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Synthesis of 2,3-Dihydroselenophene and Selenophene Derivatives by Electrophilic Cyclization of Homopropargyl Selenides

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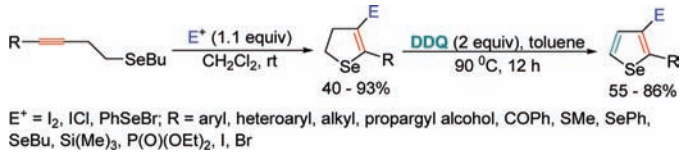
ABSTRACT



The synthesis of several highly functionalized 2,3-dihydroselenophenes from homopropargyl selenides via electrophilic cyclization is described. Electrophiles such as I_2, ICl, and PhSeBr were used in a simple process employing CH_2Cl_2 as solvent at room temperature, which gave the cyclized products in high yields. 4-Iodo-2,3-dihydroselenophenes obtained by this methodology were submitted to a dehydrogenation reaction using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give 3-iodoselenophenes. 4-Iodo-5-phenyl-2,3-dihydroselenophene was also submitted to the thiol copper-catalyzed and Heck-type reactions giving the desired products under mild reaction conditions.

Selenophene heterocycles and their derivatives have numerous uses in the fields of biochemistry, physical organic chemistry, materials chemistry and organic synthesis. For example, selenophene oligomers are compounds of current interest because many of them show photoenhanced biological activities[1] and alpha-type chalcogenophene oligomers, such as 5,2′:5′,2″-thiophene, produce crystalline, and electroconductive polythiophenes in electrochemical polymerizations.[2] Thus, a wide variety of oligomers and related chalcogen compounds including mixed thiophene-pyrrole oligomers, have been synthesized mainly with the expectation of obtaining excellent precursor compounds for molecular devices and electroconductive polymers.[3] In addition, selenophenes are widely studied agents with a diverse array of biological effects, these include antioxidant action,[4] antinociceptive[5] and antiinflammatory properties,[6] as well as efficacy as maturation inducing agents.[7] A great number of these heterocycles have been synthesized and their chemistry has attracted a good deal of interest and activity from a

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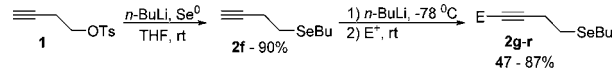
variety of standpoints such as structures, stereochemistry, reactivities, and applications to organic synthesis.[8] However, the synthetic study of a partially saturated version, 2,3-dihydroselenophene derivatives of selenophenes, has been surprisingly limited.[9] In the context of heterocycles, the transition-metal catalyzed cyclization reaction of simple acyclic precursors is one of the most attractive ways to directly construct complicated molecules under mild conditions.[10] In this way, palladium is one of the most common transition metals used,[11] although it sometimes displays intolerance to some functionalities or proceeds with a lack of regioselectivity. On the other hand, the electrophilic cyclization appears as an alternative route to generate highly functionalized heterocycles. This methodology takes advantage, in the most of cases, by the presence of an halogen atom suitable to suffer further transformations. This cyclization has been used as an efficient tool in the synthesis of highly substituted indoles,[12] furans,[13] thiophenes,[14] selenophenes,[15] benzo[*b*]furans,[16] benzo[*b*]thiophenes,[17] benzo[b]selenophenes,[18] lactones,[19] and pyrroles,[20] employing electrophiles, like I_2, ICl or chalcogen derivatives. Among the known protocols for the synthesis of dihydrothiophenes, Flynn and co-workers have reported that the reaction of homopropargyl sulfides with iodine gave the title compounds in almost quantitative yields.[14] The superiority of this method was proved by the high yields of the desired products, the tolerance for various substituents, and successful applications to synthesis of analogues of combretastatin A-4, a prodrug, which exhibits potent pharmacological activities. Inspired by Flynn's reaction, we extended this method to access new 2,3-dihydroselenophenes **3a**−**r** and to examine their ability as precursors of 3-iodoselenophenes.

