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Electrophilic Cyclization of 2-Chalcogenealkynylanisoles: Versatile Access to 2-Chalcogen-benzo[*b*]furans

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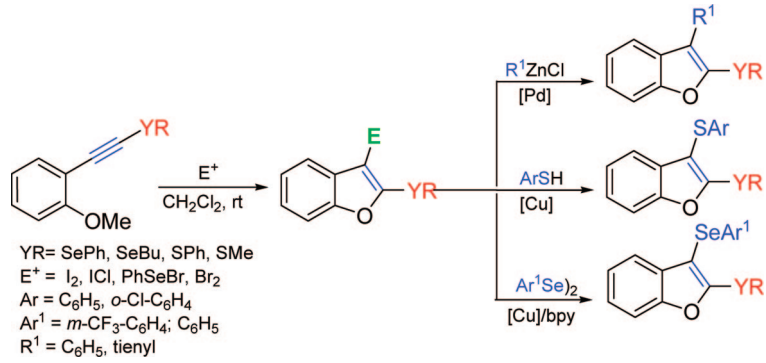

An efficient synthesis of 2-chalcogen-3-substituted-benzo[*b*]furan compounds has been accomplished via electrophilic cyclization reaction of 2-chalcogenealkynyl anisoles using I_2, ICl, Br_2, and PhSeBr as electrophile sources. The product distributions were strongly dependent on the nature of substituents in the aromatic ring of anisole and on the chalcogen atom directly bonded to the triple bond. The 2-chalcogen-3-iodo-benzo[*b*]furans obtained smoothly underwent conversion to more complex structures of benzo[*b*]furan derivatives via palladium- or copper-catalyzed cross-coupling reaction with thiols, diphenyl diselenides, and zincates.

Introduction

The benzo[*b*]furan moiety is a versatile and useful class of heterocycles as a result of the prevalence of this structure in a great number of biologically active compounds and isolated natural products, including a wide variety of therapeutic applications such as anti-HIV, anticancer, and antiinflamatory.[1]

Recently, a series of structures containing the benzofuran nucleus, such as SKF-64346 and SKF-63058, have been identified as efficient inhibitors of β-amyloid aggregation, affording a new class of potential multifunctional drugs for Alzheimer's disease (Figure 1).[2]

In this context, considerable effort has been applied to development of efficient strategies for the synthesis of benzo[*b*]furans. During the past years numerous protocols have been reported in the literature,[3] and one of the reliable approaches for the synthesis of this class of compounds has been based on electrophilic cyclization of unsatured compounds.[4] Important heterocycles such as indoles,[4a,b] benzo[*b*]thiophenes,[4c,d] benzo[*b*]selenophenes,[4e] thiophenes,[4f] furans,[4g] and pyrroles,[4h] among others,[4i−v] have been prepared using this protocol.

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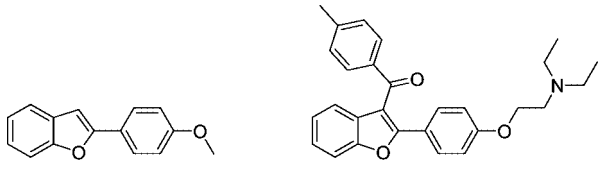
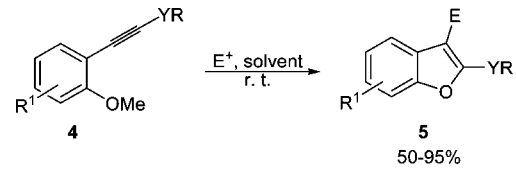


FIGURE 1. Potential multifunctional drugs for Alzheimer's disease.

Similar approaches of cyclization reactions containing chalcogen atoms, such as sulfur, selenium, and tellurium, have been scarcely explored in such methodologies, although chalcogenide compounds have found such wide utility because of their effects on an extraordinary number of very different reactions, including many carbon−carbon bond formations,[5] under relatively mild reaction conditions. In addition, they have become attractive synthetic targets because of their chemo-, regio-, and stereoselective reactions,[6] use in a wide variety of functional groups, thus avoiding protection group chemistry, and useful biological activities.[7] The selenium group can be introduced in an organic substrate via both nucleophile and electrophile reagents. After being introduced in an organic substrate, the organoselenium group can easily be removed by selenoxide *syn* elimination[8] and [2,3] sigmatropic rearrangement.[9] Conversely, the carbon−selenium bond can also be replaced by a carbon−hydrogen,[10] carbon−halogen,[11] carbon−lithium,[12] or carbon−carbon bond.[13]

SCHEME 1



YR = SePh, SeBu, SCH_3, SPh; R^1= H, Me, OMe, F; E^+= I_2, ICl, Br_2, PhSeBr; E = I, Br, SePh

Among chalcogenides, heterocycles containing a chalcogen atom play an important role in organic synthesis because of their excellent electrical properties and environmental stability. In addition, they are widely studied agents with a diverse array of biological effects. These include potent antitumor and antiviral activities, as well as efficacy as a maturation-inducing agent.[14] Halochalcogenophenes are also important derivatives that provide an useful opportunity for further functionalization.[15] In particular, iodo- and bromoselenophenes are useful as substrates in a variety of C−C,[15a,b] C−N,[15c] and C−S[15d] bond-forming reactions. However, to the best of our knowledge, there is no protocol describing the preparation of 2,3-chalcogen benzo[*b*]furan using 2-chalcogenealkynylanisoles as substrate via electrophilic cyclization. Thus, it is necessary to design a simple, efficient, and versatile method for the construction of furan rings having two different groups at the 2- and 3-positions. The applicability of the selectivity of these two functionalities can constitute a synthetic approach to the preparation of biologically active furan compounds. Combining the knowledge that our group has accumulated in the synthesis of the heterocycles containing a chalcogen[16] with the opportunity for further functionalization in these compounds, herein we suggest an entirely new approach that focuses on the electrophilic cyclization of 2-chalcogenealkynylanisoles **4** to obtain 3-iodo-2-chalcogen-benzo[*b*]furans **5** (Scheme 1).

