HETEROCYCLES, Vol. 67, No. 2, 2006, pp. 749 - 762. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd August, 2005, Accepted, 26th September, 2005, Published online, 30th September, 2005. COM-05-S(T)77

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-1*H*-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.

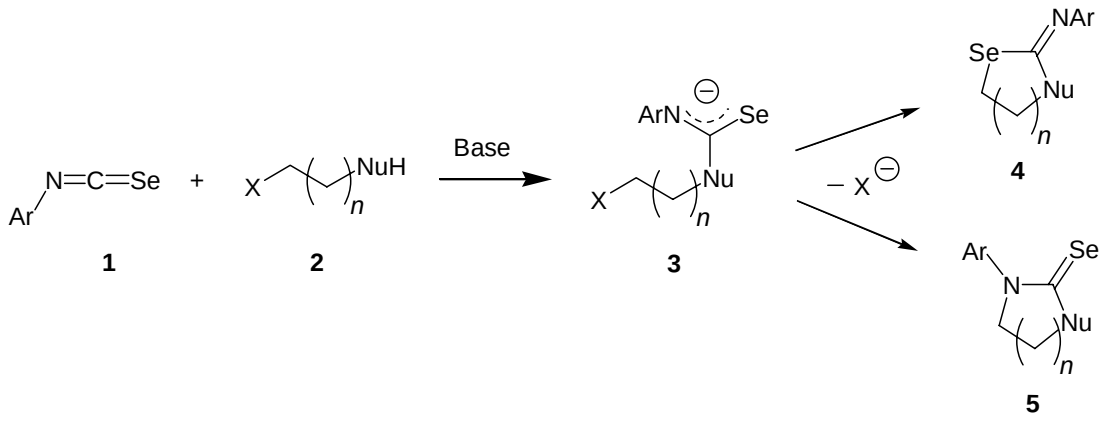
INTRODUCTION

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]

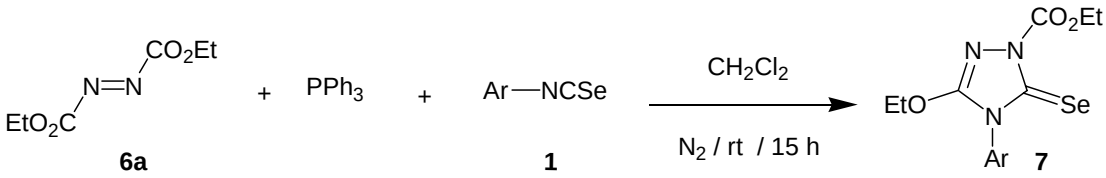
Isoselenocyanates have already been used for the synthesis of mesoionic 1,2,4-triazolo-3-selones.[38] This preparation, published in 1976 by *Egorochkin*[39] and in 2000 by *Miller*,[40] was

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 (Ph_3P) 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* procedure[41] from the corresponding *N*-arylformamide 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 triphenylphospine oxide (Ph_3PO; TLC detection), and separation by column chromatography (SiO_2, hexane/ethyl acetate) was necessary to get the ethyl 5-selenoxo-1*H-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



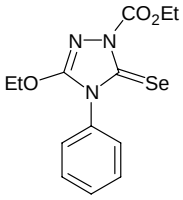
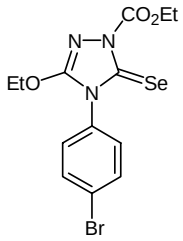
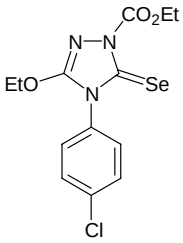
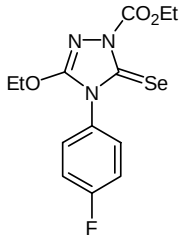
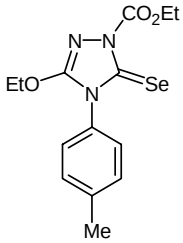
Ar = Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Me-C_6H_4

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 ^{13}C-NMR spectra ($CDCl_3$), indicative absorptions for CO_2Et, 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**)

Entry	Ar	**4**	Yield (%)
a	Ph		81
b	4-Br-C_6H_4		82
c	4-Cl-C_6H_4		97
d	4-F-C_6H_4		84
e	4-Me-C_6H_4		78

