SYNTHESIS OF 5-SELENOXO-1,2,4-TRIAZOLE-1-CARBOXYLATES FROM ISOSELENOCYANATES AND AZODICARBOXYLATES

Francesco Favero,1 Geoffroy L. Sommen,2 Anthony Linden, and Heinz Heimgartner*

Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland; E-mail: heimgart@oci.unizh.ch

Dedicated to Professor Barry M. Trost at the occasion of his 65th birthday

Abstract – A mixture of an azodicarboxylate and triphenylphosphine in dichloromethane reacted with aryl isoselenocyanates (1) at room temperature to give 4,5-dihydro-5-selenoxo-1H-1,2,4-triazole-1-carboxylates (4a-f) in a one-pot reaction in good to excellent yields. The isoselenocyanates (1) have been prepared conveniently from formamides by treatment with elemental selenium and phosgene according to Barton’s procedure.

INTRODUCTION

Organoselenium compounds have continued to attract the attention of organic and medicinal chemists owing to their unique biological and pharmaceutical activities.3 It has been shown that the deficiency of selenium in human and animal organisms constitutes the basis of various chronic diseases.4,5 Despite the high toxicity of many selenium compounds, organic derivatives of selenium have been synthesized as antitumor,6,7 anticancer,8-10 anticarcinogenic,11 and other medicinal preparations,12 as well as biologically active substances exhibiting antiviral,13 antimicrobial,14 antihypertensive,15 and fungicidal activities.16

The main drawbacks of some syntheses are the toxicity of commonly used selenium reagents
and the instability of some intermediates. With the aim of developing syntheses of new selenaheterocycles and heterocyclic selones by using less-toxic, conveniently accessible and safely usable selenium reagents, we have investigated reactions with various isoselenocyanates. \(^{17-29}\) They are materials of choice \(^{30}\) for the synthesis of numerous Se-containing heterocycles, \(^{31}\) since they are easy to prepare and can be stored. We have already shown that aryl isoselenocyanates (1) are very useful precursors for the introduction of selenium into four, five, six and seven membered heterocycles like selenazetidines, \(^{25}\) selenazolones, \(^{29}\) selenazolidines, \(^{26}\) selenazines, \(^{26}\) perhydroselenazin-4- and -5-ones, \(^{29}\) and selenazepanes. \(^{28}\) The general concept of these reactions is shown in Scheme 1: nucleophilic addition of a suitably substituted compound (2) to the isoselenocyanate (1) to give a zwitterion (3), which undergoes ring closure to yield selenaheterocycles (4) (see refs. \(^{20-23,26}\)). An alternative cyclization via the nitrogen atom leads to N-heterocyclic selones (5) (see refs. \(^{24,27}\)).

**Scheme 1**

As a continuation of our studies, we investigated the reaction of isoselenocyanates with diethyl azodicarboxylate (6) and triphenylphosphine under Mitsunobu conditions. This reaction was expected to give either 1,3,4-selenatriazole or 1,2,4-triazoleselone derivatives. \(^{32}\) To the best of our knowledge, only a few 1,2,4-triazoleselones \(^{34}\) and their isomeric 1,2,4-triazoleselenols \(^{35}\) have been described. The main synthesis starts from a triazole, which is a good precursor for the preparation of the carbene 1,2,4-triazol-3-ylidene. \(^{36}\) The latter reacts with elemental selenium by forming the carbon-selenium double bond. \(^{37}\)

Isoselenocyanates have already been used for the synthesis of mesoionic 1,2,4-triazolo-3-selones. \(^{38}\) This preparation, published in 1976 by Egorochkin \(^{39}\) and in 2000 by Miller, \(^{40}\) was
carried out by reacting 1,1-diacylhydrazines with an isoselenocyanate in the presence of triethylamine in boiling THF.