Results and Discussion

As was mentioned above, using the key starting materials 2-chalcogenealkynylanisoles **4**, the cyclization required the introduction of a terminal alkyne in the aromatic ring and

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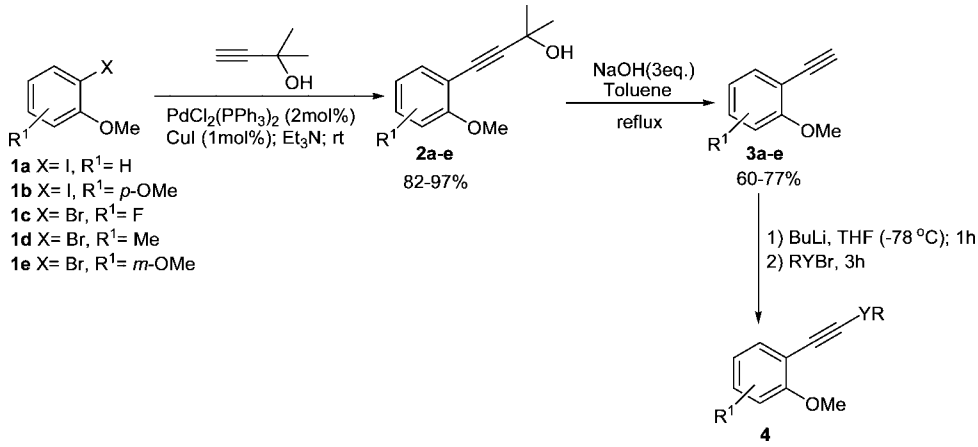
SCHEME 2



subsequently of a chalcogen group in this terminal alkyne **3**. For the introduction of the terminal alkyne, we chose the Sonogashira cross-coupling[17] followed by retro-Favorskii reaction.[18] Thus, the cross-coupling of commercial 2-haloanisoles with 2-methylbut-3-yn-2-ol using $PdCl_2(PPh_3)_2$ (2 mol %) as palladium source, CuI (1 mol %) as co-catalyst and Et_3N as solvent and base, at room temperature for 12 h, gave propargyl alcohols **2a**−**e** in high yields. With the subunit **2** in hand the terminal alkynes were easily obtained by retro-Favorskii reaction using NaOH (3 equiv) in toluene at reflux. For the introduction of the chalcogen group, we first generated the lithium acetylide intermediate by reaction of terminal alkynes **3a**−**e** with 1 equiv of *n*-BuLi, in THF at −78 °C for 1 h, followed by the reaction with an electrophilic chalcogen species (Scheme 2). By this way, we prepared a number of novel 2-chalcogenealkynylanisoles and applied these new compounds as starting materials in the electrophilic cyclization reactions (Table 1).

Inspection of Table 1 shows that the reaction worked well for a variety of substituents in the aromatic ring of anisole. A closer inspection of the results revealed that the reaction significantly depends on the electronic effects of substituents in the aromatic ring bonded at the selenium atom of the electrophilic-chalcogen species (Table 1, entries 2 and 3). For example, arylselanyl bromide with an electron-donating substituent (Table 1, entry 3) in the aromatic ring gave a worse yield than arylselanyl bromide with an electron-withdrawing group (Table 1, entry 2). It is noteworthy the electron-donating groups in the aromatic ring decrease the electrophilicity of phenylselanyl bromide.

After the success in the synthesis of 2-chalcogenealkynylanisoles **4**, we next focus our attention on the development of an optimum set of the electrophilic cyclization conditions. For this purpose, the reaction of **4a** with iodine was chosen as a model system. We found that the reaction of **4a** with I_2 in CH_2Cl_2 as solvent yielded the desired product **5a** in 90% yield, after 1 h at room temperature (Scheme 3). Encouraged by these results, we further investigated the reaction behavior with other solvents, electrophilic sources, and temperature with the aim to improve the protocol. The outcome of this study and an investigation of other reaction parameters are depicted in Table 2.

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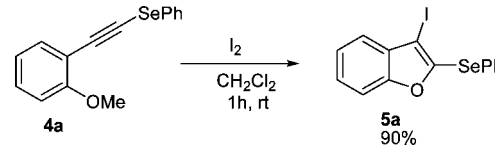
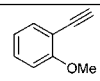
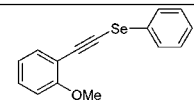
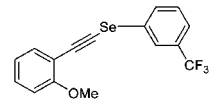
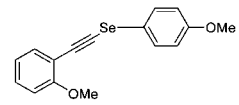
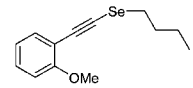
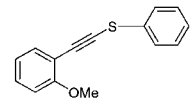
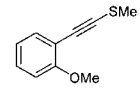
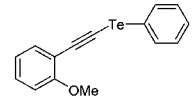
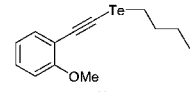
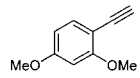
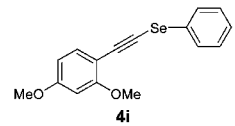
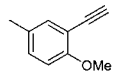
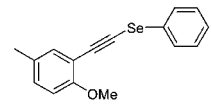
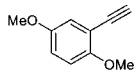
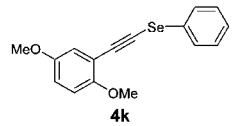
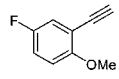
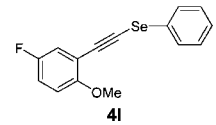
SCHEME 3