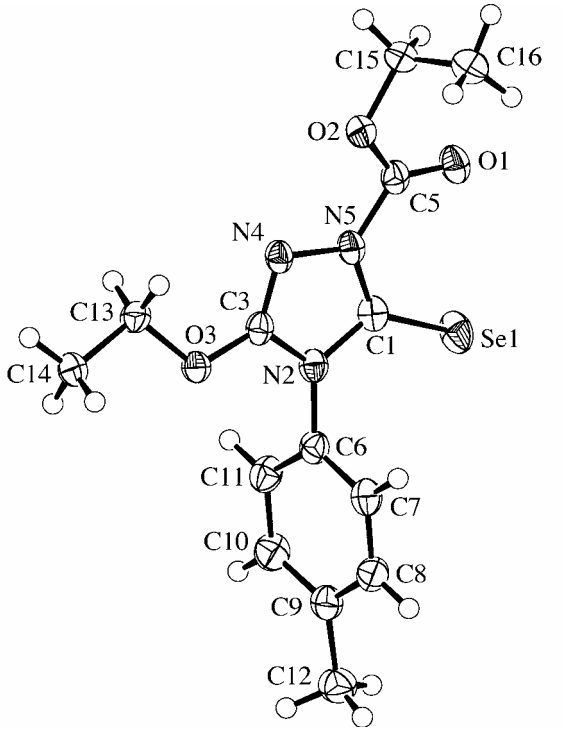
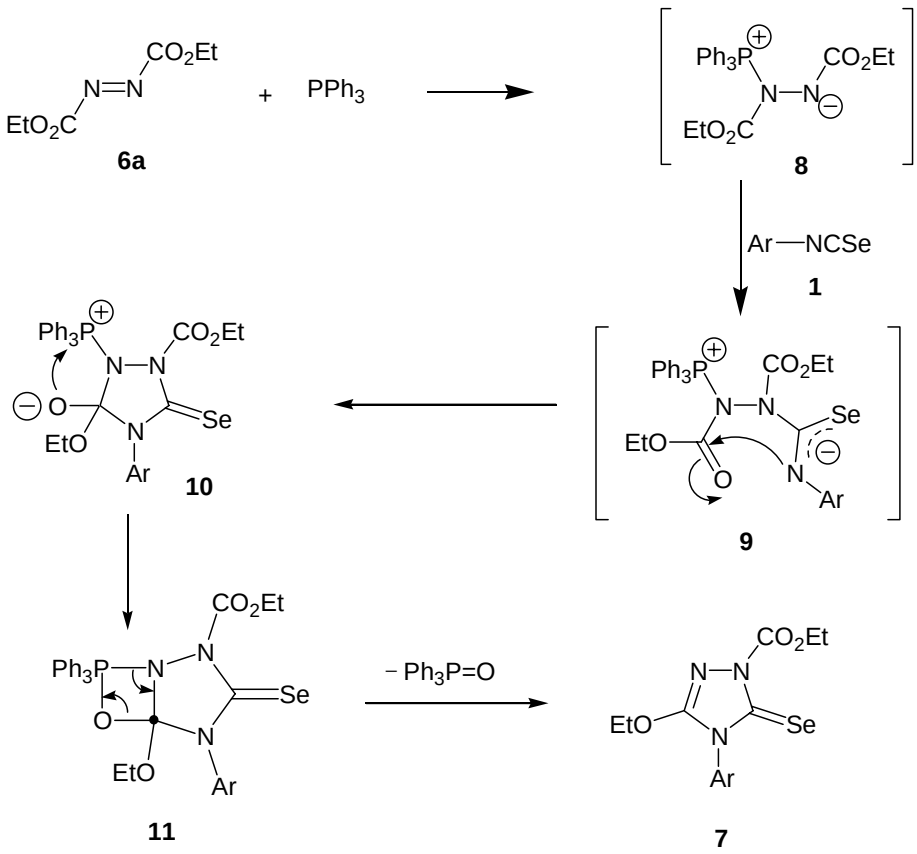


Figure 1. ORTEP plot[45] of the molecular structure of **7e** (arbitrary numbering of atoms; 50% probability ellipsoids).