We initially focused on experiments to find a route which gave the required starting materials, the homopropargylic selenides, in good yields. We envisioned that this route could start with the introduction of a chalcogen group in the homopropargyl tosylates and subsequent functionalization of the terminal alkyne. For the introduction of the chalcogen group, we chose the substitution reaction in the homopropargyl alcohol protected as tosylate, using selenolate anion as nucleophile.[21] Thus, the addition of butylselenolate (easily prepared by reaction of *n*-BuLi with elemental selenium, in THF at 0 °C) to a solution of tosylate **1** in THF at room temperature for 6 h, gave the selenide **2f** in high yield. With the subunit **2f** in hand to the functionalization of terminal alkynes, we first generated the lithium acetylide intermediate by reaction of terminal alkyne **2f** with 1 equiv of *n*-BuLi, in THF at −78 °C for 1 h, followed by the addition of an electrophile (Scheme 1). By this method, we prepared a number of novel homopropargylic selenides **2g**−**r** and applied these new compounds as starting materials in the electrophilic cyclization reactions (Table 1).[22]

Scheme 1. Synthesis of Homopropargyl Selenides



E = aryl, heteroaryl, alkyl, propargyl alcohol, COPh, SMe, SePh, SeBu, $Si(Me)_3$, $P(O)(OEt)_2$, I, Br.

The conditions for the cyclization were optimized by varying parameters such as solvent, reaction temperature, amount and identity of electrophile sources. For these studies, the reaction of homopropargyl selenide **2a** with iodine was chosen as a model system. To identify the solvent potentially suitable for the cyclization, we first chose MeOH, hexane, MeCN, THF, and CH_2Cl_2. For this process, CH_2Cl_2 was the most effective solvent giving the cyclized product in 93% yield. The study to screen the electrophile source showed that ICl (**3a**) and PhSeBr (**3a′**) (1.1 equiv) gave the target products in 70 and 62% yields, respectively. It is important to note that when the amount of electrophile was increased from 1.1 to 2.0 equiv a decrease in the yield was observed. After optimizing the reaction parameters, the functional group tolerance was explored. The results are presented in Table 1. Many functional groups were compatible with the reaction conditions. In general, all the reactions proceeded smoothly with good results. Most importantly, the cyclization turned out to be general with respect of a diverse array of functionalities. The experiments showed that the electrophilic cyclization of substrate having an aromatic ring directly bonded to the terminal alkyne was not sensitive to the electronic effects of the substituents. For example, the

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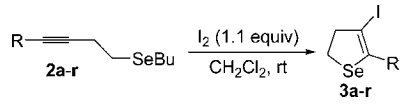
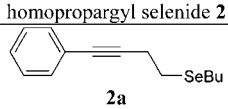
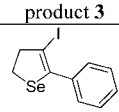
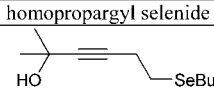
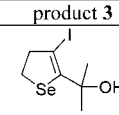
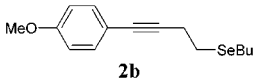
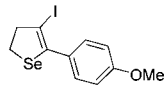
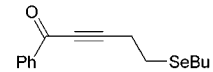
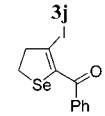
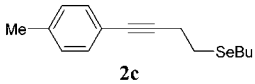
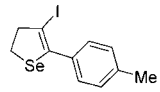
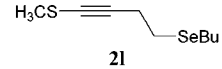
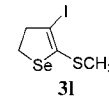
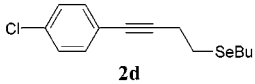
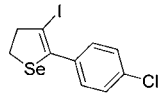
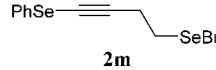
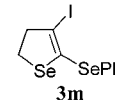
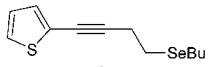
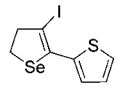
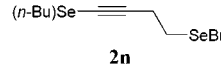
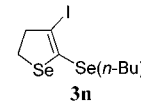
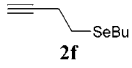
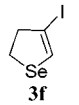
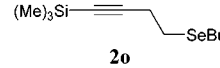
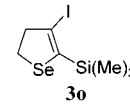
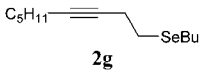
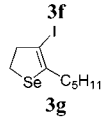
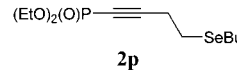
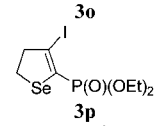
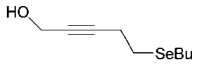
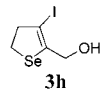
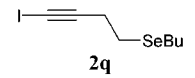
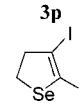
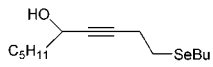
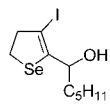
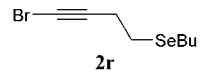
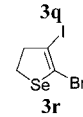
(22) For preparation of compounds **2a**−**e**, see the Supporting Information.