Regarding the influence of the solvent, better results were achieved using CH_2Cl_2, which furnished the desired product **5a** in 90% yield after a short reaction time (Table 2, entry 2). When THF, Et_2O, EtOH, and MeCN were used as solvent, good yields were also obtained; however, these reactions proceeded more slowly. The use of another electrophilic source such as ICl, with the standard reaction condition, failed to produce the electrophilic cyclization. In this case only a complex nonseparable mixture of multiple products was observed (Table 2, entry 3). However, it was gratifying to discover that the simple change in the temperature to −20 °C had a dramatic effect, giving the desired product **5a** in 93% yield (Table 2, entry 5). It was pointed out that the amount of electrophilic source also played an important role in the reaction. The amount of 1.1 equiv was better than 2 equiv (Table 2, entries 1 and 2). Thus, careful analysis of the optimized reaction revealed that the optimum condition for this electrophilic cyclization reaction was the combination of 1.0 equiv of 2-chalcogenealkynylanisoles, 1.1 equiv of electrophile source, and CH_2Cl_2 as solvent, at room temperature. Using this reaction condition we were able to prepare benzofuran derivative **5a** in 90% yield. In order to demonstrate the efficiency of this reaction, we explored the generality of our method by extending the conditions to various 2-chalcogenealkynylanisoles **4a**−**l**, as well as other electrophilic moieties, and the results are summarized in Table 3.

Inspection of Table 3 shows that in general, all of the reactions proceeded smoothly under mild conditions, ease of isolation, and high yields. Most importantly, the cyclization turned out to be general with respect to a diverse array of functionality and electrophile sources. Satisfactorily, all electrophile sources tested were effective. After the success in the cyclization reactions using ICl and I_2 as eletrophilic source, we next applied this method to the synthesis of disubstituted 2,3-bis-chalcogen-benzo[*b*]furans using PhSeBr as electrophilic sources. Table 3 shows our results, and in most cases the corresponding substituted 2-chalcogen-benzofurans were obtained in good yields. Based on the experiments, the reaction with 2-chalcogenealkynylanisoles **4a**−**d**, having Se-aryl, Se-aryl-substituted, and Se-alkyl groups attached to the triple bond

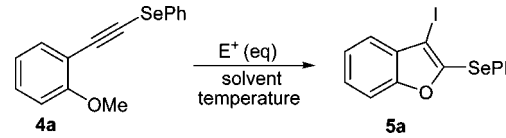
TABLE 1. Synthesis of 2-Chalcogenealkynylanisoles

entry	alkyne	product	Yield (%)
1	 **3a**	 **4a**	81
2	**3a**	 **4b**	55
3	**3a**	 **4c**	30
4	**3a**	 **4d**	70[a]
5	**3a**	 **4e**	91[b]
6	**3a**	 **4f**	72[b]
7	**3a**	 **4g**	84
8	**3a**	 **4h**	63[a]
9	 **3b**	 **4i**	70
10	 **3c**	 **4j**	71
11	 **3d**	 **4k**	67
12	 **3e**	 **4l**	65

[a] This reaction was carried out using elemental Se or Te and trapped with bromobutane. [b] This reaction was performed with diorganoyl disulfides as electrophilic agent.

has been successfully employed in this electrophilic cyclization, providing the desired products in high yields (Table 3, entries 1−7). In the case of an aromatic ring directly bonded to the selenium atom, the results revealed that the reaction is not sensitive to the electronic effects of the substituents. For example, an aromatic ring having either neutral **4a**, electron-withdrawing **4b**, or electron-donating **4c** substituents gave the cyclized products in very similar yields. In the case of 2-chalcogenealkynylanisoles with chalcogen-alkyl groups, our reaction system was suitable for the cyclization of both short and long aliphatic chains, giving the desired cyclized products in good yields. In addition, our reaction system was appropriate for cyclization of sulfide compounds. Arylsulfide **4e** and alkylsulfide **4f** derivatives were efficiently cyclized under the standard conditions. The introduction of sulfide groups at the 2-position of benzofuran is significant, since it could be easily oxidized to 2-sulfonylbenzofurans,[19] a class of compounds that has attracted tremendous interest of the pharmaceutical industry. In fact 2-sulfonylbenzofurans are potent inhibitors of the matrix metalloproteinase-13 and therefore offer a possible therapy for osteoarthritis.[20]

TABLE 2. Effect of Reaction Conditions on the Cyclization Reaction[a]



4a **5a**

entry	E^+ (equiv)	solvent	temp, time	yield (%)
1	I_2 (2.0)	CH_2Cl_2	rt, 1 h	81
2	I_2 (1.1)	CH_2Cl_2	rt, 1 h	90
3	ICl (2.0)	CH_2Cl_2	rt, 10 min	*b*
4	ICl (1.1)	CH_2Cl_2	−20 °C, 10 min	54
5	ICl (1.1)	CH_2Cl_2	−20ºC, 1 h	93
6	I_2 (1.1)	ether	rt, 6 h	73
7	I_2 (1.1)	CH_3CN	rt, 6 h	87
8	I_2 (1.1)	EtOH	rt, 6 h	78
9	I_2 (1.1)	THF	rt, 6 h	79

[a] Reactions performed in the presence of **4a** (0.25 mmol), I_2 (0.275 mmol). [b] A complex nonseparable mixture of multiple products was observed.

However, there is a limitation in our methodology since considerable difficulties were found when we attempted to react 2-chalcogenealkynylanisoles having an electron-donating group at the *para* position in the aromatic ring of anisole. In this case, we observed only the triple bond reduction product and byproduct with no formation of benzofuran product. These suggest that the presence of an electron-donating group at the *para* position increases the electronic density in C-2 at the triple bond,[3k] which is stabilized by the selenium atom,[21] making this center susceptive to nucleophilic attack on iodine instead of the cyclization process, providing exclusively the reduction product (Scheme 4 and Table 3, entry 20).

