PREPARATIONS OF SELENIUM-CONTAINING HETEROCYCLES
BASED ON AN INTRAMOLECULAR CYCLIZATION OF SELENOLS
AND RELATIVES

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Abstract – The preparation of the five- to nine-membered selenium-containing heterocycles using the intramolecular cyclization of selenols and relative compounds is mainly described in this review based on recent advances in our findings. Some reactions and chemical properties of the obtained products are also described.

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1. INTRODUCTION

In addition to selenium, which is a rare element essential to the human body,\(^1\) inorganic and organic selenium-containing molecules have been much less developed because of their high toxicity and instability. Recently, organoselenium compounds, especially selenium-containing heterocycles, are of increasing interest because of their chemical properties, biological activity\(^2\) and medicinal applications, such as anticancer, antiviral, antibacterial, antihypertensive and fungicidal properties. Much effort has been expended not only in the preparation of new structural heterocycles containing a selenium element but also in the development for the synthetic methodologies of selenaheterocycles.

It is already known that the intermolecular \textit{trans}-addition of selenols\(^3\) and tellurols\(^4\) into a carbon-carbon triple bond regio- and stereo-specifically proceed to form vinylselenides or vinyltellurides. Therefore, this

\begin{equation}
\text{C≡C-R} \quad \text{SeH} \quad \text{endo-dig mode} \quad \text{and/or} \quad \text{exo-dig mode}
\end{equation}

\textbf{Scheme 1.} Synthetic Strategy for the Preparation of Selenium-Containing Heterocycles
addition of the selenols to a triple bond using intramolecular cyclization systems for our objective, which is the synthesis of various types of selenium-containing heterocycles, was extended. Scheme 1 shows our synthetic strategy for the preparation of selenium-containing heterocycles.

2. BENZOSELENEPINES

2.1. 3-Benzoselenepines and 3-benzotellurepines

In 1991, we succeeded in the synthesis and isolation of the novel 3-benzotellurepines, fully unsaturated tellurium-containing seven-membered heterocycles, by the reaction of o-diethynylbenzene with sodium telluride (Na\textsubscript{2}Te) as shown in Scheme 2. Diethynylbenzene (1) reacted with Na\textsubscript{2}Te in the presence of hydrazine hydrate and a phase-transfer catalyst (n-Oct\textsubscript{3}MeN\textsuperscript{+} Cl\textsuperscript{-}) in benzene-water at room temperature to give the desired C-unsubstituted 3-benzotellurepine (2) in ca. 60% yield as a yellow oil. Tellurepine (2) is relatively unstable and gradually decomposes to naphthalene and tellurium. Treatment of 2 with SO\textsubscript{2}Cl\textsubscript{2} gave 3,3-dichlorotellurepine (3a) and treatment with Br\textsubscript{2} afforded the 3,3-dibromo derivative 3b. The halogeno compounds 3 are somewhat more stable than the parent 2 and reverted back to 2 upon treatment with Na\textsubscript{2}S in hexane-water.

![Scheme 2](image)

3-Benzotellurepines (2, 3), which were obtained in this study, are the first synthetic examples of seven-membered tellurium-containing heterocycles. Unfortunately, under similar conditions using Na\textsubscript{2}Se instead of Na\textsubscript{2}Te, 3-benzoselenepine (5) could not be isolated in spite of many efforts; naphthalene and element selenium were obtained. The selenol (4) generated by the addition of Na\textsubscript{2}Se to an ethynyl moiety of 1 cyclized into an alternative triple bond to give the desired 3-benzoselenepine (5). 5 undergoes ring contraction to form the selenanorcaradiene (6). The resulting tautomer 6 immediately extrudes a selenium element to give naphthalene. 3-Benzoselenepine having no substitutions is too unstable to be isolated.
2.2. 1-Benzoselenepines

It is known that simple monocyclic and benzene ring-fused thiepines are thermally unstable due to ready extrusion of the sulfur via the corresponding norcaradiene derivatives, but the stability of the heteropine rings can be enhanced by introduction of bulky groups in the α-position. Therefore, the synthesis of the 1-benzoselenepines, the regioisomers of 3-benzoselenepines having a bulky group at the 2-position, was examined next. The retro-synthesis of the 1-benzoselenepine is illustrated in Scheme 3.

![Scheme 3](image)

**Scheme 3**

Several key starting ene-yne compounds **11a-h** were prepared as shown in Scheme 4, and obtained in 4 steps including the palladium-catalyzed Sonogashira reaction of the styrylbromide (**10**) with 1-alkynes to give 77-93% yields from o-bromoiodobenzene (**7**). Compound **11** were lithiated with tert-ButLi in dry THF at -80 °C and then treated with elemental selenium, followed by oxidation with K₃Fe(CN)₆ to produce di[o-(buten-3-ynyl)pheny] diselenides (**13**) in one pot in 53-85% yields. NaBH₄ reduction of the
diselenides 13 in THF-EtOH resulted in the direct 7-endo-dig mode ring closure to give the expected 1-benzoselenepines (14) with reductive cleavage of the Se-Se bond together with the 6-exo-dig 2H-selenochromenes (15) in the yields shown in Scheme 5. As expected, selenepine 14c having the bulkiest tert-butyl group is stable and can be stored for several weeks at room temperature; the methyl derivative 14a is unstable and decomposes to methylnaphthalene during the purification operations.

