_2, is used. Therefore, we were pleased to find that the cyclization with **1e** smoothly afforded the corresponding tetrahydroselenophene **2e** via a *Se*-cyclization, in the complete absence of furan derivatives. We conclude that our result is in complete agreement with the study reported by Larock, who showed that if the substrate has selenium and oxygen competing, the *Se*-cyclization is predominant.[10] Furthermore, we found that the effect of changing aryl to alkyl or propargyl alcohol substituents directly bonded to the triple bond of 1-butylseleno-4-alkynes was not significant, although the propargyl alcohol susbtituent gave the products in moderated yields (Table 2, entries 10−11). We were delighted to observe that heteroatoms, such as selenium and silicon, could be added directly to the triple bond of 1-butylseleno-4-alkynes, giving the corresponding vinyl selenides **2l** and vinylsilane **2m** in good yields (Table 1, entries 12 and 13). Another competitive reaction, using hydroxyl and benzyloxy groups at the homopropargyl position of 1-butylseleno-4-alkynes, was also perfomed. Similarly to Table 1, entry 5, the sole product isolated was the selenophene derivative, obtained by the nucleophilic attack of the selenium atom at the triple bond (Table 1, entries 14 and 15). We then investigated whether terminal 1-butylseleno-4-alkyne might be used as a susbtrate to this cyclization. Unfortunately, all attempts at the cyclization reaction of **1p** led to its decomposition even when we changed the reaction parameters (Table 1, entry 16). Based on the electrophilic cyclization mechanism we believe that the molecular iodine is responsible to generate a cationic iodonium ion **a**, via coordination of the carbon−carbon triple bond to the electrophilic species. An intramolecular

(12) (a) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307. (b) Schumacher, R. F.; Rosário, A. R.; Souza, A. C. G.; Menezes, P. H.; Zeni, G. *Org. Lett.* **2010**, *12*, 1952.

(13) Perin, G.; Lenardão, E. J.; Jacob, R. G.; Panatieri, R. B. *Chem. Rev.* **2009**, *109*, 1277.

(14) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513.

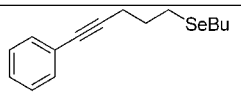
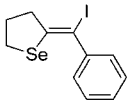
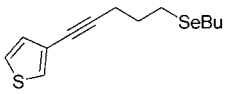
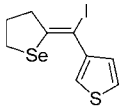
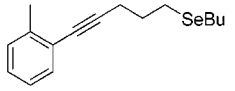
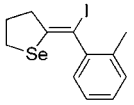
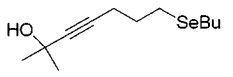
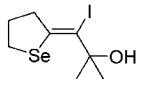
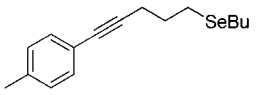
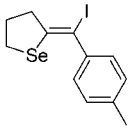
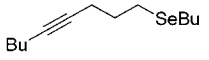
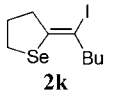
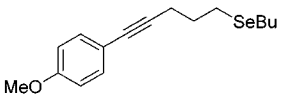
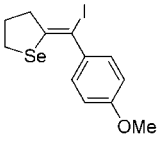
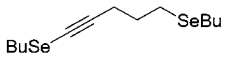
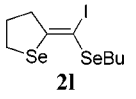
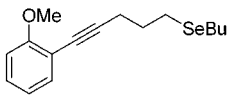
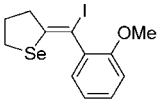
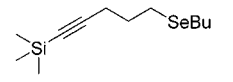
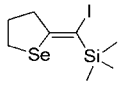
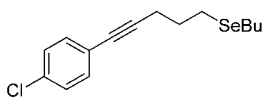
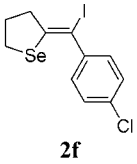
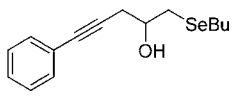
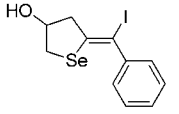
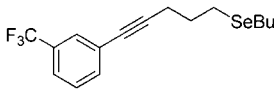
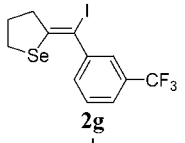
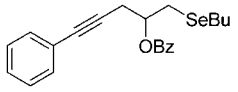
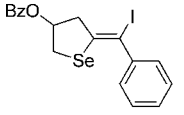
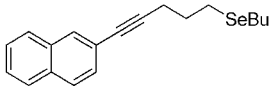
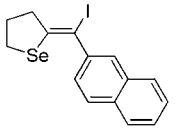
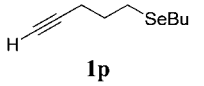
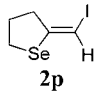
(15) Flynn, B. L.; Flynn, G. P.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2341.

(16) (a) Roehrs, J. A.; Pistoia, R. P.; Back, D. F.; Zeni, G. *Adv. Synth. Catal.* **2012**, *354*, 1791. (b) Stein, A. L.; Bilheri, F. N.; da Rocha, J. T.; Back, D. F.; Zeni, G. *Chem.—Eur. J.* **2012**, *18*, 10602.

(17) For preparation of compounds **1a**−**p**, see the Supporting Information.

(18) The *E*/*Z* stereochemistry of **2b** was determined by conversion to the hydrogen derivative through I/Li exchange reactions via reaction with *n*-BuLi in hexane. The stereochemistry was assigned via analysis of the *J*-coupling constant.