Scheme 3

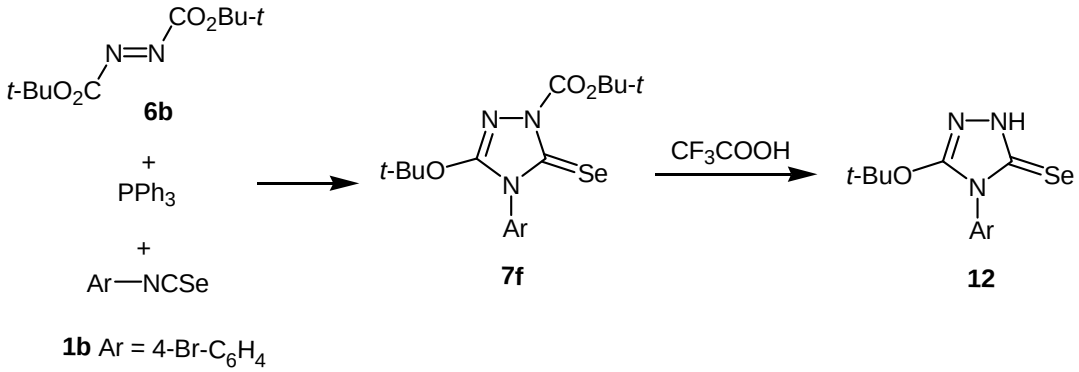


A likely reaction mechanism for the formation of **7** is proposed in *Scheme 3*. The addition of Ph_3P onto the azodicarboxylate (**6**) generates the zwitterion (**8**), which, as a nucleophile, attacks the isoselenocyanate (**1**) to give **9**. Ring closure by nucleophilic addition of the N-atom at the ester group leads to **10**, and elimination of Ph_3PO *via* the intermediate (**11**) yields the product (**7**).

The use of the system diethyl azodicarboxylate (oxidant)/Ph_3P (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 Ph_3P gave the triazoloselone (**7f**) in almost quantitative yield. This product was transformed into the 3-*tert*-butoxy-4,5-dihydro-1*H*-1,2,4-triazole-5-selone (**12**) by decarboxylation with trifluoroacetic acid at room temperature in quantitative yield (*Scheme 4*).

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_3P) 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_2O) and washed with diluted acetic acid (5%), water and aqueous $NaHCO_3$ (5%). The aqueous layer was extracted with Et_2O, 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) azodicarboxylate (**6a** and **6b**, respectively) (0.92 mL, 2.0 mmol) and Ph_3P (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*, 1328*s*, 1308*s*, 1220*s*, 1175*w*, 1155*w*, 1109*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, CH_3); 1.49 (*t*, *J* = 7.1, CH_3); 4.49-4.62 (*m*, 2 CH_2); 7.35 (*d*, *J* = 8.1, 2 arom. H); 7.52-7.59 (*m*, 3 arom. H). ^{13}C-NMR: 14.0 (CH_3); 14.1 (CH_3); 65.0 (CH_2); 68.5 (CH_2); 128.1 (2 arom. CH);

129.4 (2 arom. CH); 130.0 (1 arom. CH); 132.6, 148.2 (1 arom. C, C(3)); 156.3 (C=Se); 167.8 (C=O). ESI-MS: 360 (14), 361 (13), 362 (52), 363 (3), 364 (100, [*M*+Na]$^+$), 365 (11), 366 (15). Anal. Calcd for $C_{13}H_{15}N_3O_3Se$: C, 45.89; H, 4.44; N, 11.86. Found: C, 45.58; H, 4.58; N, 12.64.

*Ethyl 4-(4-bromophenyl)-3-ethoxy-4,5-dihydro-5-selenoxo-1*H-*1,2,4-triazole-1-carboxylate* (**7b**). Yield: 686 mg (82%). Yellowish crystals; mp 147-149°C (AcOEt). IR: 3444*w* (br), 2982*w*, 2935*w*, 1755*s*, 1718*m*, 1638*s*, 1591*w*, 1493*m*, 1451*m*, 1392*m*, 1366*m*, 1327*s*, 1303*s*, 1286*s*, 1215*w*, 1170*w*, 1154*w*, 1104*w*, 1068*w*, 1030*m*, 1011*m*, 988*w*, 909*w*, 850*w*, 754*w*, 711*w*. ^{1}H-NMR: 1.31 (*t*, *J* = 7.1, CH_3); 1.41 (*t*, *J* = 7.1, CH_3); 4.41-4.51 (*m*, 2 CH_2); 7.20, 7.58 (*AA'BB'*, *J* ≈ 8, 4 arom. H). ^{13}C-NMR: 14.1 (CH_3); 14.3 (CH_3); 65.1 (CH_2); 68.7 (CH_2); 124.2 (1 arom. C); 129.8 (2 arom. CH); 132.7 (2 arom. CH); 131.5, 148.9 (1 arom. C, C(3)); 155.6 (C=Se); 166.8 (C=O). ESI-MS: 438 (15), 439 (12), 440 (55), 441 (4), 442 (100, [*M*+Na]$^+$), 443 (14), 444 (12). Anal. Calcd for $C_{13}H_{14}N_3O_3BrSe$: C, 37.25; H, 3.37; N, 10.03. Found: C, 37.12; H, 3.23; N, 9.99.