Scheme 5

2.3. Other 1-benzoheteroepines

Scheme 6
In a similar way, 2-alkyl-1-benzotellurepines (17)\textsuperscript{10,11} and 2-methylidene-2H-tellurochromenes (18) were also obtained by the use of Na\textsubscript{2}Te instead of Na\textsubscript{2}Se through the intramolecular ring closure of the tellurols (16) in nearly similar yields with the selenium compounds. On the other hand, the thiols (19) and tin hydrides (21), which were also easily generated from the bromides 11, gave the 2-substituted 1-benzothiepines (20)\textsuperscript{11} and 1,1-dibutyl-1-benzostannepines (22)\textsuperscript{12} in only the 7-endo-dig mode reaction, respectively. The 1-benzostannepines (22) are hitherto unknown heterocyclic systems, and are converted into the seven-membered 1-benzostibepines\textsuperscript{13} and 1-benzoborepines\textsuperscript{13} involving the 1-benzotellurepines via a tin-metal exchange reaction.\textsuperscript{14}

\section*{2.4. 2-Methylidenesilachromenes}

The platinum-catalyzed silylation of compound 23, which were isolated in the reaction of the bromides 11 with Me\textsubscript{2}SiHCl, proceeded to give the (E)-1,1-dimethyl-2-methylidenesilachromenes (24)\textsuperscript{15} as the sole products in moderate yields during the 6-exo-dig mode cyclization as shown in Scheme 6.

\section*{3. BENZOSELENOPHENES}

\subsection*{3.1. Benzo[b]selenophenes}

Next, this intramolecular cyclization of phenylselenols to a triple bond for the selenium-containing heterocycles was applied for the preparation of the benzo[b]selenophenes which was the simplest system.\textsuperscript{16} The key starting compounds, \textit{o}-bromoethynylbenzenes (25) were readily prepared by the Sonogashira reaction\textsuperscript{9} of \textit{o}-bromoiodobenzene (7) with 1-substituted acetylenes in high yields. The treatment of 25 with \textit{tert}-BuLi in dry Et\textsubscript{2}O at -80 °C and then treatment with elemental selenium, followed by the addition of EtOH, gave the selenophenes (27) \textit{via} intermediates 26 as the sole products in good yields in one pot, as shown in Scheme 7. The treatment of 2-TMS derivative 27e with alkali in MeOH, and fluoride-anion containing H\textsubscript{2}O or NaBH\textsubscript{4} reduction in EtOH afforded the unsubstituted selenophene. Benzotellurophenes (28) and thiophenes (29) were also conveniently obtained \textit{via} similar

\begin{equation}
\begin{align*}
\text{Scheme 7}
\end{align*}
\end{equation}
reactions in moderate to good yields. Thus, this ring-closure reaction was found to be a versatile simple method for the one-pot preparation of 2-substituted and unsubstituted benzo[\textit{b}]chalcogenophenes (27, 28, 29).

3.2. [1]Benzoseleno[3,2-\textit{b}][1]benzoselenophene
An extension of our synthetic methodology for the preparation of this title compound to the tandem system\textsuperscript{17} is also described. The dimeric-type compound of benzoselenophene, [1]benzoseleno[3,2-\textit{b}][1]benzoselenophene (32) is similarly synthesized from 7, as shown in Scheme 8. The starting diphenylacetylene 30 was easily prepared by the palladium-catalyzed coupling reaction of 7 with acetylene gas in 77\% yield. The dibromide 30 was lithiated with \textit{tert}-BuLi in dry Et\textsubscript{2}O at -80 °C and then treated with elemental selenium, affording the desired selenophene (32) in 52\% yield, together with diphenylacetylene in ca. 10\% yield. In the case of the cyclization for preparing the benzoselenophenes (27), the addition of a proton source such as EtOH after elemental selenium insertion was essential; if not, the product were produced in quite low yields. However, this tandem cyclization did not require a proton source. Thus, this reaction for 32 may probably proceed \textit{via} the radical intermediate 31. The structural isomer 33 was never produced. The tellurophene (34) and the thiophene derivatives (35) were also obtained in about 50\% yield.

![Scheme 8](image)

These chalcogenophenes (27-29, 32, 34, 35) and their synthetic methodologies were evaluated as an active semiconducting materials for organic thin film transistors.\textsuperscript{18}
4. SELENOPHTHALIDES

This section describes the synthesis of the selenolactone-type compounds, (Z)-3-methylideneselenophthalides (39) from the common starting o-ethynylbromobenzenes (25). Compounds 25 were lithiated with tert-BuLi in dry THF and then successively treated with excess dry ice to produce the corresponding o-ethynylbenzoic acids (36) in 70-75% yields. The acid chlorides (37) were generated by treatment of 36 with SOCl₂ in the usual manner and used for the next reaction without purification. The reaction of 37 with NaHSe in two phase solvents of H₂O-toluene in the presence of n-Bu₄N⁺ HSO₄⁻ as the phase-transfer catalyst resulted in the direct 5-exo-dig mode ring closure to regioselectively give the (Z)-3-methylideneselenophthalides (39) as the sole products via the probable intermediate 38. The five derivatives of selenophthalides (39) were obtained in moderate to good yields; no 6-endo-dig mode products (40) were produced. This cyclization is also effective for the tellurium analogues 41 by the use of NaHTe instead of NaHSe.

![Scheme 9](image)

On the other hand, the intramolecular cyclizations of the o-ethynylbenzoic acids (36) and benzamides (42), which are the oxygen and nitrogen analogues of 38, proceeded to afford the corresponding 6-endo-(43, 45) and 5-exo-dig mode products (44) by the palladium catalysis in moderate to good yields, respectively.²⁰

![Scheme 10](image)
5. SELENOCHROMONES AND RELATIVES

5.1. Synthesis of selenochromones

Scheme 11 shows the preparation of the selenochromones (49).\(^{21}\) o-Bromobenzoyl chloride (46) was coupled with various 1-acetylenes under the Sonogashira reaction conditions or trimethylethynylstannane under the Stille coupling conditions\(^{22}\) to give the corresponding ynones 47 in 70-89% yields. The treatment of the ethynyl ketones (47) with NaHSe in DMF gave the selenochromones (49) in one pot as the sole products via the 6-endo-dig mode intramolecular cyclization of the presumed intermediate 48 in moderate to high yields.