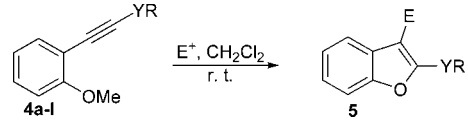
Conversely the cyclization of substrates **4g** and **4h** containing the tellurium atom did not react in the same way as the substrates containing selenium or sulfur atoms. Our experiments showed

(19) Kakarla, R.; Dulina, R. G.; Hatzenbuhler, N. T.; Hui, Y. W.; Sofia, M. J. *J. Org. Chem.* **1996**, *61*, 8347.

(20) Hu, Y.; Xiang, J. S.; DiGrandi, M. J.; Du, X.; Ipek, M.; Laakso, L. M.; Li, J.; Li, W.; Rush, T. S.; Schmid, J.; Skotnicki, J. S.; Tam, S.; Thomason, J. R.; Wang, Q.; Levin, J. I. *Bioorg. Med. Chem.* **2005**, *13*, 6629.

(21) (a) Patai, S.; Rappoport, Z. *The Chemistry of Organic Selenium and Tellurium Compounds*; Wiley: New York, 1986; Vol. 1. (b) Liotta, D. *Organoselenium Chemistry*; Wiley: New York, 1987. (c) Wirth, T. *Organoselenium Chemistry−Modern Developments in Organic Synthesis (Topics in Current Chemistry Vol. 208)*; Springer-Verlang: Heidelberg, 2000.

TABLE 3. Synthesis of 2-Chalcogen-3-substituted-benzo[*b*]furans 5 via Electrophilic Cyclization of 2-Chalcogenealkynylanisoles 4[a]



4a-l 5

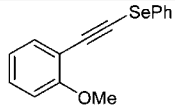
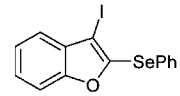
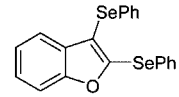
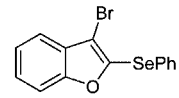
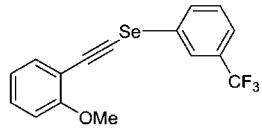
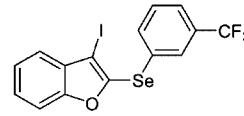
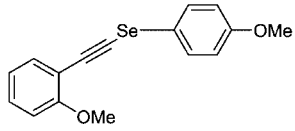
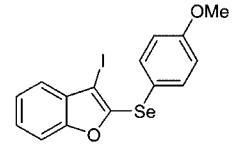
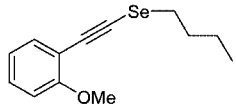
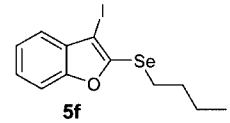
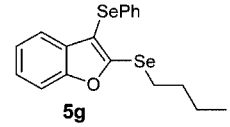
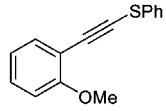
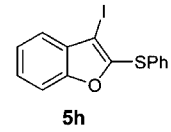
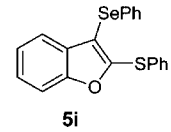
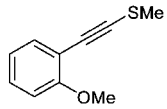
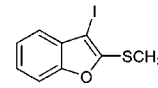
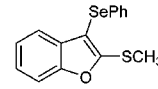
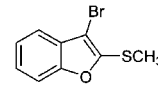
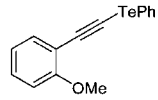
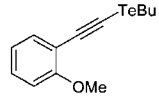
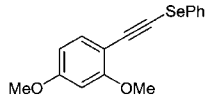
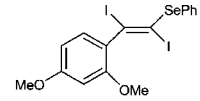
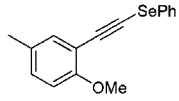
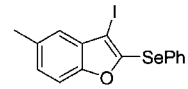
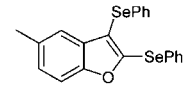
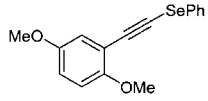
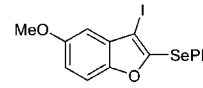
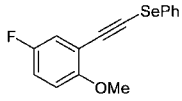
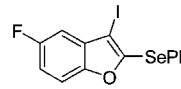
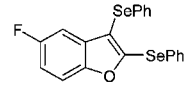
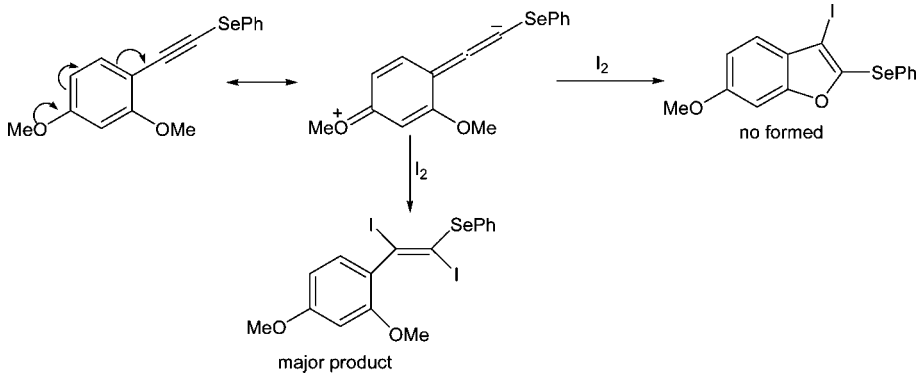
entry	substrate	E^+	time (h.)	product	yield (%)[c]
1	 **4a**	I_2	1.0	 **5a**	90
2		ICl[b]	1.0		93
3		PhSeBr	3.0	 **5b**	65
4		Br_2	1.0	 **5c**	75
5	 **4b**	I_2	3.0	 **5d**	70
6		ICl	2.0		94
7	 **4c**	I_2	1.0	 **5e**	75
8	 **4d**	I_2	1.0	 **5f**	75
9		ICl	1.0		80
10		PhSeBr	1.0	 **5g**	68
11	 **4e**	I_2	0.5	 **5h**	70
12		ICl	0.5		93
13		PhSeBr	0.5	 **5i**	86