*Ethyl 4-(4-chlorophenyl)-3-ethoxy-4,5-dihydro-5-selenoxo-1*H-*1,2,4-triazole-1-carboxylate* (**7c**). Yield: 726 mg (97%). Yellowish crystals; mp 142-144°C (AcOEt). IR: 3442*w* (br), 2982*w*, 1765*s*, 1625*s*, 1495*m*, 1469*w*, 1442*w*, 1373*m*, 1310*s*, 1289*s*, 1218*s*, 1173*w*, 1148*w*, 1089*m*, 1025*m*, 977*m*, 907*w*, 836*w*, 753*w*, 703*w*. ^{1}H-NMR: 1.31 (*t*, *J* = 7.1Hz, CH_3); 1.41 (*t*, *J* = 7.1, CH_3); 4.39-4.51 (*m*, 2 CH_2); 7.24, 7.43 (*AA'BB'*, *J* ≈ 8, 2H, 4 arom. H). ^{13}C-NMR: 14.1 (CH_3); 14.3 (CH_3); 65.1 (CH_2); 68.7 (CH_2); 124.6 1 arom. C); 129.5 (2 arom. CH); 129.7 (2 arom. CH); 131.0, 148.9 (1 arom. C, C(3)); 155.6 (C=Se); 166.9 (C=O). ESI-MS: 394 (13), 395 (14), 396 (51), 397 (4), 398 (100, [*M*+Na]$^+$), 399 (18), 400 (49). Anal. Calcd for $C_{13}H_{14}N_3O_3ClSe$: C, 41.67; H, 3.77; N, 11.21. Found: C, 41.63; H, 3.84; N, 11.34.

*Ethyl 3-ethoxy-4-(4-fluorophenyl)-4,5-dihydro-5-selenoxo-1*H-*1,2,4-triazole-1-carboxylate* (**7d**). Yield: 603 mg (84%). Yellowish crystals; mp 151-153°C (AcOEt). IR: 3442*w* (br), 3085*w*, 2982*w*, 1769*s*, 1621*s*, 1512*s*, 1475*w*, 1454*m*, 1386*m*, 1367*m*, 1311*s*, 1290*s*, 1216*s*, 1171*w*, 1150*w*, 1112*w*, 1088*w*, 1063*m*, 1024*m*, 1004*w*, 977*m*, 905*w*, 853*m*, 821*w*, 759*w*, 725*w*, 711*w*, 635*w*, 622*m*. ^{1}H-NMR: 1.35 (*t*, *J* = 7.1, CH_3); 1.49 (*t*, *J* = 7.1, CH_3); 4.41-4.51 (*m*, 2 CH_2); 6.95, 7.19 (*AA'BB'*, *J* ≈ 8, 4 arom. H). ^{13}C-NMR: 14.0 (CH_3); 14.3 (CH_3); 65.1 (CH_2); 68.6 (CH_2); 116.4 (2 arom. CH, $^2J_{C,F}$ = 23); 130.1 (2 arom. CH); 128.4, 148.9 (1 arom. C, C(3)); 155.8 (C=Se); 162.3 (CF, $^1J_{C,F}$ = 249); 167.1 (C=O). ESI-MS: 378 (15), 379 (12), 380 (55), 381 (4), 382 (100, [*M*+Na]$^+$), 383 (15), 384 (17). Anal. Calcd for $C_{13}H_{14}N_3O_3FSe$: C, 43.59; H, 3.94; N, 11.73. Found:

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

*Ethyl 3-ethoxy-4,5-dihydro-4-(4-methylphenyl)-5-selenoxo-1*H-*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*. ^{1}H-NMR: 1.37 (*t*, *J* = 7.1, CH_3); 1.49 (*t*, *J* = 7.1, CH_3); 2.43 (*s*, CH_3); 4.48-4.60 (*m*, 2 CH_2); 7.22, 7.34 (*AA'BB'*, *J* ≈ 8, 4 arom. H). ^{13}C-NMR: 14.0 (CH_3); 14.3 (CH_3); 21.3 (CH_3); 65.0 (CH_2); 68.4 (CH_2); 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 $C_{14}H_{17}N_3O_3Se$: 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-1*H-*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*, 1488*m*, 1453*w*, 1408*w*, 1372*m*, 1337*m*, 1320*s*, 1297*m*, 1278*s*, 1223*m*, 1143*s*, 1065*w*, 1000*m*, 895*w*, 848*m*, 836*m*, 804*w*, 761*w*, 655*w*. ^{1}H-NMR: 1.53 (*s*, 3 CH_3); 1.67 (*s*, 3 CH_3); 7.21, 7.62 (*AA'BB'*, *J* ≈ 8, 4 arom. H). ^{13}C-NMR: 27.6 (3 CH_3); 27.8 (3 CH_3); 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 $C_{17}H_{22}N_3O_3BrSe$: 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-1*H-*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*m*, 1278*s*, 1222*m*, 1140*s*, 1078*w*, 998*m*, 889*w*, 845*m*, 831*m*, 751*w*. ^{1}H-NMR: 1.52 (*s*, 3 CH_3); 4.36 (*br s*, NH); 7.19, 7.64 (*AA'BB'*, *J* ≈ 8, 4 arom. H). ^{13}C-NMR: 31.6 (3 CH_3); 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 $C_{17}H_{22}N_3O_3BrSe$: 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*).[48] All measurements

were made on a *Nonius KappaCCD* area-detector diffractometer[49] using graphite-monochromated MoK_α radiation (λ 0.71073 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*.[50] The intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method[51] was applied. Equivalent reflections were merged. The structure was solved by direct methods using *SHELXS97*,[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_{eq} of its parent atom (1.5U_{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 $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Neutral atom scattering factors for non-hydrogen atoms were taken from ref.,[53] and the scattering factors for H-atoms were taken from ref.[54] Anomalous dispersion effects were included in F_c;[55] the values for *f '* and *f "* were those of ref.[56] The values of the mass attenuation coefficients are those of ref.[57] All calculations were performed using the *SHELXL97*[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).
2. Postdoctoral stay at the University of Zürich (2004–2005).
3. M. Koketsu and H. Ishihara, *Curr. Org. Chem*., 2003, **7**, 175.
4. R. J. Shamberger, '*Biochemistry of Selenium*', Plenum Press, New York, 1983.
5. E. M. Alissa, S. M. Bahijri, and G. A. Ferns, *Med. Sci. Monit*., 2003, **9**, RA9.
6. P. C. Srivastava and R. K. Robins, *J. Med. Chem*., 1983, **26**, 445.

Table 2. *Crystallographic Data of Compound* (**7e**)

Crystallized from	CH_2Cl_2
Empirical formula	$C_{14}H_{17}N_3O_3Se$
Formula weight [g mol^{-1}]	354.21
Crystal color, habit	yellow, tablet
Crystal dimensions [mm]	0.10 × 0.17 × 0.28
Temperature [K]	160(1)
Crystal system	monoclinic
Space group	*C*2/*c*
Z	8
Reflections for cell determination	22257
2θ range for cell determination [°]	4 – 55
Unit cell parameters	
a [Å]	11.2907(3)
b [Å]	20.2786(6)
c [Å]	14.3222(3)
β [°]	112.352(2)
V [Å^3]	3032.8(1)
D_X [g cm^{-3}]	1.551
μ(MoK_α) [mm^{-1}]	2.488
Scan type	ϕ and ω
$2\theta_{(max)}$ [°]	55
Transmission factors (min; max)	0.667; 0.788
Total reflections measured	30892
Symmetry independent reflections	3481
Reflections with $I > 2\sigma(I)$	2790
Reflections used in refinement	3481
Parameters refined	194
Final : *R(F)* [$I > 2\sigma(I)$ reflections]	0.0318
wR(F^2) (all data)	0.0871
Weights: $w = [\sigma^2(F_o^2) + (0.0494P)^2 + 1.3898P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$	
Goodness of fit	1.038
Secondary extinction coefficient	0.0010(2)
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.51; –0.63