The TMS derivative 47g produced the 2-unsubstituted selenochromones (49h) with reductive removal of the TMS group under these conditions. No 5-exo-dig mode products 50 were obtained. These formation results of the selenochromones (49) from 47 clearly indicate the following two points. (1) The essential intermediate 48 are probably generated in situ by replacement of the bromo anion with the SeH group due to the enhancement of reactivity in the presence of the carbonyl group as the electron-withdrawing group. (2) The intramolecular regioselective Michael-type addition in 48 proceeds to give the six-membered ring heterocycles 49. This cyclization is also convenient for the synthesis of the tellurochromones (51).

In recent years, the chemistry of the selenochromones and tellurochromones, six-membered heterocycles containing a selenium or tellurium element, and relative compounds, has attracted much attention.\(^{23}\) Among the unsubstituted 49h,\(^{24}\) 2-methyl 49a\(^{24}\) and 2-phenyl derivative 49f\(^{24}\) have been synthesized; the other chromones 49b-e are new compounds.

![Scheme 11](image)

A few applications of this successive intramolecular cyclization of the phenylselenols and telluronium analogues having an ynone moiety at the ortho position are examined. The propiolanilides (53), having a
nitrogen between the phenyl and carbonyl groups, were readily prepared from o-iodobenzoic acid (52) in 3 steps and gave the tellurazepines (54) through the 7-endo-dig mode intramolecular ring-closure in low yields. However, the selenazepines (55) could unfortunately not be obtained in a similar way.

Scheme 12

5.2. Conversion into 1-benzoselenopyrylium salts

The general preparation of the 2-substituted 1-benzoselenopyrylium salts from the selenochromones in two steps and their reactions with several nucleophiles are outlined in this section. Only four examples of the 1-benzoselenopyrylium salts involving the unsubstituted and phenyl derivatives as the perchlorates have been prepared; the 1-benzoselenopyrylium salts having an alkyl substituent have never been prepared until now. In addition, their stability and reactivity toward nucleophiles have received little attention. The synthesis of the 1-benzoselenopyrylium salts (57) from the corresponding selenochromones (50) is shown in Scheme 13.

Scheme 13

In order to obtain the 4H-selenochromenes (56), the precursors for the preparation of the salts (57), DIBAL-H reduction was used for the conversion of the carbonyl group to the methylene group of 50. Treatment of the 2-tert-butyl- and 2-phenyl-chromenes (56) with Ph3C+BF4- in MeNO2, followed by the addition of dry Et2O gave the desired 1-benzoselenopyrylium salts (57) in almost quantitative isolated yields as stable yellow prisms. However, a similar treatment of the chromenes (56) having a primary alkyl group such as methyl and n-butyl at the C-2 position did not produce the corresponding stable salts due to their instability. This distinction between a primary alkyl group and other carbon functionalities at the C-2 position with respect to the stability of the selenopyrylium salts (59) is explained as shown in Scheme 14.
BF₄⁻, the counter anion of the salts, eliminated the β-hydrogen of the methylene carbon of the primary alkyl group forming the unstable exo-methylene compound 60. Figure 1 shows the molecular structure of the 2-tert-butyl-1-benzoselenopyrylium salt (57).²⁹

![Scheme 14](image)

**Figure 1.** ORTEP drawing of 57 with 50% probability level

### 5.3. Reactions of 1-benzoselenopyrylium salts

Next, the reactions of the 1-benzoselenopyrylium salts (57) with several nucleophiles³⁰ including alkoxide ions (OMe⁻, i-OPr⁻ and t-OBu⁻), amines (diethylamine and n-butylamine), cyanide ion, Grignard reagents (MeMgI, EtMgBr, PhCH₂MgBr and PhMgBr),³⁰ and an active methyl compound (acetone) were examined using the stable 2-tert-butyl and 2-phenyl substrates. Various 4H-isoselenochromenes (61,

![Scheme 15](image)

**Scheme 15**

\[ \text{Nu} = \text{OMe}, \text{i-OPr}, \text{t-OBu}, \text{NET}_{2}, \text{NHn-Bu}, \]

\[ \text{R'} = \text{Me, Et, CH}_2\text{Ph, Ph} \]
62) having an oxygen, nitrogen and carbon functional group at the C-4 position were produced in good to excellent yields.

5.4. 1,3-Benzoselenazepines
In addition, the salts (57) were treated with NaN₃ in MeCN to give the 2-azido-2\textit{H}-selenochromenes (63), which were heated at 100 °C in dioxane to expand the selenopyran ring giving the novel 1,3-benzoselenazepines (65) with denitrogenation via the azirine intermediates 64 in good yields.

![Scheme 16](image.png)

6. ISOSELENOCHROMENES AND RELATIVES
This section describes the synthesis of the isoselenochromenes, a theoretical possible structural isomer of 56 in the above section, and the transformation into the 2-benzoselenopyrylium salts.