TABLE 3. Continued

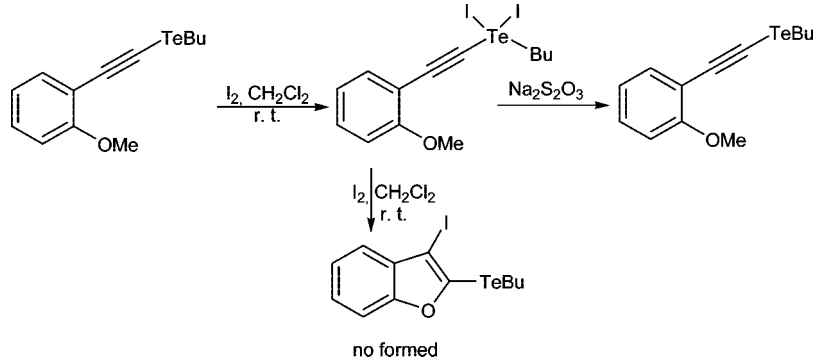
entry	substrate	E^+	time (h.)	product	yield (%)[c]
14	 **4f**	I_2	0.3	 **5j**	93
15		ICl	0.3		95
16	**4f**	PhSeBr	0.5	 **5k**	89
17	**4f**	Br_2	0.5	 **5l**	74
18	 **4g**	I_2	1.0		NR[d]
19	 **4h**	I_2	1.0		NR[d]
20	 **4i**	I_2	1.0	 **5m**	-[e]
21	 **4j**	I_2	1.0	 **5n**	76
22		ICl	1.0		93
23	**4j**	PhSeBr	2.0	 **5o**	50
24	 **4k**	I_2	2.0	 **5p**	95
25		ICl	1.0		90
26	 **4l**	I_2	1.0	 **5q**	70
27		ICl	1.0		75
28	**4l**	PhSeBr	2.0	 **5r**	72

[a] Reactions performed in the presence of alkyne (0.25 mmol), E^+ (0.27 mmol) in CH_2Cl_2 (5 mL). [b] All reactions performed with ICl were carried out at −20 °C. [c] Yields of **5a**−**r** are given for isolated products. [d] The starting material was recovered. [e] The reduction product was obtained almost exclusively.

SCHEME 4



SCHEME 5

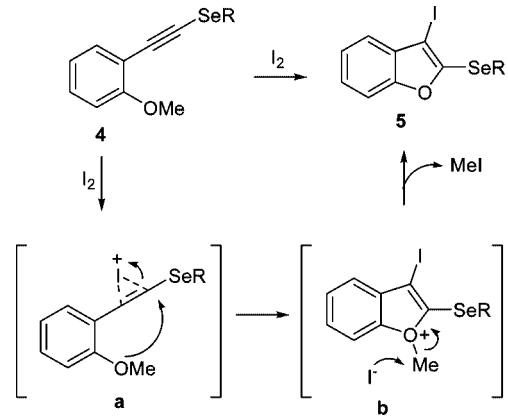


that addition of the electrophilic source consumed the starting materials; however, the formation of the product was not detected. After 10 min, we observed the formation of a red precipitate, and TLC analysis showed a very polar spot, a common characteristic of tellurium(IV) species, which were further confirmed and identified by GC/MS. In addition, treatment of these red precipitates with an excess of sodium bisulfide regenerated the starting tellurides **4g** and **4h**,[22] confirming that the reaction of these tellurides with iodide does not allow the cyclized product, even that using an excess of iodide, reflux, long reaction time, and other electrophiles such as, BuTeBr, PhSeBr (Scheme 5).

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) anti-nucleophilic attack of the oxygen 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 3-iodo-2-chalcogen-benzo[*b*]furan product and one molecule of MeI (Scheme 6).

The benzo[*b*]furans obtained by electrophilic cyclization appear highly attractive as intermediates for the preparation of more highly substituted benzo[*b*]furans, particularly when one considers that there are many ways to transform the resulting halogen and selenium functionalities into other

SCHEME 6



substituents. Thus, the resulting benzo[*b*]furan iodides could be employed as useful intermediates in many transition-metal-catalyzed processes, such as Sonogashira,[17] Suzuki,[23] Stille,[24] Heck,[25] Ullmann, and Negishi[27] cross-couplings. In this way, the potential of 3-iodo-2-chalcogen-benzo[*b*]furan derivatives as precursors for increasing molecular complexity via palladium- and copper-catalyzed reactions has been briefly investigated (Schemes 7, 8, and 9). For example, compound **5a** underwent Ullmann-type coupling with different thiols[28]

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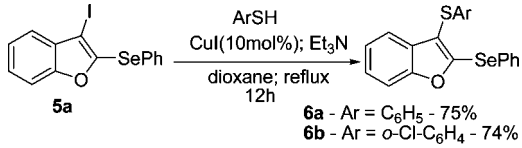
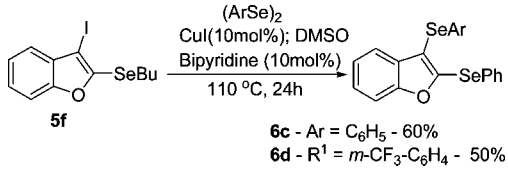
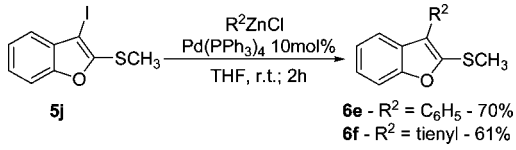
SCHEME 7