Table 1. Cyclization Reactions of 1-Butylseleno-4-alkynes **1a**–**p** Mediated by Iodo[a]

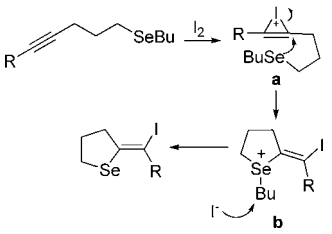
entry	selenide **1**	product **2**	yield (%)[b] (*E*/*Z*)	entry	selenide **1**	product **2**	yield (%)
1	 **1a**	 **2a**	93 (90)[c]	9	 **1i**	 **2i**	92
2	 **1b**	 **2b**	90 (5.5:1)[d]	10	 **1j**	 **2j**	62
3	 **1c**	 **2c**	77	11	 **1k**	 **2k**	87
4	 **1d**	 **2d**	80 (4.3:1)[d]	12	 **1l**	 **2l**	87
5	 **1e**	 **2e**	80 (3.2:1)[d]	13	 **1m**	 **2m**	60
6	 **1f**	 **2f**	86	14	 **1n**	 **2n**	83
7	 **1g**	 **2g**	78	15	 **1o**	 **2o**	70
8	 **1h**	 **2h**	85	16	 **1p**	 **2p**	-[e]

[a] The reactions were performed using the selenide **1** (0.5 mmol), I_2 (1.1 equiv) in CH_2Cl_2 at room temperature. [b] Isolated yield after column chromatography. [c] Reaction was carried out on a 5 mmol scale. [d] *E*/*Z* ratio obtained. [e] The desired product **2p** was not obtained.

nucleophilic attack of the lone pair of electrons of the selenium atom gives the salt **b**, which undergoes butyl group removal via S_N2 displacement by halide nucleophiles remaining in solution to form the product (Scheme 3). The NMR experiments showed that only five-membered selenophene derivatives were obtained, which was confirmed by X-ray diffraction analysis (see Supporting Information).

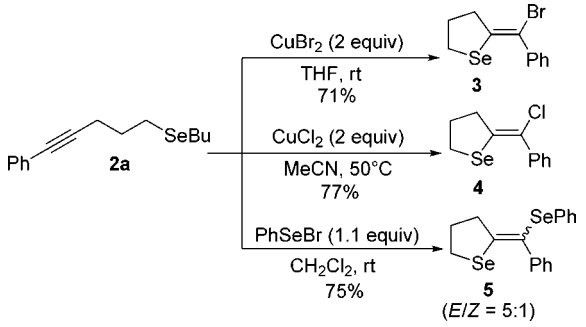
We observed that not only a halogen, such as iodine, was efficient as a cyclizing agent of 1-butylseleno-4-alkynes but also other electrophilic sources, such as $CuBr_2$, $CuCl_2$, and PhSeBr, can be used. When the $CuBr_2$ was used with THF as the solvent, at room temperature it was possible to isolate the bromo-tetrahydroselenophene **3** in 71% yield. Almost identical results were obtained when $CuCl_2$ was used as the electrophilic source, which suggests that copper salts are acting not only as a triple bond activator but also as a halogen source. We also found that PhSeBr, a selenium electrophilic species, promoted the cyclization of 1-butylseleno-4-alkynes **2a** in the presence of CH_2Cl_2 at room temperatute and produced the highly substituted

Scheme 3



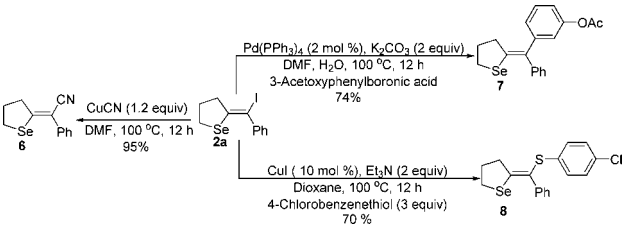
tetrahydroselenophene **5** in 75% yield in an *E*/*Z* ratio of 5:1 (Scheme 4). This type of compound is of interest, as the presence of functionality with varying reactivity, such as Br, Cl, and SePh, allowed further selective structural elaboration through conversion into other substituents.

Scheme 4



In order to evaluate the possibility of synthesizing other and more complex selenophene systems, we decided to employ the compound **2a** as starting material in a series of cross-coupling reactions with different nucleophiles. In view of this, **2a** was treated under standard Suzuki,[19] Ullmann-type coupling,[20] and cyanation conditions,[21] providing the corresponding coupling products **6**–**8** in good yields (Scheme 5).

Scheme 5



In conclusion, an efficient method for the synthesis of tetrahydroselenophene derivatives by electrophilic cyclization of 1-butylseleno-4-alkynes has been developed. This methodology was carried out in a simple process under mild conditions and provided the cyclized *5-exo-dig* products in high yields. The reaction works well with a wide range of substituents, such as aryl, heteroaryl, alkyl, $SiMe_3$, SeBu, and tertiary alcohol, in the alkynyl selenide. Electrophilic sources, such as PhSeBr, $CuCl_2$, and $CuBr_2$, were also satisfactorily used affording phenylseleno- or halogen-susbtituted selenophenes. In addition, transition metal-catalyzed cross-coupling of tetrahydroselenophenes bearing an iodide moiety produced new classes of highly functionalized tetrahydroselenophene derivatives in good yields.

Acknowledgment. We are grateful to FAPERGS (PRONEX-10/0005-1), CAPES, and CNPq (CNPq/INCT-catalise) for financial support. CAPES is also acknowledged for a fellowship (R.M.G.). CNPq is also acknowledged for G.Z. fellowship.

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

(19) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(20) Fanta, P. E. *Synthesis* **1974**, 9.
(21) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779.

The authors declare no competing financial interest.