7. W. Wu, K. Murakami, M. Koketsu, Y. Yamada, and I. Saiki, *Anticancer Res.*, 1999, **19**, 5375.
8. K. El-Bayoumy and R. Sinha, *Mutation Research*, 2004, **551**, 181.
9. L. Patrick, *Alternative Med. Chem*., 2004, **9**, 239.
10. E. Block, *Adv. Exp. Med. & Biol*., 1996, **401**, 155.
11. E. Block, S. Bird, J. F. Tyson, P. C. Uden, X. Zhang, and E. Denoyer, *Phosphorus, Sulfur, Silicon & Rel. Elem.*, 1998, **136-8**, 1.
12. S. W. May, *Exp. Opin. Invest. Drugs*, 2002, **11**, 1261.
13. M. J. Parnham and E. Graf, *Prog. Drug. Res*., 1991, **36**, 9.
14. M. Koketsu, H. Ishihara, W. Wu, K. Murakami, and I. Saiki, *Eur. J. Pharm. Sci*., 1999, **9**, 157.
15. S. W. May, L. Wang, M. M. Gill-Woznichak, R. F. Browner, A. A. Ogonowski, J. B. Smith, and S. H. Pollock, *J. Pharm. Exp. Ther*., 1997, **283**, 470.
16. (a) T. Göbel, L. Gsell, O. F. Hüter, P. Maienfisch, R. Naef, A. C. O'Sullivan, T. Pitterna, T. Rapold, G. Seifert, M. Sern, H. Szczepanski, and D. J. Wadsworth, *Pestic. Sci*., 1999, **55**, 355; (b) S. I. El-Desoky, S. B. Bondock, H. A. Etman, A. A. Fadda, and M. A. Metwally, *Sulfur Lett*., 2003, **26**, 127; (c) C. Lamberth, *J. Sulfur Chem*., 2004, **25**, 39; (d) R. M. Kedar, N. N. Vidhale, and M. M. Chincholkar, *Orient. J. Chem*., 1996, **12**, 301; (e) M. A. Metwally, E. Abdel-Latif, F. A. Amer, and G. Kaupp, *J. Sulfur Chem*., 2004, **25**, 63; (f) D. D. Erol, M. D. Aytemir, and N. Yulug, *Eur. J. Med. Chem*., 1996, **31**, 731.
17. Y. Zhou and H. Heimgartner, *Helv. Chim. Acta*, 2000, **83**, 539.
18. Y. Zhou, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2000, **83**, 1576.
19. P. K. Atanassov, Y. Zhou, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2002, **85**, 1102.
20. P. K. Atanassov, A. Linden, and H. Heimgartner, *Heterocycles*, 2003, **61**, 569.
21. P. K. Atanassov, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2003, **86**, 3235.
22. P. K. Atanassov, A. Linden, and H. Heimgartner, *Heterocycles*, 2004, **62**, 521.
23. P. K. Atanassov, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2004, **87**, 1452.
24. P. K. Atanassov, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2004, **87**, 1873.
25. G. L. Sommen, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2005, **88**, 766.
26. G. L. Sommen, A. Linden, and H. Heimgartner, *Eur. J. Org. Chem.*, 2005, **14**, 3128.
27. G. L. Sommen, A. Linden, and H. Heimgartner, *Heterocycles,* 2005, **65**, 1903.
28. G. L. Sommen, A. Linden, and H. Heimgartner, *Tetrahedron Lett.*, 2005, **46**, 6723.