SCHEME 8



SCHEME 9



and gave the corresponding 3-(arylthio)-2-(phenylselanyl)-benzo[*b*]furans **6a** and **6b** in 75% and 74% yields, respectively (Scheme 7). To further prove the utility of our cyclization products, we tested the reactivity of **5f** toward CuI/bipyridine-catalyzed[29] cross-coupling with diphenyl diselenides to afford the 2,3-bis(phenylselanyl)benzo[*b*]furan products in moderate yields (Scheme 8). In addition, the substrate **5j** has been successfully employed in Negishi cross-coupling, affording the resultant 3-aryl-2-(methylthio)benzo[*b*]furan derivatives **6e** and **6f** in good isolated yields after short reaction time, under mild conditions (Scheme 9).

Conclusion

In summary, we have demonstrated the electrophilic cyclization reaction of 2-chalcogenealkynylanisoles with different electrophilic sources under mild conditions and established a route to obtain 3-substituted-2-chalcogen-benzo[*b*]furans in good to excellent yields. We observed that the pathway of reaction was sensitive to the nature of substituents in the aromatic ring of anisole and the chalcogen atom directly bonded to the triple bond. 2-Seleno- and 2-thioalkynylanisoles provided the corresponding cyclized products in good yield, under the standard conditions. However, 2-telluroalkynylanisoles gave only the organotellurium(IV) species, even when using an excess of iodide, reflux, and long reaction time. The halobenzo[*b*]furans obtained in the current protocol appear highly promising and attractive intermediates for the synthesis of more highly substituted benzo[*b*]furans. In fact, using the palladium- or copper-catalyzed cross-coupling reactions with thiols, diphenyl diselenides, and zincates, we were able to convert 3-iodo-2-chalcogen-benzo[*b*]furan to Ullmann- or Negishi-type products in good yields. We believe that this approach to halobenzo[*b*]furans should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting halogen, selenium, and sulfur functionalities[13] into a great number of interesting substituted benzo[*b*]furans.

Experimental Section

General Procedure for the Preparation of 2-Chalcogenealkynylanisoles Derivatives 4a−c, 4g, and 4i−l. *n*-Butyllithium (0.4 mL of a 2.5 M solution in hexane, 1 mmol) was added, under argon, to a solution of appropriate 2-ethynylanisole (1 mmol) in THF (2 mL) previously cooled at −78 °C. The resulting solution was stirred for 30 min at this temperature. After this time, the mixture was cooled at 0 °C, and the phenylselanylbromide or phenyltellanylbromide desired (1.0 mmol) in THF (1 mL) was added. The reaction was warmed at room temperature and stirred for 3 h. After that the mixture was diluted with ethyl acetate (20 mL) and washed with brine (2 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum.

((2-Methoxyphenyl)ethynyl)(phenyl)selane (4a). Purified by flash chromatography and eluted with hexane/ethyl acetate (95:5). Yield: 0.232 g (81%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.66−7.59 (m, 2H), 7.45 (dd, J = 7.0 Hz and J = 2.0 Hz, 1H), 7.36−7.24 (m, 4H), 6.91 (t, J = 7.0 Hz, 2H), 3.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.2, 133.4, 129.9, 129.4, 129.3, 128.6, 126.8, 120.4, 112.4, 110.6, 99.6, 72.8, 55.7. MS (EI, 70 eV) *m*/*z* (relative intensity): 287 (7), 204 (79), 164 (84), 163 (100), 130 (47), 77 (5). Anal. Calcd for $C_{15}H_{12}OSe$: C 62.73, H 4.21. Found: C 62.91, H 4.51.

((2-Methoxyphenyl)ethynyl)(3-(trifluoromethyl)phenyl)selane (4b). Purified by flash chromatography and eluted with hexane/ethyl acetate (95:5). Yield: 0.195 g (55%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.45−7.41 (m, 2H), 7.31 (td, J = 7.0 Hz and J = 2.0 Hz, 1H), 6.94−6.89 (m, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.2, 133.1, 131.7 (q, J = 32.2 Hz), 131.5, 130.8, 130.1, 129.5, 125.2 (q, J = 3.7 Hz), 123.6 (q, J = 3.7 Hz), 122.3 (q, J = 272 Hz), 120.4, 112.0, 110.6, 101.1, 71.3, 55.7. MS (EI, 70 eV) *m*/*z* (relative intensity): 352 (100), 309 (97), 272 (78), 230 (54), 130 (53), 117 (17), 90 (28). Anal. Calcd for $C_{16}H_{11}F_3OSe$: C 54.10, H 3.12. Found: C 54.29, H 3.33.

General Procedure for Iodocyclization. To a solution of 0.25 mmol of the alkyne and 2 mL of CH_2Cl_2 was gradually added 1.1 equiv of I_2 or ICl dissolved in 3 mL of CH_2Cl_2. The reaction mixture was allowed to stir at room temperature (ICl −20 °C) for the desired time. The excess of I_2 or ICl was removed by washing with satured aqueous $Na_2S_2O_3$. The mixture was then extracted (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated under vacuum.

3-Iodo-2-(phenylselanyl)benzofuran (5a). Purified by flash chromatography and eluted with hexane. Yield: 0.090 g (91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49−7.47 (m, 2H), 7.42−7.36 (m, 2H), 7.34−7.22 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.9, 147.6, 132.0, 131.3, 129.4, 129.0, 127.7, 126.1, 123.6, 121.7, 111.4, 78.8. MS (EI, 70 eV) *m*/*z* (relative intensity): 395 (45), 270 (11), 242 (53), 163 (100), 156 (2). Anal. Calcd for $C_{14}H_9IOSe$: C 42.13, H 2.27. Found: C 42.39, H 2.39.