Table 1. Products of Iodo Cyclization[a]



entry	homopropargyl selenide **2**	product **3**	yield (%)[b]	entry	homopropargyl selenide **2**	product **3**	yield (%)[b]
1	 **2a**	 **3a**	93	10	 **2j**	 **3j**	85
2	 **2b**	 **3b**	80	11	 **2k**	 **3k**	60
3	 **2c**	 **3c**	83	12	 **2l**	 **3l**	75
4	 **2d**	 **3d**	86	13	 **2m**	 **3m**	65
5	 **2e**	 **3e**	82	14	 **2n**	 **3n**	80
6	 **2f**	 **3f**	60	15	 **2o**	 **3o**	40
7	 **2g**	 **3g**	67	16	 **2p**	 **3p**	70
8	 **2h**	 **3h**	70	17	 **2q**	 **3q**	87
9	 **2i**	 **3i**	81	18	 **2r**	 **3r**	70

[a] Reactions were performed using the selenide **2** (0.25 mmol), I_2 (1.1 equiv) in CH_2Cl_2 at room temperature. [b] Isolated yield after column chromatography.

aromatic ring having either neutral **2a**, electron-donating **2b**−**c** or electronwithdrawing **2d** substituents gave the cyclized products in very similar yields (Table 1, entries 1−4). In addition to aromatic rings, the reaction with heteroaromatic thiophene also led to the formation of the desired product in 82% yield (Table 1, entry 5). By contrast, when the reaction was carried out with homopropargyl selenides with a hydrogen atom or an alkyl group in the terminal position, a little decrease in the yields was observed, and the cyclized products were obtained in 67 and 60% yields, respectively (Table 1, entries 6 and 7). In the case of substrates with propargyl alcohols, our reaction system was also suitable for the cyclization of both hindered and nonhindered chains, giving the desired cyclized products in good yields (Table 1, entries 8−10). Finally, it is worth mentioning that, through our methodology, it was possible to prepare a series of difunctionalized selenophene rings, such as **3l**−**r** (Table 1, entries 12−18). This result is significant particular when one considers that there are many ways to transform the resulting functionalities into other substituents.

We believe that the mechanism of this cyclization reaction involves; (i) coordination of the carbon−carbon triple bond to I_2 to generate an iodonium intermediate **a**, which activates the triple bond toward nucleophilic attack, (ii) antinucleophilic attack of the selenium atom on the activated iodonium intermediate to produce the salt **b**, and (iii) facile removal of the alkyl group via S_N2 displacement by the iodide anion present in the reaction mixture to generate the 4-iodo-2,3-dihydroselenophene product and one molecule of *n*-BuI (Scheme 2).

Since selenophene derivatives exhibit a broad range of biological activities and applications as intermediates in

Scheme 2. Plausible Mechanism

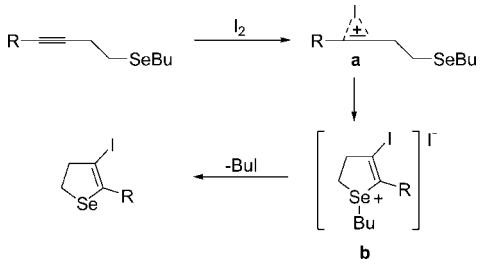
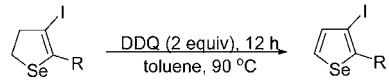
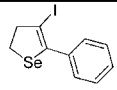
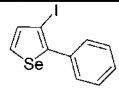
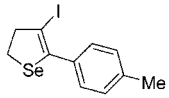
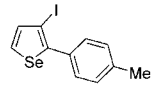
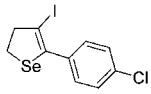
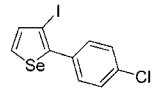
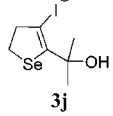
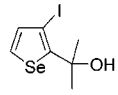
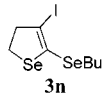
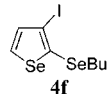