6.1. Synthesis of isoselenochromenes
It is clear that the \(\alpha\)-ethynylbenzyl selenols (69) are the precursors for the synthesis of the isoselenochromenes (70) and the related compounds. \(\alpha\)-Ethynylbenzyl alcohols (67), which were prepared by the palladium catalyzed Sonogashira reaction of \(\alpha\)-iodobenzyl alcohols (66) with 1-substituted acetylenes, were readily converted to the \(\alpha\)-ethynylbenzyl bromides (68) by the treatment with PBr\(_3\). Treatment of 68 with NaNHSe in DMF at 0 °C, followed by the addition of EtOH and then heating at 90 °C, resulted in a direct ring closure to give the 1\textit{H}-isoselenochromenes (70, 6-\textit{endo-dig} mode products) together with (Z)-1-methylidene-2-selenaindenes (71, 5-\textit{exo-dig} mode products) via the selenol intermediates 69 as shown in Scheme 17. The formation of 69 was characterized by the isolation of the diselenides 72, which were obtained by the potassium ferricyanide oxidation of 69 before heating in EtOH. The diselenides 72 reverted back to the selenols 69 by treatment with sodium borohydride with reductive fission of the Se-Se bond. The isotellurochromenes (73) and telluraindenes (74) were also obtained in nearly similar manners and yields.
6.2. Reactions with electrophiles

The isoselenochromenes (70) except for the 3-unsubstituted derivative 70f are hitherto unknown compounds. Only a few reports are known on the preparation and alkylation or arylation of the selenium-containing heterocycles, such as isoselenochroman. The alkylation of 70 gave the selenonium salts (75), i.e., tetrafluoroborates, triflates, tosylates and mesylates, in good yields as well as the isotellurochromenes (73). The phenylation reaction of 70 was conducted using the diphenyliodonium triflate and copper (II) diacetate. 3-tert-Butylisoselenochromenium triflate (75Fb) was produced in 68% yield. However, the reaction of 3-unsubstitued isochromene (70a) under the same conditions gave a complex mixture; no 2-phenylisoselenochromenium triflate (75Fa) was obtained. The obtained results are listed in Table 1.

---

**Scheme 17**

**Scheme 18**
Table 1. Selenonium Salts (75)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Electrophile</th>
<th>R’</th>
<th>X</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>a: R = H</td>
</tr>
<tr>
<td>75A</td>
<td>MeI, AgBF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Me</td>
<td>BF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>61</td>
</tr>
<tr>
<td>75B</td>
<td>TfOMe</td>
<td>Me</td>
<td>OTf</td>
<td>94</td>
</tr>
<tr>
<td>75C</td>
<td>TfOCH&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>OTf</td>
<td>95</td>
</tr>
<tr>
<td>75D</td>
<td>TsOMe</td>
<td>Me</td>
<td>OTs</td>
<td>98</td>
</tr>
<tr>
<td>75E</td>
<td>MsOMe</td>
<td>Me</td>
<td>OMs</td>
<td>87</td>
</tr>
<tr>
<td>75F</td>
<td>TfOIPh&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Ph</td>
<td>OTf</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield.

6.3. Conversion into 2-benzoselenopyrylium salts

The conversion from the 1<sup>H</sup>-isoselenochromenes (70) into the 2-benzoselenopyrylium salts (76) and their reactivity toward several nucleophiles are disclosed in this section. With regard to the 2-benzoselenopyrylium salts, the synthesis of only the unsubstituted derivative has been reported by Renson and Pirson<sup>33</sup> in 1966; no 2-benzotelluropyrylium salts have been prepared until our synthesis.<sup>32a</sup>

The isoselenochromenes (70) were treated with Ph<sub>3</sub>C<sup>+</sup> BF<sub>4</sub><sup>-</sup> in MeNO<sub>2</sub> and worked up as described for the preparation of the 1-benzoselenopyrylium salts (57) to give the 2-benzoselenopyrylium salts (76) as stable yellow or green prisms in excellent yields.

![Scheme 19](image1.png)

**Scheme 19**

The 3-<sup>tert</sup>-butyl (76c) and 3-unsubstituted selenopyrylium salts (76f) were air-stably obtained; however, the 2-benzoselenopyrylium salts having another alkyl substituted group (methyl and n-butyl) on the C-3
position could not be isolated. The reason why these selenopyrylium salts are not stable compared to the 3-tert-butyl and 3-unsubstituted derivatives might be the reaction shown in Scheme 20; this behavior is quite similar to that of the 1-benzoselenopyrylium salts (Scheme 14). Figure 2 shows the molecular structure of the 3-tert-butyl-2-benzoselenopyrylium salt (76c).

![Figure 2. ORTEP drawing of 76c](image)

### 6.4. Reactions of 2-benzoselenopyrylium salts

Next, the reactions of the salts 76 with a variety of nucleophiles have been investigated. LiAlH₄, sodium alkoxide (NaOMe, NaOi-Pr and NaOr-Bu),₃₆ Et₂NH, n-BuNH₂,₃₈ Grignard reagents (MeMgI, EtMgBr, n-BuMgCl, PhCH₂MgBr and PhMgBr),₃₉ organocopper reagents₃⁹ and allyltin reagents₄₀ reacted with 76 to give the 1H-isoselenochromenes (70) and the corresponding isoselenochromenes (79, 80) having a oxygen, nitrogen or carbon functional group at the C-1 position under mild conditions in nearly good to high yields.

While the solvent-free reactions of the salts 76 with MeNHNH₂ or PhNHNH₂ gave the

\[ 76 \xrightarrow{\text{NuH}} 79 (11-99\%) \]

\[ 76 \xrightarrow{\text{LiR'Cu}} 80 (49-94\%) \]

Nu = OMe, Oi-Pr, Ot-Bu, NEt₂, NHn-Bu, CH₂COMe
R' = Me, Et, n-Bu, CH₂Ph, Ph, allyl

Scheme 21
1-hydrazino-1H-isoselenochromenes (81), similar to the other nucleophiles, the treatment of 76 with anhydrous NH$_2$NH$_2$ in dry MeCN resulted in a ring transformation to produce the 5H-2,3-benzodiazepines (84)\textsuperscript{41} in a one-pot reaction under mild conditions in moderate yields via the probable intermediates 82 and 83.

\begin{align*}
\begin{array}{cccc}
\text{Scheme 22}
\end{array}
\end{align*}

7. TANDEM CYCLIZATIONS OF DIBENZY DISELENOLS

As an extension of our ongoing work in which we succeeded in preparing various types of selenium-
containing heterocycles using the intramolecular cyclization reaction of the selenols into a triple bond, we next decided to develop a procedure for the double or tandem cyclization of dibenzyl diselenols into an ethynyl moiety.\textsuperscript{42}