2-(Butylselanyl)-3-iodobenzofuran (5f). Purified by flash chromatography and eluted with hexane. Yield: 0.071 g (75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42−7.40 (m, 1H), 7.33−7.23 (m, 3H), 3.05 (t, J = 7.5 Hz, 2H), 1.71 (quint, J = 7.5 Hz, 2H), 1.44 (sext, J = 7.5 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.6, 147.9, 131.4, 125.2, 123.4, 120.9, 110.9, 75.3, 32.6, 28.6, 22.6, 13.5. MS (EI, 70 eV) *m*/*z* (relative intensity): 377 (28), 375 (100), 320 (71), 194 (75), 166 (40). HRMS calcd for $C_{12}H_{13}IOSe$: 379.9176, found 379.9171.

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General Procedure for PhSeBr Cyclization. To a solution of 0.25 mmol of the alkyne and CH_2Cl_2 (3 mL) was added 1.1 equiv of PhSeBr dissolved in 2 mL of CH_2Cl_2 dropwise. The mixture was allowed to stir at room temperature for the desired time. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with brine (2 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum.

2,3-Bis(phenylselanyl)benzofuran (5b). Purified by flash chromatography and eluted with hexane. Yield: 0.069 g (65%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51−7.49 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.31−7.27 (m, 3H), 7.25−7.19 (m, 4H), 7.15−7.13 (m, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2, 150.7, 132.8, 130.4, 130.3, 129.4, 129.2, 128.9, 127.8, 126.6, 125.3, 123.4, 120.9, 113.6, 111.4. MS (EI, 70 eV) *m*/*z* (relative intensity): 427 (5), 269 (47), 242 (65), 163 (100), 155 (7), 76 (15). HRMS calcd for $C_{20}H_{14}OSe_2$: 429.9375, found 429.9380.

2-(Butylselanyl)-3-(phenylselanyl)benzofuran (5g). Purified by flash chromatography and eluted with hexane. Yield: 0.069 g (68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (dt, J = 8.0 Hz and J = 1.0 Hz, 1H), 7.39 (dq, J = 7.0 Hz and J = 1.0 Hz, 1H), 7.31−7.28 (m, 2H), 7.26−7.13 (m, 5H), 3.08 (t, J = 7.5 Hz, 2H), 1.72 (quint, J = 7.5 Hz, 2H), 1.41 (sext, J = 7.5 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0, 151.9, 131.0, 130.7, 129.8, 129.1, 126.4, 124.3, 123.9, 120.1, 110.8, 32.7, 27.8, 22.7, 13.4. MS (EI, 70 eV) *m*/*z* (relative intensity): 408 (9), 349 (4), 269 (100), 242 (43), 192 (21), 163 (70). HRMS calcd for $C_{18}H_{18}OSe_2$: 409.9688, found 409.9691.

General Procedure for Bromocyclization. To a solution of 0.25 mmol of the alkyne and CH_2Cl_2 (3 mL) was added 1.1 equiv of Br_2 in benzene dropwise. The mixture was allowed to stir at room temperature for the desired time. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with brine (2 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum.

3-Bromo-2-(phenylselanyl)benzofuran (5c). Purified by flash chromatography and eluted with hexane. Yield: 0.066 g (75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52−7.48 (m, 3H), 7.45 (d, J = 7.6 Hz, 1H), 7.36−7.30 (m, 2H), 7.26−7.24 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.3, 132.0, 129.5, 128.9, 128.1, 127.8, 126.1, 123.6, 120.0, 111.6, 108.1, 99.9. MS (EI, 70 eV) *m*/*z* (relative intensity): 351 (11), 270 (58), 242 (62), 163 (100), 156 (3), 76 (15). Anal. Calcd for $C_{14}H_9BrOSe$: C 47.76, H 2.58. Found: C 47.39, H 2.32.

General Procedure for the Copper-Catalyzed Coupling Reaction of 5a with Thiols. To a Schlenck tube, under argon, containing a mixture of 3-iodo-2-(phenylselanyl)benzo[*b*]furan **5a** (0.5 mmol) in dry dioxane (3 mL) was added the appropriate thiol (0.6 mmol). After this Et_3N (1 mmol) was added dropwise, followed by CuI (0.0095 g, 10 mol %), and the reaction mixture was stirred at reflux temperature for 12 h. After this the solution was cooled to room temperature, diluted with dichloromethane (20 mL), and washed with saturated aqueous NH_4Cl (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum.

2-(Phenylselanyl)-3-(phenylthio)benzofuran (6a). Purified by flash chromatography and eluted with hexane. Yield: 0.142 g (75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54−7.52 (m, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.37 (d, J = 7.3 Hz, 1H), 7.28−7.08 (m, 11H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.1, 150.6, 135.5, 133.1, 131.6, 131.5, 130.5, 129.3, 128.9, 128.5, 127.6, 125.9, 125.3, 123.4, 120.2, 111.5. MS (EI, 70 eV) *m*/*z* (relative intensity): 380 (27), 269 (85), 242 (68), 194 (72), 163 (100), 150 (55), 76 (31). HRMS calcd for $C_{20}H_{14}OSSe$: 381.9931, found 381.9935.

