Butyltellurium Tribromide: A Suitable Electrophilic Source to Cyclization Reactions

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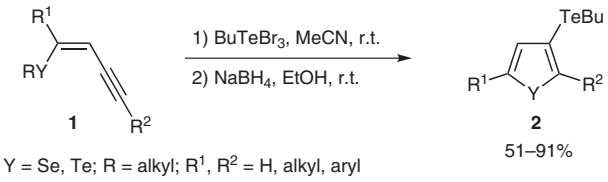
Abstract: We present here our results of the electrophilic cyclization reaction of (*Z*)-chalcogenoenynes using butyltellurium tribromide as an electrophilic source. The cyclization reaction proceeded cleanly under mild reaction conditions and 3-(butyltellanyl)chalcogenophenes were formed in moderate to excellent yields. Subsequent, using these heterocycles as substrate to palladium-catalyzed cross-coupling reactions a new carbon–carbon bond was formed in good yields.

Key words: tellurium, electrophilic cyclization, chalcogenophenes

Heteroannulation processes involving acetylenic compounds bearing a tethered nucleophilic substituent are among the most versatile and efficient synthetic way to constructing a wide array of carbocycles and heterocycles.[1] In this way, electrophilic cyclization of unsaturated compounds has proved to be an efficient method for one-step construction of a substituted heterocyclic unit.[2] Important heterocycles such as indoles,[2a,b] benzo[*b*]furans,[2c,d] benzo[*b*]thiophenes,[2e,f] benzo[*b*]selenophenes,[2g] thiophenes,[2h] furans,[2i] and pyrroles[2j] among others,[2k–r] have been accessed using this protocol. This reaction is believed to proceed through an intramolecular, stepwise mechanism involving a cationic intermediate.[2b,g,q]

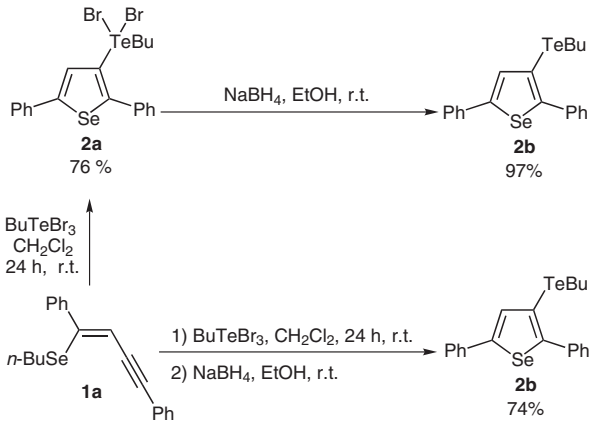
In the context of heterocyclic compounds, the chalcogenophene derivatives (selenophene and tellurophene) play an important role in organic synthesis because of their excellent electronic properties and environmental stability. Chalcogenophenes are widely studied agents with a diverse array of biological effects including potent antitumor and antiviral activities.[3]

Recently, we reported the electrophilic cyclization reaction of (*Z*)-selenoenynes with several electrophilic sources to obtain 3-functionalized selenophenes in good yields.[4] These early studies mainly focused on the preparations of 3-(butyltellanyl)selenophenes to be used as substrate in the palladium-catalyzed reactions.[5] Unfortunately, in that work, we found that the butyltellurium bromide species did not work as electrophilic sources, as a consequence, 3-(butyltellanyl)selenophene was not obtained. Herein, we provide an approach in this cyclization methodology using a tellurium species as electrophilic sources. We also report our preliminary results in the palladium-catalyzed cross-coupling reactions using these heterocycles as substrate. Since butyltellurium tribromide ($BuTeBr_3$), a tellurium(IV) species, is more electrophilic and more stable than BuTeBr,[6] we tried to use $BuTeBr_3$ in the electrophilic cyclization reaction of (*Z*)-chalcogenoenynes to obtain 3-(butyltellanyl)chalcogenophenes **2** (Scheme 1).