The preparation of the starting key \textit{o}-ethynyl dibenzyl bromides (86, 88, 91, 93) is shown in Scheme 23. The Sonogashira palladium-catalyzed coupling reaction of \textit{o}-iodobenzyl alcohol (66) with 1,4-diethynylbenzene, hexa-1,5-diene and \textit{o}-ethynylbenzyl alcohol (89), which was obtained by the desilylation of 66e, gave the desired dibenzyl alcohols (85, 87, 92) in 72, 83 and 84\% yields, respectively. Compound 66e, when subjected to a reaction with Cu(OAc)\textsubscript{2} in pyridine-MeOH as a solvent at 100 °C, directly led to the diyne 90 along with removal of the TMS group in 78\% yield. All benzyl alcohols 85, 87, 90, 92 were readily brominated with PBr\textsubscript{3}/pyridine to afford the key dibromides 86, 88, 91, 93 in good yields.

First, in order to examine the reaction of the dibenzyl diselenol (94) having a benzene ring between two ethynyl moieties, its preparation was performed as shown in Scheme 24. The treatment of 86 with NaHSe in dry DMF, followed by the addition of EtOH resulted in the direct ring closure to give the benzo[c]selenophene derivative 97 in 88\% yield without any characterized products. Compound 97 can be produced by the double 5-exo-dig mode cyclization of the specific dibenzyl diselenol intermediate 94 at the sp carbon atom of the triple bond with excellent regio- and stereoselectivity.

On the contrary, the reaction of the dibromide 95, in which two ethynyl groups are linked by the ethylene moiety, with NaHSe afforded the bis(isoselenochromenyl)ethane (98) which was the 6-endo-dig,
6-endo-dig mode cyclization product, in 61% yield as the sole product. Moreover, the dibenzyl dibromide 96 having a conjugated diyne reacted with NaHSe under the same condition described above to produce the double 5-exo-dig mode cyclization product, bi(methylidenebenzo[c]selenophene) (99) in 89% yield.

![Scheme 25]

The cyclization reaction of the dibenzyl diselenol (100) having one triple bond was finally examined. The dibromide 93 was similarly treated with NaHSe to give the trans-bi(benzo[c]selenophene) (101) in 91% yield without 6-endo-dig mode ring closure product (104). Compound 101 will be produced by the tandem 5-exo-dig mode cyclization of the benzyl selenol intermediate (100) into the triple bond with

![Figure 3. ORTEP drawing of 101 with 50% probability level.]
excellent regio- and stereoselectivity, followed by dehydrogenation from the essential cyclization product 102. The formation of trans-101 by the dehydrogenation of 102 is more favored than that of cis-103 due to the steric hindrance between the two inner peri hydrogens of the benzene rings. The structure of trans-101 including the regiochemistry of the olefin moiety was finally determined by X-ray single crystallography as shown in Figure 3.

The ORTEP drawing of 101 and crystallographic data were not given in the original paper, so they are newly provided here.

In all cases of the reaction of the dibromides 86, 88 and 91 with NaHSe, the mixed ring closure reactions of the 5-exo and 6-endo modes did not proceed; no spiro compound 105 was obtained from 93.

8. TWO CARBONS RING GROWING OF SELENOLACTONES

Here, we describe the novel method involving the one-pot synthesis of selenium-containing medium-sized α,β-unsaturated cyclic ketones by the intramolecular ring closure of selenols, which were generated in situ from selenolactones and ethynyllithiums in this section as shown in Scheme 26.

The selenolactones (106) were easily prepared from the commercially available lactones via the bromocarboxylic chlorides, which were treated with NaHSe. Compounds 106 were lithiated with ethynyllithium, followed by the addition of aqueous 5% H2SO4 as a proton source to produce the two...
carbon ring enlargement products 109. In general, eight-membered ring cyclic ketones 109B were obtained from six-membered selenolactones (106B) in good to high yields. The ring-expansion reaction of the five- and six-membered selenolactone having a methyl group at the α– or δ– position was also carried out (12 examples); the seven- and eight-membered α,β-unsaturated cyclic ketones were similarly produced in yields ranging from 31% to 82%. The formation of the ring expanded products 109 from the selenolactones (106) is the following; the hydroxyselenacycloalkane (107) probably generated by nucleophilic attack of the ethynyllithium at the carbonyl carbon of 106, and then hydrolyzed, undergoes ring opening with migration of the hydroxy proton to form the ethynylselenol (108). The regioselective intramolecular cyclization of the resulting selenol 108 to a triple bond of the ynone moiety proceeds via the Michael-type addition in the endo-dig mode to give the successful α,β-unsaturated selenacycloalkanone (109). The telluro analogue, tellurocin-4-one (111) was also obtained from the tellurolactone (110) in 42% yield.

9. 3-SELENA-1,2,3,4-TETRAHYDROQUINOLINES

1,3-Selenazines, which are a six-membered heterocyclic compound containing two heteroatoms, nitrogen and selenium, display significant bio-activities; e.g., anti-bacterial activity against both Gram-negative and Gram-positive bacteria and potential anti-tumor effects against human cancer cells.

In this chapter, we now describe the practical solvent-free non-catalyzed one-pot preparation of the 3-selenaquinoline derivatives, benzo-analogues of 1,3-selenazines by the intramolecular cyclization of the selenols, which are generated from the o-ethynylanilines and the isoselenocyanates as the selenium source. Isoselenocyanates are a powerful tool for the preparation of selenium-containing heterocycles because of their ease of preparation, storage, lower-toxicity and safety of handling, and recently introduced their utility in the review article.