3-(2-Chlorophenylthio)-2-(phenylselanyl)benzofuran (6b). Purified by flash chromatography and eluted with hexane. Yield: 0.153 g (74%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56−7.54 (m, 2H), 7.49 (d, J = 8.1 Hz, 1H), 7.39−7.19 (m, 7H), 7.01 (td, J = 6.4 Hz and J = 1.2 Hz, 1H), 6.90 (td, J = 6.6 Hz and J = 1.4 Hz, 1H), 6.67 (dd, J = 6.4 Hz and J = 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2, 152.1, 135.0, 133.5, 131.2, 129.5, 129.3, 128.9, 128.2, 127.8, 127.1, 127.0, 126.3, 125.4, 123.6, 120.0, 115.1, 111.6. MS (EI, 70 eV) *m*/*z* (relative intensity): 414 (15), 269 (100), 242 (72), 221 (71), 194 (26), 150 (48), 76 (27). HRMS calcd for $C_{20}H_{13}ClOSSe$: 415.9541, found 415.9538.

General Procedure for the Cross-Coupling Reaction of Diaryl Diselenides with 5f. To a round-bottomed flask containing diaryl diselenide (0.25 mmol), **5f** (0.5 mmol), CuI (10 mol %), and bpy (10 mol %) was added DMSO (2 mL). The reaction mixture was allowed to stir at reflux for 24 h. After this time, the solution was cooled to room temperature, diluted with dichloromethane (20 mL), and washed with saturated aqueous NH_4Cl (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum.

2-(Butylselanyl)-3-(phenylselanyl)benzofuran (6c). Purified by flash chromatography and eluted with hexane. Yield: 0.122 g (60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (dt, J = 8.0 Hz and J = 1.0 Hz, 1H), 7.39 (dq, J = 7.0 Hz and J = 1.0 Hz, 1H), 7.31−7.28 (m, 2H), 7.26−7.13 (m, 5H), 3.08 (t, J = 7.5 Hz, 2H), 1.72 (quint, J = 7.5 Hz, 2H), 1.41 (sext, J = 7.5 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0, 151.9, 131.0, 130.7, 129.8, 129.1, 126.4, 124.3, 123.9, 120.1, 110.8, 32.7, 27.8, 22.7, 13.4. MS (EI, 70 eV) *m*/*z* (relative intensity): 408 (9), 349 (4), 269 (100), 242 (43), 192 (21), 163 (70). HRMS calcd for $C_{18}H_{18}OSe_2$: 409.9688, found 409.9691.

2-(Butylselanyl)-3-(3-(trifluoromethyl)phenylselanyl)benzofuran (6d). Purified by flash chromatography and eluted with hexane. Yield: 0.119 g (50%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.44−7.37 (m, 2H), 7.34−7.27 (m, 3H), 3.06 (t, J = 7.3 Hz, 2H), 1.73 (quint, J = 7.3 Hz, 2H), 1.45 (sext, J = 7.6 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.7, 147.9, 134.8, 131.5 (q, J = 32.9 Hz), 131.4, 131.3, 129.6, 128.3 (q, J = 3.6 Hz), 125.2, 124.9 (q, J = 3.6 Hz), 123.5, 123.3 (q, J = 273 HZ), 121.0, 110.9, 99.9, 32.6, 28.6, 22.6, 13.5. MS (EI, 70 eV) *m*/*z* (relative intensity): 476 (15), 472 (100), 336 (90), 309 (60), 259 (95), 166 (58). HRMS calcd for $C_{19}H_{17}F_3OSe_2$: 477.9562, found 477.9565.

General Procedure for the Palladium-Catalyzed Negishi Coupling of 5j with Zincates. A 10 mL Schlenk tube, equipped with a magnetic bar, rubber septum, and argon, containing the previously prepared organozinc compound (1.5 mmol), was charged sequentially with the 3-iodo-2-(methylthio)benzo[*b*]furan **5j** (0.5 mmol) and $Pd(PPh_3)_4$ (0.057 g, 10 mol %). The yellow mixture was stirred at room temperature, and the reaction time was determined by monitoring the reaction by TLC. After this the solution was diluted with dichloromethane (20 mL) and washed with saturated aqueous NH_4Cl (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum.

2-(Methylthio)-3-phenylbenzofuran (6e). Purified by flash chromatography and eluted with hexane. Yield: 0.091 g (76%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.61−7.59 (m, 3H), 7.50−7.46 (m, 3H), 7.37 (t, J = 7.3 Hz, 1H), 7.29 (t, J = 7.3 Hz, 1H), 7.23 (dd, J = 7.5 Hz and J = 2.5 Hz, 1H), 2.52 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 147.5, 131.8, 129.1, 128.5, 128.3, 127.4, 124.4, 122.9, 122.5, 119.7, 110.8, 16.9. MS (EI, 70 eV) *m*/*z* (relative intensity): 238 (26), 222 (17), 194 (100), 163 (23), 151 (10), 76 (8). Anal. Calcd for $C_{15}H_{12}OS$: C 74.97, H 5.03. Found: C 75.15, H 5.39.

2-(Methylthio)-3-(thiophen-2-yl)benzofuran (6f). Purified by flash chromatography and eluted with hexane. Yield: 0.075 g (61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82−7.80 (m, 1H), 7.46−7.44 (m, 2H), 7.37 (dd, J = 4.0 Hz and J = 1.2 Hz, 1H), 7.32−7.25 (m, 2H), 7.16 (dd, J = 4.0 Hz and J = 1.4 Hz, 1H),

2.56 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.3, 147.6, 133.1, 127.6, 127.2, 126.0, 125.0, 124.6, 123.2, 120.0, 116.4, 110.8, 16.8. MS (EI, 70 eV) *m*/*z* (relative intensity): 243 (100), 228 (75), 200 (64), 169 (15), 114 (20). HRMS calcd for $C_{13}H_{10}OS_2$: 246.0173, found 246.0177.

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Supporting Information Available: Experimental procedures, additional experimental details for the preparation of all compounds, and ^{1}H and ^{13}C NMR spectra for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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