Scheme 1 General scheme for the cyclization reactions

We have found that the reaction of (*Z*)-selenoenyne **1a** with $BuTeBr_3$ in CH_2Cl_2 at room temperature yielded 3-[dibromo(butyl)tellanyl]selenophene **2a** in 76% isolated yield (Scheme 2). The treatment of compound **2a** with $NaBH_4$ in EtOH[7] gave the desired product **2b** as the product in quantitative yield (Scheme 2). Since the product **2b** was obtained in two-step processes, we tried to use a one-pot reaction to prepare the same product. In this way, when (*Z*)-selenoenyne **1a** was treated with $BuTeBr_3$ in CH_2Cl_2 at room temperature for 24 hours and after that was added a solution of $NaBH_4$ and EtOH, the product **2b** was obtained in an acceptable yield (Scheme 2).



Scheme 2 Preparation of 3-(butyltellanyl)-2,5-diphenylselenophene (**2a**)

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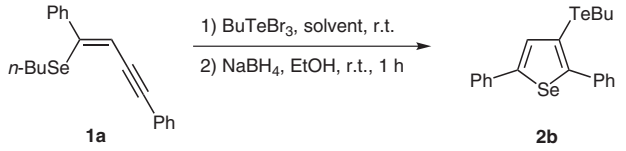
Based on the good result obtained on the one-pot procedure described above, we investigated the best experimental conditions to improve the yield of the product **2b**. Regarding the influence of the solvent in this cyclization reaction, optimal results were achieved changing CH_2Cl_2 to MeCN, furnishing the desired product **2b** in 91% yield in a short reaction time (Table 1, entry 2). By using THF, good yield was also obtained, however, this reaction proceeded more slowly (Table 1, entry 3). Other solvents such as $MeNO_2$, DMSO, EtOH, and hexane afforded the desired product in moderated yields and with longer reaction times (Table 1, entries 1 and 4–7).

Table 1 Study of the Solvent Effect on Selenoenyne Cyclization Reactions[a]

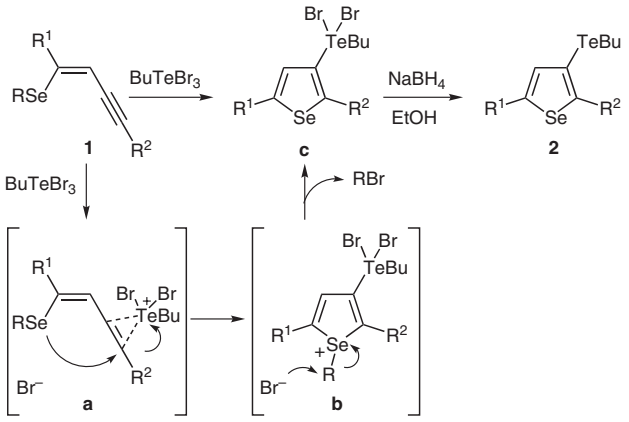


Entry	Solvent	Time (h)	Yield of **2b** (%)
1	CH_2Cl_2	24	74
2	MeCN	1	91
3	THF	12	89
4	$MeNO_2$	6	74
5	DMSO	6	58
6	EtOH	36	72
7	hexane	48	75

[a] Reactions performed in the presence of **1a** (0.50 mmol), $BuTeBr_3$ (0.55 mmol), and then $NaBH_4$ (1 mmol) in EtOH (5 mL).

We believe that the mechanism of this tellurium cyclization reactions involves the following: (i) coordination of the carbon–carbon triple bond to the $BuTeBr_3$ to generate a telluronium intermediate **a**, (ii) *anti* attack of the selenium atom on the activated telluronium intermediate to produce the salt **b**, and (iii) facile removal of the alkyl group by the bromine anion present in the reaction mixture to generate corresponding 3-[dibromo(butyl)tellanyl]selenophene **c** and one molecule of RBr. The reduction of **c** with $NaBH_4$ in EtOH[7] gave the corresponding 3-(butyltellanyl)selenophene **2** as the product (Scheme 3).