The o-ethynylanilines (112) were heated at 130 °C with the cyclohexyl isoselenocyanate (113A), a secondary aliphatic isoselenocyanate, under solvent-free conditions (method II) to afford 2-imino-3-selenquinolines (116) in yields ranging from 47% to 88%; 116 were also obtained by the normal reaction conditions, in refluxing xylene (method I) in nearly similar yields (Table 2). The plausible mechanism for the formation of the selenquinolines (116) from the anilines (112) and the isoselenocyanate 113A is shown in Scheme 27. The initial adduct, 3-phenylselenourea (114), probably generated by nitrogen nucleophilic attack of the aniline 112 at the sp carbon of the isoselenocyanate 113A, undergoes tautomerism with migration of the phenyl NH proton to form the iminoselenol 115. The regio- and stereoselective intramolecular cyclization of the resulting selenol 115 into a triple bond proceeds via the 6-exo-dig mode to give the successful 3-selenaquinoline (116). No 7-endo-dig mode cyclization
Scheme 27

Table 2. 4-Methylidene-3-selena-1,4-dihydroquinolines (116)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>Method\textsuperscript{a}</th>
<th>Time</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>n-Bu</td>
<td>c-Hex</td>
<td>I</td>
<td>6.5 h</td>
<td>116Aa</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>n-Bu</td>
<td>c-Hex</td>
<td>II</td>
<td>4 h</td>
<td>116Aa</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>n-Bu</td>
<td>c-Hex</td>
<td>III</td>
<td>25 min</td>
<td>116Aa</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>n-Bu</td>
<td>n-Bu</td>
<td>I</td>
<td>22 min</td>
<td>116Ba</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>n-Bu</td>
<td>n-Bu</td>
<td>II</td>
<td>7 h</td>
<td>116Bb</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>n-Bu</td>
<td>c-Hex</td>
<td>I</td>
<td>7 h</td>
<td>116Ca</td>
<td>0\textsuperscript{c}</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>n-Bu</td>
<td>c-Hex</td>
<td>II</td>
<td>7 h</td>
<td>116Cb</td>
<td>0\textsuperscript{c}</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>n-Bu</td>
<td>Ph</td>
<td>II</td>
<td>3.5 h</td>
<td>116Db</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>n-Bu</td>
<td>Ph</td>
<td>II</td>
<td>3.5 h</td>
<td>116Db</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>Me</td>
<td>c-Hex</td>
<td>II</td>
<td>8 h</td>
<td>116Ab</td>
<td>63</td>
</tr>
<tr>
<td>11</td>
<td>H</td>
<td>Me</td>
<td>c-Hex</td>
<td>III</td>
<td>26 min</td>
<td>116Ab</td>
<td>54</td>
</tr>
<tr>
<td>12</td>
<td>H</td>
<td>t-Bu</td>
<td>c-Hex</td>
<td>II</td>
<td>11 h</td>
<td>116Ac</td>
<td>53</td>
</tr>
<tr>
<td>13</td>
<td>H</td>
<td>t-Bu</td>
<td>c-Hex</td>
<td>III</td>
<td>34 min</td>
<td>116Ac</td>
<td>59</td>
</tr>
<tr>
<td>14</td>
<td>H</td>
<td>Ph</td>
<td>c-Hex</td>
<td>II</td>
<td>13 h</td>
<td>116Ad</td>
<td>68</td>
</tr>
<tr>
<td>15</td>
<td>H</td>
<td>Ph</td>
<td>c-Hex</td>
<td>III</td>
<td>48 min</td>
<td>116Ad</td>
<td>72</td>
</tr>
<tr>
<td>16</td>
<td>H</td>
<td>TMS</td>
<td>c-Hex</td>
<td>II</td>
<td>20 h</td>
<td>116Ae</td>
<td>47</td>
</tr>
<tr>
<td>17</td>
<td>H</td>
<td>TMS</td>
<td>c-Hex</td>
<td>III</td>
<td>26 min</td>
<td>116Ae</td>
<td>53</td>
</tr>
<tr>
<td>18</td>
<td>H</td>
<td>H</td>
<td>c-Hex</td>
<td>II</td>
<td>16 h</td>
<td>116Af</td>
<td>51</td>
</tr>
<tr>
<td>19</td>
<td>H</td>
<td>H</td>
<td>c-Hex</td>
<td>III</td>
<td>28 min</td>
<td>116Af</td>
<td>46</td>
</tr>
<tr>
<td>20</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>II</td>
<td>2.5 h</td>
<td>116Dd</td>
<td>87</td>
</tr>
<tr>
<td>21</td>
<td>Me</td>
<td>n-Bu</td>
<td>c-Hex</td>
<td>II</td>
<td>20 h</td>
<td>117Aa</td>
<td>0\textsuperscript{d}</td>
</tr>
<tr>
<td>22</td>
<td>Bn</td>
<td>n-Bu</td>
<td>c-Hex</td>
<td>II</td>
<td>20 h</td>
<td>118Aa</td>
<td>0\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Method I: xylene, reflux; method II: neat, 130 °C; method III: microwave irradiation at 115 °C.

\textsuperscript{b}Isolated yield.

\textsuperscript{c}Decomposed.

\textsuperscript{d}No reaction.
products were obtained in this case. When the \( o \)-ethynylanilines (112) were similarly heated with the
\( n \)-butyl (113B) and phenyl isoselenocyanate (113C) without a solvent, the corresponding
3-selenaquinolines (106) were obtained in moderate yields (9 examples). However, tert-butyl
isoselenocyanate (113D) reacted with the anilines (112) to give a complex mixture without any
characterized products (entries 6 and 7). Furthermore, no 1-substituted selenaquinolines (117, 118) were
also produced by the reaction of \( N \)-methylaniline and \( N \)-benzylaniline with isoselenocyanate 113 (entries
20 and 21).