Table 2. Aromatization of 2,3-Dihydroselenophenes with DDQ



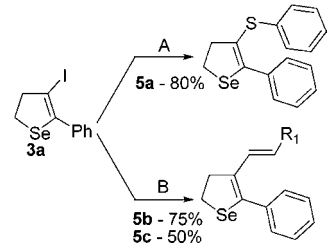
entry	selenide **3**	product **4**	yield (%)[a]
1	 **3a**	 **4a**	77
2	 **3c**	 **4b**	86
3	 **3d**	 **4c**	80
4	 **3g**	 **4d**	55
5	 **3j**	 **4e**	70
6	 **3n**	 **4f**	68

[a] Yield of isolated product after column chromatography.

organic synthesis, we wondered if it would be possible to prepare selenophenes directly from 2,3-dihydroselenophenes. Otsubo and co-workers have reported that 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is a useful promoter for the oxidation of 5,6-dihydroseleno[2,3-*d*]-1,3-dithiole-2-thione to aromatic seleno[2,3-*d*]-1,3-dithiole-2-thione.[23] Gratifyingly, we found that the reaction of 2,3-dihydroselenophenes **3a** (1 equiv) with DDQ (2 equiv) in toluene at 90 °C gave the selenophene **4a** in 77% yield (Table 2, entry 1). As demonstrated in Table 2, the reaction of DDQ with other 2,3-dihydroselenophenes was also carried out smoothly to give the corresponding products **4** in good yields. It is interesting to note that the oxidation reaction tolerated a variety of functional groups, such as halides, hydroxyl, and butylseleno groups (Table 2, entries 2−6).

In order to complete our investigation and to further prove the potential of 2,3-dihydroselenophene derivatives as precursors for increasing molecular complexity, we tested the reactivity of these compounds toward thiol and Heck cross-coupling via copper- or palladium-catalyzed reactions. In this way, the reaction of **3a** with benzenethiol, using CuI as catalyst in dioxane, afforded the product **5a** in 80% (isolated yield). In addition, the reaction of **3a** with methyl acrylate or styrene gave the corresponding Heck products **5b** and **5c** in 75 and 50% yields, respectively (Scheme 3).

Scheme 3. Thiol and Heck Cross-Coupling using **3a** as Substrate[a]



[a] Method A: CuI (10 mol %), benzenethiol (1.2 equiv) in dioxane at 100 °C. Method B: $Pd(OAc)_2$ (5 mol %), *n*-BuNI (1 equiv), Na_2CO_3 (2.5 equiv), methyl acrylate (1.2 equiv, **5b**) or styrene (1.2 equiv, **5c**), DMF, 100 °C.

In summary, we have explored the electrophilic cyclization of easily accessible alkynyl selenides establishing a route to 2,3-dihydroselenophene derivatives **3** in good yields. The reaction could be carried out using different electrophiles in CH_2Cl_2 at room temperature. The reaction works well with a wide range of substituents, such as aryl, heteroaryl, alkyl, propargyl alcohol, and halogen groups in the homopropargyl selenides. 4-Iodo-2,3-dihydroselenophenes obtained by this methodology were submitted to a dehydrogenation reaction using DDQ to give 3-iodoselenophenes in high yields. In addition, 2,3-dihydroselenophene derivatives **3** were submitted to a copper-catalyzed thiol cross-coupling reaction and Heck-type reaction giving the desired products in moderate to good yields.

Acknowledgment. We are grateful to CNPq (CNPq/INCT-catalise), CAPES (SAUX), and FAPERGS for financial support. CNPq is also acknowledged for a fellowship (to G.Z. and R.F.S.).

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.

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(23) Jigami, T.; Takimiya, K.; Otsubo, T. *J. Org. Chem.* **1998**, *63*, 8865.