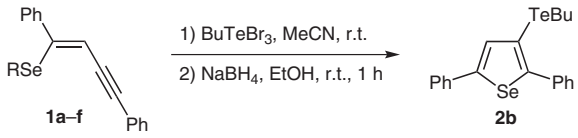
Since the accomplishment of this reaction probably is dependent on the nature of the group directly linked to the selenium atom, we decided to explore this influence using different groups, and the results are shown in Table 2. Table 2 shows that the efficiency of selenophene synthesis significantly depends on the steric effects of the groups bonded at selenoenynes. The cyclization reaction occurs only with selenoenynes having a Se–Csp^3 group bonded. A closer inspection of these results revealed that methyl, ethyl, and *n*-butyl groups bonded at the selenium atom resulted in the formation of products in high yields after



Scheme 3 Proposed mechanism for the cyclization reactions

very short reaction times (Table 2, entries 1–3). The selenoenynes having a *tert*-butyl or benzyl groups also gave the product **2b** in good yield, however, with higher reaction times (Table 2, entries 4 and 5). However, performing the reaction with selenoenyne **1f**, which has a phenyl group bonded at the selenium atom, the desired product was not observed, even under a long reaction time (Table 2, entry 6).

Table 2 Influence of the Group Bonded to a Selenium Atom in the Cyclization Process[a]



Entry	(*Z*)-Selenoenyne **1**	Time (h)	Yield of **2b** (%)
1	**1a** (R = *n*-Bu)	1	91
2	**1b** (R = Me)	1	90
3	**1c** (R = Et)	1	90
4	**1d** (R = *t*-Bu)	4	85
5	**1e** (R = Bn)	2	88
6	**1f** (R = Ph)	48	–

[a] Reactions performed in the presence of (*Z*)-selenoenyne (0.50 mmol), $BuTeBr_3$ (0.55 mmol) in MeCN (5 mL), and then $NaBH_4$ (1 mmol) in EtOH (5 mL).

Thus, the careful analysis of the optimized reactions revealed that the optimum conditions for this electrophilic cyclization reaction[8] were the combination of 1.0 equivalent of (*Z*)-selenoenyne, 1.1 equivalents of $BuTeBr_3$, using MeCN as the solvent at room temperature, and afterwards treatment with $NaBH_4$ and EtOH. To demonstrate the efficiency of this reaction, we explored the generality of our method extending the conditions to other (*Z*)-selenoenynes, and these results are summarized in Table 3.

Table 3 Scope and Generality of the Cyclization Reaction Using $BuTeBr_3$ as Electrophile[a]