In this reaction, the microwave-assisted (method III) synthesis of 116 was efficient and more effective,
and the results indicate the following benefits; (1) a reduced reaction time from 1 h to almost within 30
minutes; (2) a solvent-free system; and (3) the products could be directly obtained by a short
chromatography purification.

![Figure 4. ORTEP drawing of 116Dd](image)

The structure of 116 including the regiochemistries of the olefin moiety and the C=N bond was finally
determined by X-ray single crystallography\(^{29}\) using 116Dd as shown in Figure 4.

**10. 1,3-BENZOSELENAZOLES**

Next, an efficient and simple preparation of the 2-amino-1,3-benzoselenazoles\(^ {47} \) by the copper catalyzed
one-pot reaction of 2-iodoanilines and isoselenocyanates is described in this chapter. There are only a few
reports on the preparation of the 2-substituted benzoselenazoles\(^ {48} \) and related compounds,\(^ {49} \) and their
chemistry still remains unknown. After a careful survey to optimize the reaction conditions, the
combination of copper(II) triflate [\( \text{Cu(OTf)}_2 \)] and \( \text{Cs}_2\text{CO}_3 \) in refluxing xylene was found to be the best
conditions for this tandem addition-cyclization reaction for the synthesis of 2-aminobenzoselenazoles.
Table 3. 2-Aminobenzoselenazoles (120)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Anilines</th>
<th>Isoselenocyanate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>119a</td>
<td>113A</td>
<td>120Aa</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>119b</td>
<td>113A</td>
<td>120Ab</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>119c</td>
<td>113A</td>
<td>120Ac</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>119d</td>
<td>113A</td>
<td>120Ad</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>119e</td>
<td>113A</td>
<td>120Ac</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>119f</td>
<td>113A</td>
<td>120Af</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>119g</td>
<td>113A</td>
<td>120Ag</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>119h</td>
<td>113A</td>
<td>120Ah</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>119i</td>
<td>113A</td>
<td>120Ai</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>119j</td>
<td>113A</td>
<td>120Aj</td>
<td>62</td>
</tr>
<tr>
<td>11</td>
<td>119a</td>
<td>n-Bu-N=C=Se</td>
<td>120B</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>119a</td>
<td>Ph-N=C=Se</td>
<td>120C</td>
<td>77</td>
</tr>
<tr>
<td>13</td>
<td>119a</td>
<td>t-Bu-N=C=Se</td>
<td>120D</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield.
The extension of this reaction to 2-iodoanilines having various functional groups involving an electron-withdrawing and -donating group at the C-4 or C-5 position with some isoselenocyanates was carried out, and the results are summarized in Table 3. The primary aliphatic isoselenocyanate, \( n\)-butyl isoselenocyanate (113B), and aromatic isoselenocyanate (113C) also reacted with 2-iodoaniline (119a) to afford the corresponding 2-aminobenzoselenazoles (120Ba and 120Ca) in 57 and 77\% yields, respectively. However, replacing the isoselenocyanate by tert-butyl isoselenocyanate (113D) gave a complex mixture involving a slight yield of 2-tert-butylamino-selenazole (120Da); the starting 2-iodoaniline (119) was recovered because of the gradual decomposition of the isoselenocyanate under the same conditions. The lower reactivity of tert-butyl isoselenocyanate (113D) may be due to the steric hindrance by the bulky tertiary butyl group. A possible mechanism for the 2-aminoselenazoles (120) from 119 and 113 is shown in Scheme 28.

![Scheme 28](image)

The structures of these 2-aminobenzoselenazoles (120) were determined by their spectra and elemental analyses and finally established by single-crystal X-ray studies using cyclohexyl derivative (120Aa).\(^ {28}\)
11. BENZOF[c]SELENOPHENES

The synthesis of the benzo[c]selenophene derivatives by the tandem addition-cyclization of the \( o \)-ethynylphenyllithiums and the isoselenocyanates was achieved.\(^{50}\) The reaction of isoselenocyanates with the active methylene compounds such as a malononitrile and cyanoacetate is well known.\(^{51}\) However, there are only a few reports on the reaction with a carbanion.\(^{52}\) The \( o \)-bromopropynylbenzene (25a) was lithiated with \textit{tert}-BuLi in anhydrous Et\(_2\)O, followed by treatment with cyclohexyl isoselenocyanate (113A) at room temperature, and then ethanolyzed to give the desired (\(Z\))-3-methylidenebenzo[c]selenophene (123Aa) in 78% yield in a one-pot reaction (Table 1, entry 1).

When 25b was similarly treated with 113A in anhydrous Et\(_2\)O, 123Ab was produced in 61% yield (entry 2). On the contrary, use of anhydrous THF as a solvent gave the benzo[c]selenophene (123Ab) in only 13% yield; no starting material was recovered (entry 3). Similarly, this tandem addition-cyclization of \( o \)-ethynylphenyl lithiums (25c-e) having \textit{tert}-butyl, phenyl and TMS groups at the triple bond with cyclohexyl isoselenocyanate (2A) proceeded to afford the corresponding (\(Z\))-3-methylidenebenzo[c]-selenophenes (123Ac-e) in good to high yields (entries 4-6). The reaction of \( o \)-bromohexynylbenzene (25b) with \( n \)-butyl isoselenocyanate (113B), the primary aliphatic isoselenocyanate, also occurs under the same conditions to afford the selenophene 123Ba in 54% yield (entry 7). However, the use of \textit{tert}-butyl