29. G. L. Sommen, A. Linden, and H. Heimgartner, in preparation.
30. a) Z. J. Witczak, *Tetrahedron*, 1985, **41**, 4781; b) W. J. Stec, K. Lesiak, and M. Sudol, *Synthesis*, 1975, 785; c) K. Sukata, *J. Org. Chem*., 1989, **54**, 2015.
31. M. L. Petrov and N. I. Zmitrovich, *Russ. J. Gen. Chem*., 1999, **69**, 245.
32. Analogous reactions with isocyanates and isothiocyanates leading to 1,2,4-triazolones and 1,2,4-triazolethiones, respectively, have been reported recently.[33]
33. A. Alizadeh, *Helv. Chim. Acta*, 2005, in press.
34. U. Svanholm, *Acta. Chem. Scand*., 1972, **26**, 459.
35. a) J. C. Brown, *Ger. Offen*., 1971, *DE 2063575* (*Chem. Abstr.*, 1971, **75**, 76805); b) J. C. Brown, D. J. Fry, and P. J. Keogh, *Ger. Offen*., 1972, *DE 2162855* (*Chem. Abstr.*, 1972, **77**, 140086).
36. N. I. Korotkikh, G. F. Rayenko, O. P. Shvaika, T. M. Pekhtereva, A. H. Cowley, J. N. Jones, and C. L. B. Macdonald, *J. Org. Chem*., 2003, **68**, 5762.
37. a) D. Enders, K. Breuer, U. Kallfass, and T. Balensiefer, *Synthesis*, 2003, **8**, 1292; b) D. Enders, K. Breuer, J. Runsink, and J. H. Teles, *Liebigs Ann.*, 1996, 2019.
38. W. Bocian, J. Jazwinski, and L. Stefaniak, *Pol. J. Chem*., 1995, **69**, 85.
39. A. Y. Lazaris and A. N. Egorochkin, *Izv. Akad. Nauk. SSSR, Ser. Khim*., 1976, **5**, 1191.
40. P. Filgueiras de Athayde-Filho, A. M. Simas, S. M. Cruz Goncalvez, and J. Miller, *Phosphorus, Sulfur, Silicon & Rel. Elem*., 2000, **161**, 115.
41. a) D. H. R. Barton, S. I. Parekh, M. Tajbakhsh, E. A. Theodorakis, and C. -L. Tse, *Tetrahedron*, 1994, **50**, 639 ; b) M. T. Bakhsh, Y. S. Behshtiha, and M. M. Heravi, *J. Chem. Soc. Pakistan*, 1996, **18**, 159.
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.[43] The most efficient way is to use a polymer-supported alkyl azodicarboxylate described in 1989 by *Vederas*.[44]
43. R. Dembinski, *Eur. J. Org. Chem*., 2004, **13**, 2763.
44. L. D. Arnold, H. I. Assil, and J. C. Vederas, *J. Am. Chem. Soc*., 1989, **111**, 3973.
45. C. K. Johnson, *ORTEPII*, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
46. a) S. Bittner, Y. Assaf, P. Krief, M. Pomerantz, B. T. Ziemnicka, and C. G. Smith, *J. Org. Chem*., 1985, **50**, 1712; b) T. Mukaiyama, *Angew. Chem., Int. Ed. Engl*., 1976, **15**, 94; c) O. Mitsunobu, *Synthesis*, 1981, 1; d) H. Fauduet and R. Burgada, *C.R. Acad. Sci. Ser. C*, 1980, **291**, 81; e) M. Von Itzstein and I. D. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, 1986,

437; f) D. Camp and I. D. Jenkins, *J. Org. Chem*., 1989, **54**, 3049; g) M. Von Itzstein and I. D. Jenkins, *Aust. J. Chem.*, 1983, **36**, 557; h) H.-J. Niclas and D. Martin, *Tetrahedron Lett*., 1978, **42**, 4031.

47. D. L. Hughes, *Org. Reactions*, 1992, **42**, 335.
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.
49. R. Hooft, *KappaCCD Collect Software*, Nonius BV, Delft, The Netherlands, 1999.
50. Z. Otwinowski and W. Minor, in *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, ed. by C. W. Carter Jr. and R. M. Sweet, Academic Press, New York, 1997, p. 307.
51. R. H. Blessing, *Acta Crystallogr., Sect A*, 1995, **51**, 33.
52. G. M. Sheldrick, *SHELXS97, Program for the Solution of Crystal Structures*, University of Göttingen, Germany, 1997.
53. E. N. Maslen, A. G. Fox, and M. A. O'Keefe, in *International Tables for Crystallography*, ed. by A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477.
54. R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.,* 1965, **42**, 3175.
55. J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.,* 1964, **17**, 781.
56. D. C. Creagh and W. J. McAuley, in *International Tables for Crystallography*, ed. by A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.6.8, p. 219.
57. D. C. Creagh and J. H. Hubbell, in *International Tables for Crystallography*, ed. by A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.4.3, p. 200.
58. G. M. Sheldrick, *SHELXL97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.