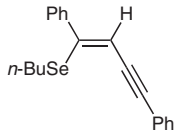
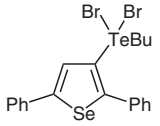
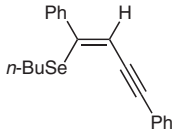
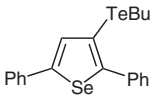
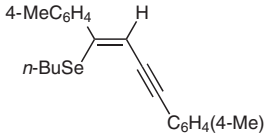
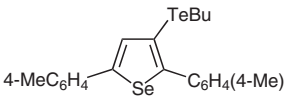
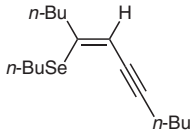
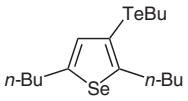
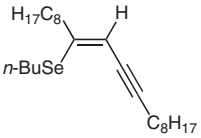
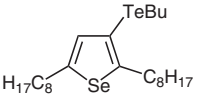
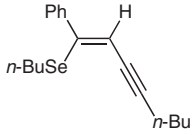
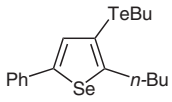
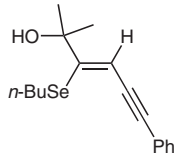
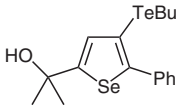
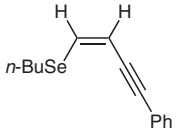
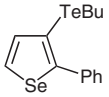
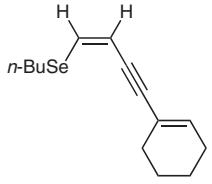
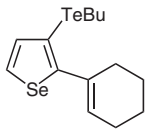
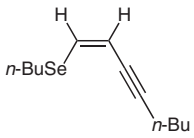
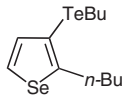
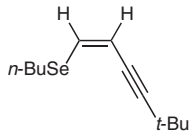
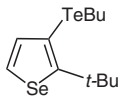
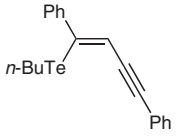
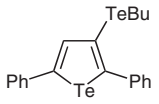
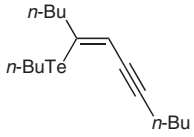
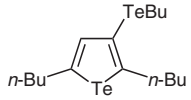
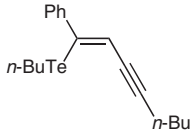
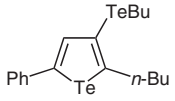
Entry	(*Z*)-Selenoenyne	Time (h)	Product	Yield (%)[c]
1[b]	 **1a**	1	 **2a**	92
2	 **1a**	1	 **2b**	91
3	 **1g**	2	 **2c**	82
4	 **1h**	0.5	 **2d**	81
5	 **1i**	1.5	 **2e**	79
6	 **1j**	3	 **2f**	87
7	 **1k**	0.25	 **2g**	51
8	 **1l**	4	 **2h**	85
9	 **1m**	1	 **2i**	87

Table 3 Scope and Generality of the Cyclization Reaction Using $BuTeBr_3$ as Electrophile[a] (continued)

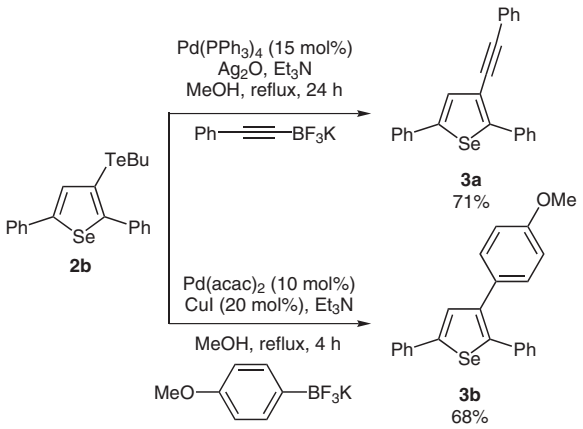
Entry	(*Z*)-Selenoenyne	Time (h)	Product	Yield (%)[c]
10	 **1n**	3	 **2j**	83
11	 **1o**	2	 **2k**	67
12	 **1p**	3	 **2l**	82
13	 **1q**	12	 **2m**	76
14	 **1r**	10	 **2n**	75

[a] Reactions performed in the presence of (*Z*)-selenoenyne (0.50 mmol), $BuTeBr_3$ (0.55 mmol) in MeCN (5 mL), and afterwards $NaBH_4$ (1 mmol) in EtOH (5 mL).
[b] Reaction without treatment with $NaBH_4$ and EtOH.
[c] Yields of **2a**–**n** are given for isolated products.

Inspection of Table 3 shows that, in general, all of the reactions proceeded efficiently with good yields. The experiments showed that the reaction with selenoenynes having aryl, aryl-substituted, and alkyl groups gave 3-(butyltellanyl)selenophene derivatives in good yields (Table 3, entries 1–5). To our satisfaction, cyclization of unsymmetrical selenoenynes also afforded the desired products in satisfactory yields (Table 3, entries 6 and 7), although the yields were lower for selenoenynes with a hydroxyl function at the propargyl position. Finally, via the protocol described in this study we were able to use the terminal (*Z*)-selenoenynes **1l**–**o** as subtracts which yielded the corresponding 3-(butyltellanyl)selenophenes **2h**–**k** in good yields of isolated products. These products are important since the 5-position in the selenophene ring is suitable to a new transformation (Table 3, entries 8–11).