RESULTS AND DISCUSSION

Equimolar amounts of diethyl azodicarboxylate (6, DEAD) and triphenylphosphine (Ph₃P) were dissolved in dichloromethane, and the pale yellow solution was stirred for 30 min at 0°C. Then, an equimolar amount of an aryl isoselenocyanate (1), which had been prepared conveniently by a slightly modified Barton procedure²¹ from the corresponding N-arylamide by treatment with phosgene and elemental selenium, was added and the mixture stirred at room temperature overnight. After evaporation of the solvent, the crude products were obtained as mixtures with triphenylphosphine oxide (Ph₃PO; TLC detection), and separation by column chromatography (SiO₂, hexane/ethyl acetate) was necessary to get the ethyl 5-selenoxo-1H-1,2,4-triazole-1-carboxylates (7a-e) (Scheme 2, Table 1). It has to be noted that this purification process is not easy. A side-product always polluted the final product, and only trituration with diethyl ether or dichloromethane and recrystallization from ethyl acetate led to pure 7.⁴²

Scheme 2

The structure of the products (7) was determined on the basis of their elemental analyses and spectroscopic data. The IR spectra (KBr) show two strong bands at 1765-1773 and 1619-1625 cm⁻¹ for the carboxylate and the C=N group, respectively. In the ¹³C-NMR spectra (CDCl₃), indicative absorptions for CO₂Et, C(5)=Se, and C(3) appear at ca. 167, 156, and 148 ppm, respectively. The ESI-MS spectra show the characteristic sets of the selenium isotope peaks for [M+Na]⁺. Finally, the structure of 7e was established by an X-Ray crystal-structure determination (Figure 1).

The five-membered ring of 7e is planar and the attached atoms Se(1), C(6), O(3), and C(5)
deviate only slightly from the ring plane (maximum derivation is 0.148(2) Å for C(6)). Whereas the ethoxy group at C(3) is co-planar with the heterocycle and the ester group, with the exception of the terminal CH$_3$ group, is only slightly twisted out of the heterocyclic ring plane (angle between the planes is 8.1(1)°), the benzene ring at N(2) is oriented almost orthogonal to the plane of the heterocyclic ring (angle between the planes is 74.2(1)°).

Table 1. *Preparation of Triazole Derivatives (7)* from Isoselenocyanates (1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>4</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td><img src="image1.png" alt="Image" /></td>
<td>81</td>
</tr>
<tr>
<td>b</td>
<td>4-Br-C$_6$H$_4$</td>
<td><img src="image2.png" alt="Image" /></td>
<td>82</td>
</tr>
<tr>
<td>c</td>
<td>4-Cl-C$_6$H$_4$</td>
<td><img src="image3.png" alt="Image" /></td>
<td>97</td>
</tr>
<tr>
<td>d</td>
<td>4-F-C$_6$H$_4$</td>
<td><img src="image4.png" alt="Image" /></td>
<td>84</td>
</tr>
<tr>
<td>e</td>
<td>4-Me-C$_6$H$_4$</td>
<td><img src="image5.png" alt="Image" /></td>
<td>78</td>
</tr>
</tbody>
</table>
Figure 1. ORTEP plot\textsuperscript{45} of the molecular structure of 7e (arbitrary numbering of atoms; 50\% probability ellipsoids).

Scheme 3
A likely reaction mechanism for the formation of 7 is proposed in Scheme 3. The addition of \( \text{Ph}_3\text{P} \) onto the azodicarboxylate (6) generates the zwitterion (8), which, as a nucleophile, attacks the isoselenocyanate (1) to give 9. Ring closure by nucleophilic addition of the N-atom at the ester group leads to 10, and elimination of \( \text{Ph}_3\text{PO} \) via the intermediate (11) yields the product (7).

The use of the system diethyl azodicarboxylate (oxidant)/\( \text{Ph}_3\text{P} \) (reducing agent) is well established\(^{46} \) and is known as the Mitsunobu reaction\(^{47} \) when the reactant is an alcohol. The betaine (8) is the initially formed intermediate in all cases and it reacts with the alcohol. In the present case, this intermediate reacts as a nucleophile with the strongly electrophilic isoselenocyanate (1).