![Table 4. 3-Methylidenebenzo[c]selenophenes (123)](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Isoselenocyanate</th>
<th>Solvent (temp.)</th>
<th>Product</th>
<th>Yield (%)(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25a (( R^1 = \text{Me} ))</td>
<td>113A (( R^2 = c)-Hex)</td>
<td>Et(_2)O (r.t.)</td>
<td>123Aa</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>25b (( R^1 = n)-Bu)</td>
<td>113A</td>
<td>Et(_2)O (r.t.)</td>
<td>123Ab</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>25b</td>
<td>113A</td>
<td>THF (r.t.)</td>
<td>123Ab</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>25c (( R^1 = \text{tert}-Bu ))</td>
<td>113A</td>
<td>Et(_2)O (r.t.)</td>
<td>123Ac</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>25d (( R^1 = \text{Ph} ))</td>
<td>113A</td>
<td>Et(_2)O (r.t.)</td>
<td>123Ad</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>25e (( R^1 = \text{TMS} ))</td>
<td>113A</td>
<td>Et(_2)O (r.t.)</td>
<td>123Ae</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>25b</td>
<td>113B (( R^2 = n)-Bu)</td>
<td>Et(_2)O (r.t.)</td>
<td>123Bb</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>25b</td>
<td>113C (( R^2 = \text{tert}-Bu ))</td>
<td>Et(_2)O (r.t.)</td>
<td>123Cb</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td>25b</td>
<td>113D (( R^2 = \text{Ph} ))</td>
<td>Et(_2)O (r.t.)</td>
<td>123Db</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>25b</td>
<td>113D</td>
<td>Et(_2)O (reflux)</td>
<td>123Db</td>
<td>64</td>
</tr>
</tbody>
</table>

\(^{a}\)Isolated yield.
isoselenocyanate 113C gave a complex mixture; no corresponding selenophene 123Ca was obtained (entry 8). The lower reactivity of tert-butyl isoselenocyanate (113C) may be due to the steric hindrance by the bulky tertiary butyl group. Although 25a also reacted with phenyl isoselenocyanate (113D) to produce the phenylimino derivative 123Da in Et₂O at room temperature in only 2% yield, 123Da was obtained in refluxing Et₂O in 64% yield (entry 9 vs. 10).

Next, the iodocyclization of o-ethynylphenyllithiums with isoselenocyanates (113) was found to proceed affording the (E)-1’-iodo-3-methylidenebenzo[c]selenophenes (128) stereoselectively as shown in Scheme 29. o-Ethynylphenyllithium generated from 25b was similarly treated with cyclohexyl isoselenocyanate (113A) and then protonated with t-BuOH, followed by iodination with I₂, gave the desired (E)-1’-iodobenzo[c]selenophene (128) in a one-pot reaction in 40% yield. This iodobenzo[c]selenophene (128) can be reduced to 123 by treatment with HCOOH/Et₃N in the presence of a palladium catalyst and further functionalized by palladium-catalyzed Suzuki and Sonogashira coupling reactions.

12. BENZO[c]SELENOPHENIUM SALTS
As an extension of our more ongoing work, the high regioselective 5-exo-dig mode electrophilic ring-closure reaction of the benzyl selenides, in which the hydrogen of the selenol is replaced by a phenyl group, is described in the final section of this review as shown in Scheme 30.
The starting materials, \( o\)-ethynylbenzyl phenyl selenides (129A) were readily synthesized in good yields by the coupling reaction of the benzyl bromides (68)\(^{32c}\) with lithium phenylselenolate, which was freshly generated from elemental selenium and phenyllithium in dry THF. The reaction of the \( o\)-ethynylbenzyl
phenyl selenides (129A) having an alkyl group at the ethynyl moiety with a small excess of TfOH in CH$_2$Cl$_2$ at 0 °C provided the 5-exo-dig mode cyclization products, (Z)-1-methylidene-2-phenyl-1H-benzo[c]selenophenium triflates (Z-130) as major products, together with the E-derivatives E-130 (Table 5, entries 1-3). However, a similar treatment of methyl selenide (129B) and benzyl selenide (129C) with TfOH resulted in decomposition to give a complex mixture without any identifiable products (entries 4, 5).

The structures of these 2-phenyl-1,3-dihydro1H-benzo[c]selenophenium salts (130) were determined by their spectra and elemental analyses and were finally established by single-crystal X-ray studies using the t-butyl derivative (130Ca).$^{29}$

**Figure 6.** ORTEP drawing of 130Ca

13. CONCLUSION

Recent advances in our laboratory concerning the preparations of the selenium-containing heterocycles, e.g., 1-benzoselenepines, benzo[b]selenophenes, selenophthalides, selenochromones, isoselenochromenes, γ-selena-α,β-unsaturated cyclic ketones, 3-selenaquinolines, benzoselenazoles and other related compounds were reviewed. The simple and versatile synthetic methods for the selenahe terocycles are mainly based on our original intramolecular cyclization of selenols to a triple bond and using isoselenocyanates as a selenium source. I hope that this review will be useful and helpful to synthetic, heterocyclic and also medicinal chemists.
14. ACKNOWLEDGEMENTS

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REFERENCES AND NOTES


29. See the details of the X-ray data in the original papers and reviews, Ref. 27.


35. H. Sashida and S. Nakabayashi, unpublished data.


46. (a) D. R. Garud, M. Koketsu, and H. Ishihara, Molecules, 2007, 12, 504; (b) H. Heimgartner, Y.


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**Haruki Sashida** was born in Tokyo in 1950 and received his Master’s degree from Tokyo University of Sciences (Professor Bunsuke Umezawa, Tokyo, Japan) in 1976. Then he started his academic career as a research assistant at the Faculty of Pharmaceutical Sciences, Hokuriku University (Kanazawa, Japan), is now professor. In 1984 he received his Ph. D. degree from Tokyo University of Sciences in synthetic studies of nitrogen-containing heterocyclic compounds. His chemical research interests are focused on the heterocyclic and heteroatom chemistry, amino acid chemistry, and medicinal chemistry. Recently, he is engaged in research on the design and synthesis of novel heterocycles containing a chalcogen element.