In an attempt to broaden the scope of procedure described here, we also investigated the possibility of performing the reaction with (*Z*)-telluroenynes. As illustrated in Table 3, the electrophilic cyclization reaction of **1p**–**r** with $BuTeBr_3$ in MeCN led to corresponding products **2l**–**n** in good yields (Table 3, entries 12–14).

The compounds obtained by this protocol appear highly promising as intermediates in the preparation of more highly substituted selenophenes. Recently, applications of aryl tellurides utilizing palladium-catalyzed cross-coupling have been described and these compounds act in a manner similar to iodine or bromide analogues.[5] For instance, the resulting 3-(butyltellanyl)selenophenes should be particularly useful intermediates in many transition-metal-catalyzed processes, such as Suzuki cross-coupling.[9] For example, compound **3a** has been successfully obtained in a 71% isolated yield by the Suzuki cross-coupling of **2b** with phenylethynyl trifluorborate (Scheme 4).[9d] In a similar manner, the cross-coupling of **2b** with 4-methoxyphenyl trifluorborate gave the corresponding selenophene derivative **3b** in 68% yield (Scheme 4).[9e] These results were considered acceptable when compared to iodine analogues.[10]



Scheme 4 Reactivity of compound **2b** in palladium-catalyzed cross reactions

In summary, we have explored the electrophilic cyclization reaction of (*Z*)-chalcogenoenynes using butyltellurium tribromide as an electrophilic source. The cyclization reactions proceed cleanly under mild reaction conditions and 3-(butyltellanyl)chalcogenophenes were obtained in moderate to excellent yields. Subsequently, Suzuki cross-coupling reactions of compound **2b** with alkynyl- or aryltrifluorborates proceeded smoothly in satisfactory yields. Since the yields to the Suzuki cross-coupling using butyltellurium at the 3-position are very similar, compared to iodine derivatives, we are also studying the behavior of these compounds using other palladium/copper cross-coupling reactions. These studies will appear in the literature in the near future.

Acknowledgment

We are grateful to FAPERGS, CAPES (SAUX), and CNPq for financial support.

References and Notes

(1) For representative illustrations, see the following reviews: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (d) Vizer, S. A.; Yerzhanov, K. B.; Al Aziz Al Quntar, A.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 5499.

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(8) **General Procedure for the $BuTeBr_3$ Cyclizations**
To a solution of 0.50 mmol of the appropriate (*Z*)-selenoenyne in MeCN (5 mL) was added $BuTeBr_3$ (0.233 g, 0.55 mmol). The reaction mixture was allowed to stir at r.t. for the time showed in Table 3. After this time, EtOH (5 mL) and $NaBH_4$ (0.037 g, 1 mmol) were added under vigorous stirring (gas evolution was observed during this addition). The reaction mixture was stirred at r.t. for one additional hour, diluted with EtOAc (20 mL) and washed with H_2O (10 mL) and brine (3 × 10 mL). The organic layer was dried over anhyd Mg_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexane as the eluent.
Analysis of the ^1H NMR and ^{13}C NMR spectra showed that all the obtained products presented data in full agreement with their assigned structures.
Selected Spectral and Analytical Data for 2b
Yield 0.212g (91%). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.51–7.49 (m, 5 H), 7.44–7.28 (m, 6 H), 2.79 (t, *J* = 7.6 Hz, 2 H), 1.67 (quin, *J* = 7.6 Hz, 2 H), 1.29 (sext, *J* = 7.6 Hz, 2 H), 0.84 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.92, 150.21, 137.67, 135.75, 135.14, 129.31, 128.93, 128.25, 127.97, 127.76, 126.20, 104.55, 36.64, 24.88, 13.32, 8.88. MS: *m/z* (rel. intensity) = 468 (37), 411 (11), 284 (72), 202 (100), 77 (6), 57 (5). HRMS: *m/z* calcd for $C_{20}H_{20}SeTe$: 469.9792; found: 469.9798.

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