Similar to the reaction with 6a, treatment of 4-bromophenyl isoselenocyanate (1b) with bis(tert-butyl) azodicarboxylate (6b) and \( \text{Ph}_3\text{P} \) gave the triazoloselone (7f) in almost quantitative yield. This product was transformed into the 3-tert-butoxy-4,5-dihydro-1H-1,2,4-triazole-5-selone (12) by decarboxylation with trifluoroacetic acid at room temperature in quantitative yield (Scheme 4).

In conclusion, we have shown that aryl isoselenocyanates (1) under Mitsunobu conditions can be applied for the synthesis of 5-selenoxo-1,2,4-triazole derivatives in a one-pot procedure.

**EXPERIMENTAL**

**General remarks.** TLC: silica gel 60 F\(_{254}\) plates (0.25 mm, Merck). Column chromatography
(CC): silica gel 60 (0.040–0.063 mesh, Merck). Melting points: Büchi B-540 apparatus, in a capillary, uncorrected. IR spectra: Perkin-Elmer 1600-FT-IR spectrometer; in KBr, absorptions in cm\(^{-1}\). \(^1\)H-NMR (300 MHz) and \(^{13}\)C-NMR (75 MHz) spectra: Bruker ARX-300 instrument, in CDCl\(_3\); chemical shifts in ppm, coupling constants \(J\) in Hz. EI-MS: Finnigan SSQ-700 instrument.

Starting materials. Diethyl and bis(tert-butyl) azidodicarboxylate (6a and 6b) and triphenylphosphine (Ph\(_3\)P) are commercially available (Fluka). Isoselenocyanates were prepared according to Barton's procedure\(^{41}\) starting from the corresponding formamides. Formanilide was purchased (Fluka), \(N\)-(4-chlorophenyl)-, \(N\)-(4-bromophenyl)-, \(N\)-(4-fluorophenyl)-, and \(N\)-(4-methylphenyl)formamide were prepared from the respective anilines and 95% formic acid. The solution was heated to reflux for 30 min and evaporated to dryness in vacuo. The residue was dissolved in ether (Et\(_2\)O) and washed with diluted acetic acid (5%), water and aqueous NaHCO\(_3\) (5%). The aqueous layer was extracted with Et\(_2\)O, the combined organic extracts were dried with MgSO\(_4\) and evaporated under reduced pressure. The crude products were purified by recrystallization in ethanol/water.

Synthesis of 3-alkoxy-4,5-dihydro-5-selenoxo-1\(H\)-1,2,4-triazole-1-carboxylates (7a-d).

General procedure. A 25 mL round-bottom flask equipped with magnetic stirrer and condenser was charged with a mixture of diethyl or bis(tert-butyl) azidodicarboxylate (6a and 6b, respectively) (0.92 mL, 2.0 mmol) and Ph\(_3\)P (524 mg, 2.0 mmol) in dichloromethane (20 mL). The mixture was stirred under an N\(_2\)-atmosphere at 0°C (ice bath) for 30 min. An isoselenocyanate (1, 2.0 mmol) was added in one portion, the mixture was stirred for 15 h at rt, and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on SiO\(_2\) using hexane/ethyl acetate (AcOEt; 100/0 to 50/50) as eluant and recrystallization in AcOEt.

Ethyl 3-ethoxy-4,5-dihydro-4-phenyl-5-selenoxo-1\(H\)-1,2,4-triazole-1-carboxylate (7a). Yield: 552 mg (81%). Yellowish crystals; mp 142-144°C (AcOEt). IR: 3422\(^w\) (br), 2981\(^w\), 2931\(^w\), 1773\(^s\), 1619\(^s\), 1595\(^w\), 1501\(^w\), 1451\(^m\), 1386\(^m\), 1368\(^m\), 1328s, 1308s, 1220s, 1175\(^w\), 1155\(^w\), 1190\(^w\), 1088\(^w\), 1066\(^w\), 1028\(^m\), 1005\(^m\), 979\(^w\), 902\(^w\), 861\(^w\), 847\(^w\), 776\(^w\), 710\(^w\), 689\(^w\). \(^1\)H-NMR: 1.36 \((t, J = 7.1, \text{CH}_3); 1.49 \((t, J = 7.1, \text{CH}_3); 4.49-4.62 \((m, 2 \text{CH}_2); 7.35 \((d, J = 8.1, 2 \text{ arom. H}); 7.52-7.59 \((m, 3 \text{ arom. H}). \(^{13}\)C-NMR: 14.0 \((\text{CH}_3); 14.1 \((\text{CH}_3); 65.0 \((\text{CH}_2); 68.5 \((\text{CH}_2); 128.1 \((2 \text{ arom. CH});
Yield: 726 mg (97%). Yellowish crystals; mp 142-144°C (AcOEt). IR: 3442

Ethyl 4-(4-chlorophenyl)-3-ethoxy-4,5-dihydro-5-selenoxo-1H-1,2,4-triazole-1-carboxylate (7b).

Yield: 686 mg (82%). Yellowish crystals; mp 147-149°C (AcOEt). IR: 3444

Ethyl 3-ethoxy-4-(4-fluorophenyl)-4,5-dihydro-5-selenoxo-1H-1,2,4-triazole-1-carboxylate (7c).

Yield: 726 mg (97%). Yellowish crystals; mp 142-144°C (AcOEt). IR: 3442

Ethyl 3-ethoxy-4-(4-fluorophenyl)-4,5-dihydro-5-selenoxo-1H-1,2,4-triazole-1-carboxylate (7d).

Yield: 603 mg (84%). Yellowish crystals; mp 151-153°C (AcOEt). IR: 3442

C, 43.37; H, 4.00; N, 11.88.

Ethyl 3-ethoxy-4,5-dihydro-4-(4-methylphenyl)-5-selenoxo-1H-1,2,4-triazole-1-carboxylate (7e). Yield: 554 mg (78%). Yellowish crystals; mp 120-122°C (AcOEt). IR: 3442 w (br), 2979 w, 2956 w, 1768 s, 1619 s, 1514 m, 1477 w, 1454 m, 1389 m, 1368 m, 1327 s, 1307 s, 1294 s, 1220 s, 1173 w, 1152 w, 1109 w, 1099 w, 1064 w, 1029 m, 981 w, 905 w, 850 w, 817 w, 753 w, 712 w, 622 w. ¹H-NMR: 1.37 (t, J = 7.1, CH₃); 1.49 (t, J = 7.1, CH₃); 2.43 (s, CH₃); 4.48-4.60 (m, 2 CH₂); 7.22, 7.34 (AA’BB’, J ≈ 8, 4 arom. H). ¹³C-NMR: 14.0 (CH₃); 14.3 (CH₃); 21.3 (CH₃); 65.0 (CH₂); 68.4 (CH₂); 127.7 (2 arom. CH); 130.0 (2 arom. CH); 127.3, 140.2 (1 arom. C, C(3)); 149.0 (1 arom. C); 156.0 (C=Se); 167.1 (C=O). ESI-MS: 374 (12), 375 (14), 376 (48), 377 (4), 378 (100, [M+Na]⁺), 379 (11), 380 (13), 733 (3). Anal. Calcd for C₁₄H₁₇N₃O₃Se: C, 47.46; H, 4.84; N, 11.86. Found: C, 47.25; H, 4.85; N, 11.85.

tert-Butyl 3-tert-butoxy-4-(4-bromophenyl)-4,5-dihydro-5-selenoxo-1H-1,2,4-triazole-1-carboxylate (7f). Yield: 855 mg (90%). Yellowish crystals; mp 118-120°C (AcOEt). IR: 3443 w (br), 2985 w, 2931 w, 1764 s, 1701 w, 1612 s, 1588 m, 1508 w, 1490 w, 1453 w, 1408 w, 1374 m, 1337 m, 1320 s, 1297 m, 1278 s, 1223 m, 1143 s, 1065 w, 985 w, 848 m, 836 m, 804 w, 761 w, 655 w. ¹H-NMR: 1.53 (s, 3 CH₃); 1.67 (s, 3 CH₃); 7.21, 7.62 (AA’BB’, J ≈ 8, 4 arom. H). ¹³C-NMR: 27.6 (3 CH₃); 27.8 (3 CH₃); 86.6, 88.1 (2 C); 123.8 (1 arom. C); 129.8 (2 arom. CH); 132.5 (2 arom. CH); 132.1, 147.1 (1 arom. C, C(3)); 153.5 (C=Se); 165.1 (C=O). ESI-MS: 494 (17), 495 (15), 496 (55), 497 (25), 498 (100, [M+Na]⁺), 499 (18), 500 (75), 501 (12), 502 (10). Anal. Calcd for C₁₇H₂₂N₃O₃BrSe: C, 42.96; H, 4.67; N, 8.83. Found: C, 43.22; H, 4.95; N, 9.15.

Decarboxylation of 7f. 3-tert-Butoxy-4-(4-bromophenyl)-4,5-dihydro-1H-1,2,4-triazole-5-selone (12). Yield: 713 mg (95%). Yellowish crystals; mp 235-237°C (AcOEt). IR: 3329 w (br), 3088 w, 2986 w, 1612 s, 1488 m, 1410 w, 1374 m, 1343 m, 1325 s, 1298 w, 1278 s, 1222 m, 1140 s, 1078 w, 998 m, 889 w, 845 m, 831 m, 751 w. ¹H-NMR: 1.52 (s, 3 CH₃); 4.36 (br s, NH); 7.19, 7.64 (AA’BB’, J ≈ 8, 4 arom. H). ¹³C-NMR: 31.6 (3 CH₃); 86.5 (C); 121.5 (1 arom. C); 129.2 (2 arom. CH); 131.7 (2 arom. CH); 132.1, 146.0 (1 arom. C, C(3)); 153.1 (C=Se). ESI-MS: 394 (16), 395 (14), 396 (57), 397 (28), 398 (100, [M+Na]⁺), 399 (17), 400 (75), 401 (10), 402 (12). Anal. Calcd for C₁₇H₂₂N₃O₃BrSe: C, 38.42; H, 3.76; N, 11.20. Found: C, 38.54; H, 3.57; N, 11.56.

X-Ray Crystal-Structure Determination of 7e (see Table 2 and Figure 1). All measurements
were made on a Nonius KappaCCD area-detector diffractometer\textsuperscript{49} using graphite-monochromated MoK\textsubscript{α} radiation (\(\lambda = 0.71073 \text{ Å}\)) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given in Table 1, and a view of the molecule is shown in Figure 1. Data reduction was performed with HKL Denzo and Scalepack.\textsuperscript{50} The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method\textsuperscript{51} was applied. Equivalent reflections were merged. The structure was solved by direct methods using SHELXS97,\textsuperscript{52} which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U\textsubscript{eq} of its parent atom (1.5U\textsubscript{eq} for the methyl groups). Refinement of the structure was carried out on \(F^2\) using full-matrix least-squares procedures, which minimized the function \(\sum w(F_o^2 - F_c^2)^2\). A correction for secondary extinction was applied. Neutral atom scattering factors for non-hydrogen atoms were taken from ref.,\textsuperscript{53} and the scattering factors for H-atoms were taken from ref.\textsuperscript{54} Anomalous dispersion effects were included in \(F_c\),\textsuperscript{55} the values for \(f'\) and \(f''\) were those of ref.\textsuperscript{56} The values of the mass attenuation coefficients are those of ref.\textsuperscript{57} All calculations were performed using the SHELXL97\textsuperscript{58} program.

ACKNOWLEDGMENTS

We thank the analytical services of our institute for NMR and MS spectra and elemental analyses, and Miss S. Blumentritt for her assistance with the determination of the crystal structure. Financial support of this work by the Dr. Helmut Legerlotz-Foundation and F. Hoffmann-La Roche AG, Basel, is gratefully acknowledged.

REFERENCES AND NOTES

1. Stay at the University of Zürich (5.–7. 2005; trainee project).
Table 2. Crystallographic Data of Compound (7e)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystallized from</td>
<td>CH$_2$Cl$_2$</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C$<em>{14}$H$</em>{17}$N$_3$O$_3$Se</td>
</tr>
<tr>
<td>Formula weight [g mol$^{-1}$]</td>
<td>354.21</td>
</tr>
<tr>
<td>Crystal color, habit</td>
<td>yellow, tablet</td>
</tr>
<tr>
<td>Crystal dimensions [mm]</td>
<td>0.10 $\times$ 0.17 $\times$ 0.28</td>
</tr>
<tr>
<td>Temperature [K]</td>
<td>160(1)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>C2/c</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Reflections for cell determination</td>
<td>22257</td>
</tr>
<tr>
<td>$2\theta$ range for cell determination [$^\circ$]</td>
<td>4–55</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td></td>
</tr>
<tr>
<td>$a$ [Å]</td>
<td>11.2907(3)</td>
</tr>
<tr>
<td>$b$ [Å]</td>
<td>20.2786(6)</td>
</tr>
<tr>
<td>$c$ [Å]</td>
<td>14.3222(3)</td>
</tr>
<tr>
<td>$\beta$ [$^\circ$]</td>
<td>112.352(2)</td>
</tr>
<tr>
<td>$V$ [Å$^3$]</td>
<td>3032.8(1)</td>
</tr>
<tr>
<td>$D_x$ [g cm$^{-3}$]</td>
<td>1.551</td>
</tr>
<tr>
<td>$\mu$(MoK$_{\alpha}$) [mm$^{-1}$]</td>
<td>2.488</td>
</tr>
<tr>
<td>Scan type</td>
<td>$\phi$ and $\omega$</td>
</tr>
<tr>
<td>$2\theta_{(\text{max})}$ [$^\circ$]</td>
<td>55</td>
</tr>
<tr>
<td>Transmission factors (min; max)</td>
<td>0.667; 0.788</td>
</tr>
<tr>
<td>Total reflections measured</td>
<td>30892</td>
</tr>
<tr>
<td>Symmetry independent reflections</td>
<td>3481</td>
</tr>
<tr>
<td>Reflections with $I &gt; 2\sigma(I)$</td>
<td>2790</td>
</tr>
<tr>
<td>Reflections used in refinement</td>
<td>3481</td>
</tr>
<tr>
<td>Parameters refined</td>
<td>194</td>
</tr>
<tr>
<td>Final : $R(F)$ [$I &gt; 2\sigma(I)$ reflections]</td>
<td>0.0318</td>
</tr>
<tr>
<td>$wR(F^2)$ (all data)</td>
<td>0.0871</td>
</tr>
<tr>
<td>Weights: $w = [\sigma^2(F_o^2) + (0.0494P)^2 + 1.3898P]^{-1}$</td>
<td>where $P = (F_o^2 + 2F_c^2)/3$</td>
</tr>
<tr>
<td>Goodness of fit</td>
<td>1.038</td>
</tr>
<tr>
<td>Secondary extinction coefficient</td>
<td>0.0010(2)</td>
</tr>
<tr>
<td>Final $\Delta_{\text{max}}/\sigma$</td>
<td>0.001</td>
</tr>
<tr>
<td>$\Delta\rho$ (max; min) [e Å$^{-3}$]</td>
<td>0.51; −0.63</td>
</tr>
</tbody>
</table>
32. Analogous reactions with isocyanates and isothiocyanates leading to 1,2,4-triazolones and 1,2,4-triazolethiones, respectively, have been reported recently.\footnote{33}
42. The formation of this side-product is well known and several articles deal with the use of modified azodicarboxylates to avoid the purification problem.\footnote{43} The most efficient way is to use a polymer-supported alkyl azodicarboxylate described in 1989 by Vederas.\footnote{44}


48. CCDC-279972 contains the supplementary crystallographic data for compound 7e. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


